



GLOBAL HEALTH 2014

The Third International Conference on Global Health Challenges

ISBN: 978-1-61208-359-9

August 24 - 28, 2014

Rome, Italy

GLOBAL HEALTH 2014 Editors

Hassan Khachfe, Lebanese International University, Lebanon

Matthieu-P. Schapranow, Hasso Plattner Institute, Germany

Vesselin Gueorguiev, TU Sofia, Bulgaria

GLOBAL HEALTH 2014

Foreword

The Third International Conference on Global Health Challenges (GLOBAL HEALTH 2014), held on August 24 - 28, 2014 - Rome, Italy, took a global perspective on population health, from national to cross-country approaches, multiplatform technologies, from drug design to medicine accessibility, everything under mobile, ubiquitous, and personalized characteristics of new age population.

Recent advances in technology and computational science influenced a large spectrum of branches in approaching population health. Despite significant progresses, many challenges exist, including health informatics, cross-country platforms interoperability, system and laws harmonization, protection of health data, practical solutions, accessibility to health services, and many others. Along with technological progress, personalized medicine, ambient assistance and pervasive health complement patient needs. A combination of classical and information-driven approach is developing now, where diagnosis systems, data protection mechanisms, remote assistance and hospital-processes are converging.

We take here the opportunity to warmly thank all the members of the GLOBAL HEALTH 2014 Technical Program Committee, as well as the numerous reviewers. The creation of such a high quality conference program would not have been possible without their involvement. We also kindly thank all the authors who dedicated much of their time and efforts to contribute to GLOBAL HEALTH 2014. We truly believe that, thanks to all these efforts, the final conference program consisted of top quality contributions.

Also, this event could not have been a reality without the support of many individuals, organizations, and sponsors. We are grateful to the members of the GLOBAL HEALTH 2014 organizing committee for their help in handling the logistics and for their work to make this professional meeting a success.

We hope that GLOBAL HEALTH 2014 was a successful international forum for the exchange of ideas and results between academia and industry and for the promotion of progress in the field of global health.

We hope Rome provided a pleasant environment during the conference and everyone saved some time for exploring this beautiful city.

GLOBAL HEALTH 2014 Chairs:

GLOBAL HEALTH Steering Committee

Hassan Khachfe, Lebanese International University, Lebanon

Shunji Shimizu, Tokyo University of Science, Suwa, Japan

Sten Hanke, IPN Instituto Pedro Nunes, Portugal | AIT Austrian Institute of Technology GmbH, Austria

Michael Bremseth, Winthrop University, USA

Jean-Pierre Cordeau, McGill University Health Centre, Canada

Ivan Evgeniev, TU Sofia, Bulgaria

Matthieu-P. Schapranow, Hasso Plattner Institute, Germany

GLOBAL HEALTH Technology Advisory Committee

Fei Wang, IBM Almaden Research Center - San Jose, USA

Marika Hettinga, Windesheim University of Applied Sciences, Netherlands

Shirley Coyle, Centre for Sensor Web Technologies / Dublin City University, Ireland

Vasa Curcin, Imperial College London, UK

Anna Cysewska-Sobusiak, Poznan University of Technology, Poland

Kevin Daimi, University of Detroit Mercy, USA

Ravi Janardan, University of Minnesota-Twin Cities, USA

Jose M. Juarez, University of Murcia, Spain

Jochen Meyer, OFFIS Institute for Computer Science, Germany

Vesselin Gueorguiev, TU Sofia, Bulgaria

Miki Sirola, Aalto University, Finland

Daniel Steffen, German Research Center for Artificial Intelligence (DFKI) GmbH - Kaiserslautern, Germany

Maria Taboada Iglesias, University of Santiago de Compostela, Spain

Jari Veijalainen, University of Jyväskylä, Finland

Pierangelo Veltri, University Magna Graecia of Catanzaro, Italy

Brijesh Verma, Central Queensland University, Australia

Liangjiang Wang, Clemson University - Greenwood, USA

Hans C. Ossebaard, National Institute for Public Health and the Environment - Bilthoven, The Netherlands

GLOBAL HEALTH Public/Government/Research Advisory Committee

William Cherniak, TO-the WORLD, Canada

Christopher Mayer, AIT Austrian Institute of Technology GmbH, Austria

João Quintas, Instituto Pedro Nunes, Portugal

Yoshikazu Seki, National Institute of Advanced Industrial Science and Technology (AIST) - Ibaraki, Japan

Hrvoje Belani, Croatian Health Insurance Fund - Zagreb, Croatia

Stefan J. Darmoni, Rouen University Hospital, France

Chih-Lin Chi, University of Minnesota-Twin Cities, USA

Siddhartha Jonnalagadda, Northwestern University, USA

Bin Song, Oracle, Inc., USA

Egon L. van den Broek, TNO Technical Sciences - Delft | University of Twente - Enschede | Radboud University Medical Center Nijmegen - Nijmegen, The Netherlands

Zhongming Zhao, Vanderbilt University / Medical Center, USA

Hua Xu, Vanderbilt University/School of Medicine, The Netherlands

GLOBAL HEALTH 2014

Committee

GLOBAL HEALTH Steering Committee

Hassan Khachfe, Lebanese International University, Lebanon
Shunji Shimizu, Tokyo University of Science, Suwa, Japan
Sten Hanke, IPN Instituto Pedro Nunes, Portugal | AIT Austrian Institute of Technology GmbH, Austria
Michael Bremseth, Winthrop University, USA
Jean-Pierre Cordeau, McGill University Health Centre, Canada
Ivan Evgeniev, TU Sofia, Bulgaria
Matthieu-P. Schapranow, Hasso Plattner Institute, Germany

GLOBAL HEALTH Technology Advisory Committee

Fei Wang, IBM Almaden Research Center - San Jose, USA
Marika Hettinga, Windesheim University of Applied Sciences, Netherlands
Shirley Coyle, Centre for Sensor Web Technologies / Dublin City University, Ireland
Vasa Curcin, Imperial College London, UK
Anna Cysewska-Sobusiak, Poznan University of Technology, Poland
Kevin Daimi, University of Detroit Mercy, USA
Ravi Janardan, University of Minnesota-Twin Cities, USA
Jose M. Juarez, University of Murcia, Spain
Jochen Meyer, OFFIS Institute for Computer Science, Germany
Vesselin Gueorguiev, TU Sofia, Bulgaria
Miki Sirola, Aalto University, Finland
Daniel Steffen, German Research Center for Artificial Intelligence (DFKI) GmbH - Kaiserslautern, Germany
Maria Taboada Iglesias, University of Santiago de Compostela, Spain
Jari Veijalainen, University of Jyväskylä, Finland
Pierangelo Veltri, University Magna Graecia of Catanzaro, Italy
Brijesh Verma, Central Queensland University, Australia
Liangjiang Wang, Clemson University - Greenwood, USA
Hans C. Ossebaard, National Institute for Public Health and the Environment - Bilthoven, The Netherlands

GLOBAL HEALTH Public/Government/Research Advisory Committee

William Cherniak, TO-the WORLD, Canada
Christopher Mayer, AIT Austrian Institute of Technology GmbH, Austria
João Quintas, Instituto Pedro Nunes, Portugal
Yoshikazu Seki, National Institute of Advanced Industrial Science and Technology (AIST) - Ibaraki, Japan
Hrvoje Belani, Croatian Health Insurance Fund - Zagreb, Croatia
Stefan J. Darmoni, Rouen University Hospital, France

Chih-Lin Chi, University of Minnesota-Twin Cities, USA
Siddhartha Jonnalagadda, Northwestern University, USA
Bin Song, Oracle, Inc., USA
Egon L. van den Broek, TNO Technical Sciences - Delft | University of Twente - Enschede | Radboud University Medical Center Nijmegen - Nijmegen, The Netherlands
Zhongming Zhao, Vanderbilt University / Medical Center, USA
Hua Xu, Vanderbilt University/School of Medicine, The Netherlands

GLOBAL HEALTH 2014 Technical Program Committee

Charlie Abela, University of Malta - Msida, Malta
Sachiyo Aburatani, Computational Biology Research Center - National Institute of Advanced Industrial Science and Technology, Japan
Esko Alasaarela, University of Oulu, Finland
Giner Alor Hernández, Instituto Tecnológico de Orizaba - Veracruz, México
Thierry Badard, Centre for Research in Geomatics - Laval University, Canada
Hrvoje Belani, Croatian Health Insurance Fund - Zagreb, Croatia
Mounir Bousbia-Salah, Badji Mokhtar University - Annaba, Algeria
Pamela Briggs, School of Life Sciences / Northumbria University, UK
Sabin-Corneliu Buraga, "A. I. Cuza" University, Romania
Rita Casadio, Biocomputing Group - University of Bologna, Italy
Bolin Chen, University of Saskatchewan, Canada
Dechang Chen, Uniformed Services University of the Health Sciences - Bethesda, USA
Po-Hsun Cheng, National Kaohsiung Normal University, Taiwan
William Cherniak, University of Toronto, Canada
Chih-Lin Chi, University of Minnesota-Twin Cities, USA
Meyrick Chow, Hong Kong Polytechnic University, Hong Kong
Diane Cook, Washington State University, USA
Michel Cotsaftis, LACSC/ECE - Paris, France
Shirley Coyle, Centre for Sensor Web Technologies / Dublin City University, Ireland
Vasa Curcin, Imperial College London, UK
Anna Cysewska-Sobusiak, Poznan University of Technology, Poland
Kevin Daimi, University of Detroit Mercy, USA
Stefan J. Darmoni, Rouen University Hospital, France
Lucio Tommaso De Paolis, University of Salento, Italy
M. Jamal Deen, McMaster University - Hamilton, Canada
Wolfgang Deiters, Fraunhofer Institute for Software and Systems Engineering ISST, Germany
Steven A. Demurjian, University of Connecticut, USA
Gayo Diallo, University of Bordeaux, France
Elton Domnori, Epoka University - Tirana, Albania
Julie Doyle, Dundalk Institute of Technology - Dundalk, Ireland
Ye Duan, University of Missouri - Columbia, USA
Marwan Dwairy, Cross-Cultural Researcher - Nazerat Ellit, Israel
Zakaria Elberrichi, Djillali Liabes University, Algeria
Frank Emmert-Streib, Queen's University Belfast, UK
Paul Fergus, Liverpool John Moores University, UK
Aleksandra Fucic, Institute for Medical Research and Occupational Health - Zagreb, Croatia
Xiaohing Gao, Middlesex University, UK

Nuno M. Garcia, Lusophone University of Humanities and Technologies - Lisbon, Portugal
Bela Genge, Petru Maior University of Tg. Mures, Romania
Hassan Ghasemzadeh, University of California Los Angeles (UCLA), USA
David Greenhalgh, University of Strathclyde, Scotland
Yi-Ke Guo, Imperial College London, UK
Martha Harrell, Institute of Mathematical Physics (IMP) - Williamsburg, USA
Harry Stewart Hochheiser, University of Pittsburgh, USA
Vasant Honavar, Iowa State University - Ames, USA
Jun (Luke) Huan, The university of Kansas, USA
Kun Huang, Ohio State University, USA
Hamidah Ibrahim, Universiti Putra, Malaysia
Yoshiro Imai, Kagawa University, Japan
Ivan Evgeniev Ivanov, Technical University of Sofia, Bulgaria
Ravi Janardan, University of Minnesota-Twin Cities, USA
Siddhartha Jonnalagadda, Northwestern University, USA
Jose M. Juarez, University of Murcia, Spain
Aravind Kailas, University of North Carolina - Charlotte, USA
Mehmed Kantardzic, University of Louisville, USA
Ayten Karataş, Istanbul Technical University, Turkey
Anastasia N. Kastania, Athens University of Economics and Business, Greece
Okba Kazar, Biskra University, Algeria
Hassan M. Khachfe, Lebanese International University, Lebanon
Frank Klawonn, Helmholtz Centre for Infection Research - Braunschweig, Germany
Peter Kokol, University of Maribor, Slovenia
Antonio Lanatà, University of Pisa, Italy
Tao Li, Florida International University, USA
Yaohang Li, Old Dominion University, USA
Marius George Linguraru, Sheikh Zayed Institute for Pediatric Surgical Innovation, USA
Igor Ljubi, University College for Applied Computer Engineering - Zagreb, Croatia
Samia Loucif, ALHOSN University, UAE
Emilio Luque, University Autònoma of Barcelona (UAB), Spain
Zhiyuan Luo, Royal, Royal Holloway University of London, UK
Malika Mahoui, IUPUI - Indianapolis, USA
Massimiliano Masi, Tiani "Spirit" GmbH, Austria
Christopher Mayer, AIT Austrian Institute of Technology GmbH, Austria
Jochen Meyer, OFFIS Institute for Computer Science, Germany
Christo El Morr, York University, Canada
Fleur Mougín, University of Bordeaux, France
Radha Nagarajan, University of Arkansas for Medical Sciences, USA
Kazumi Nakamatsu, University of Hyogo, Japan
Brendan O'Flynn, Tyndall National Institute, Ireland
Michael Ochs, The College of New Jersey, USA
Carlos Oberdan Rolim, Federal University of Rio Grande do Sul (UFRGS), Brazil
Chika Oshima, Japan Society for the Promotion of Science / Faculty of Medicine - Saga University, Japan
Chaoyi Pang, CSIRO, Australia
Danilo Pani, University of Cagliari, Italy
Julien Penders, imec / Holst Centre, The Netherlands
George Perry, The University of Texas at San Antonio, USA

Miodrag Potkonjak, University of California - Los Angeles, USA
Rosario Pugliese, Università di Firenze, Italy
David Riaño, Universitat Rovira i Virgili, Spain
Carsten Röcker, RWTH Aachen University, Germany
Alejandro Rodríguez González, Centre for Biotechnology and Plant Genomics - UPM-INIA, Spain
Marcos A. Rodrigues, Sheffield Hallam University, UK
Saqib Saeed, Bahria University Islamabad, Pakistan
Maytham Safar, Focus Consultancy, Kuwait
Antonio J. Salazar E., Institute for Systems and Computer Engineering - Biomedical Research Center, Portugal
Abdel-Badeeh M. Salem, Ain Shams University - Cairo, Egypt
Nickolas S. Sapidis, University of Western Macedonia, Greece
Majid Sarrafzadeh, UCLA, USA
Matthieu-P. Schapranow, Hasso Plattner Institute, Germany
Bettina Schnor, Potsdam University, Germany
Shunji Shimizu, Tokyo University of Science - Suwa, Japan
Jatinder Singh, University of Cambridge, UK
Miki Sirola, Aalto University, Finland
Bin Song, Oracle, Inc., USA
Nathalie Souf, Institut de Recherche en Informatique de Toulouse (IRIT), France
Daniel Steffen, German Research Center for Artificial Intelligence (DFKI) GmbH - Kaiserslautern, Germany
Maria Taboada, University of Santiago de Compostela, Spain
Adel Taweel, King's College London, UK
Francesco Tiezzi, IMT Institute for Advanced Studies Lucca, Italy
Chrisa Tsinaraki, European Union - Joint Research Center (JRC), Italy
Alexey Tsymbal, Siemens AG, Germany
Hayato Uchida, University of Hyogo, Japan
Lorna Uden, Staffordshire University, UK
Ugo Vaccaro, University of Salerno, Italy
Aristides Vagelatos, Computer Technology Institute and Press "Diophantus", Greece
Egon L. van den Broek, TNO Technical Sciences - Delft | University of Twente - Enschede | Radboud University Medical Center Nijmegen - Nijmegen, The Netherlands
Jari Veijalainen, University of Jyväskylä, Finland
Pierangelo Veltri, University Magna Graecia of Catanzaro, Italy
Brijesh Verma, Central Queensland University, Australia
Fei Wang, IBM Almaden Research Center - San Jose, USA
Liangjiang Wang, Clemson University - Greenwood, USA
Chunhua Weng, Columbia University, USA
Hua Xu, Vanderbilt University/School of Medicine, The Netherlands
Mingjing Yang, University of Ulster, UK
Juan Ye, University of St Andrews, UK
Yanbin Yin, University of Georgia, USA
Wang Yu-Ping, Tulane University - New Orleans, USA
Constantin-Bala Zamfirescu, "Lucian Blaga" Univ. of Sibiu, Romania
Erliang Zeng, University of Notre Dame, USA
Zhongming Zhao, Vanderbilt University / Medical Center, USA

Wei Zhong, University of South Carolina Upstate - Spartanburg, USA
Bin Zhou, University of Maryland, Baltimore County, USA

Copyright Information

For your reference, this is the text governing the copyright release for material published by IARIA.

The copyright release is a transfer of publication rights, which allows IARIA and its partners to drive the dissemination of the published material. This allows IARIA to give articles increased visibility via distribution, inclusion in libraries, and arrangements for submission to indexes.

I, the undersigned, declare that the article is original, and that I represent the authors of this article in the copyright release matters. If this work has been done as work-for-hire, I have obtained all necessary clearances to execute a copyright release. I hereby irrevocably transfer exclusive copyright for this material to IARIA. I give IARIA permission to reproduce the work in any media format such as, but not limited to, print, digital, or electronic. I give IARIA permission to distribute the materials without restriction to any institutions or individuals. I give IARIA permission to submit the work for inclusion in article repositories as IARIA sees fit.

I, the undersigned, declare that to the best of my knowledge, the article does not contain libelous or otherwise unlawful contents or invading the right of privacy or infringing on a proprietary right.

Following the copyright release, any circulated version of the article must bear the copyright notice and any header and footer information that IARIA applies to the published article.

IARIA grants royalty-free permission to the authors to disseminate the work, under the above provisions, for any academic, commercial, or industrial use. IARIA grants royalty-free permission to any individuals or institutions to make the article available electronically, online, or in print.

IARIA acknowledges that rights to any algorithm, process, procedure, apparatus, or articles of manufacture remain with the authors and their employers.

I, the undersigned, understand that IARIA will not be liable, in contract, tort (including, without limitation, negligence), pre-contract or other representations (other than fraudulent misrepresentations) or otherwise in connection with the publication of my work.

Exception to the above is made for work-for-hire performed while employed by the government. In that case, copyright to the material remains with the said government. The rightful owners (authors and government entity) grant unlimited and unrestricted permission to IARIA, IARIA's contractors, and IARIA's partners to further distribute the work.

Table of Contents

Usage of E-Health Services in Health Institutions and Opinions of Patients <i>Merve Deniz Pak, Andac Anildi, and Meric Yavuz Colak</i>	1
Studies on the Use of Electrolyzed Water as a Disinfectant at Home Care <i>Koichi Umimoto, Aki Kamada, Masahiro Miyata, Syunji Nagata, and Junichiro Yanagida</i>	5
Timeline-based Clinical Case Manager <i>Cristian Taslitchi, Florica Moldoveanu, Alin Moldoveanu, and Alexandru Egner</i>	8
The Implementation of Teledentistry for Pediatric Patients <i>Rodrigo Marino, David Manton, Parul Marwaha, Kerrod Hallet, Ken Clark, Matthew Hopcraft, Michael McCullough, and Ann Borda</i>	14
Introducing a Patient-Centered e-Health Record Over the Cloud <i>Konstantinos Koumaditis, Marinos Themistocleous, George Vassilacopoulos, Andriana Prentza, Flora Malamateniou, Dimosthenis Kyriazis, and George Pittas</i>	20
Sono-Contrast Spectroscopy for Cancer Virtual Biopsy in LMIC Settings <i>Yan Yu and Lydia Liao</i>	25
New Approach to Information Extraction from X-ray Plates <i>Ivan Evg. Ivanov, Vesselin Gueorguiev, and Desislava Georgieva</i>	31
A Future Strategy Towards Smoking Cessation: Persuasive Multimedia Application (PMA) in Strengthening Motivation towards Smoking Prevention and Cessation <i>Wan Ahmad Jaafar Wan Yahaya, Rosli Che Din, and Munira Hashim</i>	37
An Objective Program for the Evaluation of Medical Equipment for Updates and Maintenance <i>Hassan Khachfe, Mona Aridi, Bassam Hussein, and Mohamad Hajj-Hassan</i>	42
Modelling and Simulation of Mechanical Behaviour of an Ultra-Long Porous Silicon Neural Microelectrode <i>Hassan Khachfe, Rayan Fayad, Soumaya Berro, Bakri AbdulHay, Houssein Hajj-Hassan, and Mohamad Hajj-Hassan</i>	50
Standards for Medical Information Interchange <i>Dimitar Tcharaktchiev, Ivan Evgeniev Ivanov, and Vesselin Gueorguiev</i>	55
An Optimized Research Process for Real-time Drug Response Analysis <i>Matthieu-P. Schapranow, Konrad Klinghammer, Cindy Fahrnich, and Hasso Plattner</i>	60
Probing the Inflammatory Pathways Associated With Increased Levels of Oxidized LDL Through the Structural	67

Analysis of B17

Hassan Khachfe, Soumaya Berro, Bassam Hussein, Mohamad Hajj-Hassan, Bassam Hamam, and Wiam Ramadan

A Health VC for Chronic Disease Management in a Global Context

71

Christo El Morr, Shadi Saleh, Walid Ammar, Nabil Natafqi, and Karen Kazandjian

The Development of Action Model that Integrate Tuberculosis Case Detection and Completeness of Treatment through Women Empowerment at District Level in Indonesia

76

Indang Trihandini, Poppy Yuniar, and Sutiawan Sutiawan

Constituting a Model for Obesity Control: Possible Experience From the WHO Framework Convention on Tobacco Control

81

Xiangcheng Wang and Tao Sun

Effect of Chlorpyrifos Exposure during Development on Skeletal and Smooth Muscles in Juvenile and Adult Rats

89

Hassan Khachfe, Walaa Darwiche, Stephane Delanaud, Veronique Bach, Jerome Gay-Queheillard, Wiam Ramadan, and Wissam Joumaa

Usage of E-Health Services in Health Institutions and Opinions of Patients

Merve Deniz Pak, Andaç Anıldı, Meriç Yavuz Çolak

Baskent University

Faculty of Health Sciences

Healthcare Management Department

Ankara, Turkey

mervedenizpak@gmail.com, andacanildi@hotmail.com, meric@baskent.edu.tr

Abstract— E-Appointment, E-Family Practice, E-Information, E-Prescription, E-Pharmacy, Electronic Health Registration (E-Registration), Nursery Information System, E-Radiology, E-Laboratory, E-Smart Card, Tele-Medicine, Biometric Authentication System, are used within the E-Healthcare system in Turkey. Main objective of this research is to evaluate opinions of patients about E-healthcare services provided in healthcare institutions and utilization status of these services. The research is important in terms of understanding the E-healthcare using patients' views on the national usage of technology in healthcare in Turkey. The public survey consists of 19 questions and among them there are questions to measure the participants' sociodemographic status along with the ones to evaluate participants' awareness of E-Healthcare services and their satisfaction of these services.

Keywords- E-Healthcare; Patient Opinions; Hospital Information System; Healthcare Institutions; Healthcare Informatics in Turkey.

I. INTRODUCTION

Nowadays, technology is one of the best ways to gather information. Storage of information, systematic arrangement, processing, transmission and accessibility are possible thanks to the existing technology [1]. In healthcare services, hospitals and healthcare institutions also use computers to interact with complicated environments in order to be effective [2] [3]. Quick developments in both healthcare and computer science sectors result in both of these sectors to be intertwined and to change drastically [4] [5].

According to the World Health Organization (WHO), Technology concept in terms of healthcare technology can greatly contribute to the solution of a medical problem, and including its users; is a combination of methods, technique and equipment [6]. E-Healthcare is defined as the usage of communication and information technologies in their full function to improve the health of individuals and the accessibility of healthcare services provided in forms of high quality, efficient and effective healthcare services [7]. Also, E-Healthcare is used for healthcare services that are supported by communication and information technologies [4] [8].

In this paper, patients' opinions about E-healthcare services and evaluation of usage status of these services in Turkey are the main objective of the research. In parallel with the main objective of the research within the extent of E-healthcare services concept, it is aimed to evaluate patients' opinions about services that are executed in healthcare institutions like Electronic Patient Registration (E-Registration), E-Prescription, E-Appointment System, Biometric Authentication, E-Radiology, Pharmacy, Laboratory, Surgery Room Information systems and their knowledge, opinions about Tele-medicine and also, usage status of the current services. The research is important in terms of understanding the E-healthcare using patients' views on the national usage of technology in healthcare in Turkey. The research was conducted between the dates of 1 of June 2013 and 31 of August-2013. Therefore, time can be boundary of this project.

In Section II, we give state of the art in E-Healthcare. In Section III, we introduce E-healthcare applications in Turkey. More details of historical development of the E-healthcare services in Turkey are described in Section IV. In Section V, we give methods of research. Results of the research are given in Section VI. Finally, we drew a conclusion and suggestions for future work in Section VII.

II. STATE-OF-THE-ART IN E-HEALTHCARE

In the article "Acceptance of Swedish E-Health Services" which was written by Mary-Louise Jung and Karla Loria in Sweden, 12 old patients were interviewed in order to determine the attitude towards technology usage in healthcare sector [9]. The research contains only the inspection of services that are provided by public healthcare hosts in Sweden that provide online healthcare services, online doctor and e-prescription services. In order to collect data, interviews were conducted about the difficulty level of e-health systems and about the attitude towards each one of the services.

In the research that was conducted by Fatma Gül Altın in Turkey "Application of Information Technologies in The Healthcare Sector" doctors' opinions towards usage of e-health services were evaluated [10].

Opinions of the patients that use e-health services directly and the evaluation of these services' usage status are significantly important. There is no research about usage of e-health systems with patients in Turkey. Our work is the one and only in this perspective. In order to conduct the research, a large

focus group was considered (656 Patients). The evaluation of all the e-health services that are used in public and private sector is the main purpose of this research.

III. E-HEALTHCARE APPLICATIONS IN TURKEY

By using E-Healthcare services, healthcare institutions' expenses will be lowered, thus their efficiency will be improved along with the efficiency of serving healthcare services and distribution of sources and the communication among healthcare staff. It will be easier to benefit from healthcare services for individuals who have problems such as accommodating in rural areas or having hardship with transportation. Individuals and healthcare staff will be able to reach information more easily thus time will be used much more efficiently [10] [11].

Services that are already in use in Turkey are E-Family Practice, E-Appointment, E-Information, E-Prescription, E-Pharmacy, E-Registration (Electronic Healthcare Registrations), Nursery Information Systems, E-Radiology, E-Laboratory, Tele medicine, Biometric Authentication Services [9].

Electronic Patient Registration is a storage, in which all the information about a patient is stored virtually, to be used when needed [12] [13].

Family Practice is a computer program for the use of the family doctor on duty under the extent of "Family Doctor Implementation" and healthcare staff who works in the field of family healthcare [4] [14].

E-Appointment System is the scheduled acceptance of patients to the polyclinics through a set of pre-determined rules. Patients that are going to be examined are given a certain date. Scheduling is about using time and sources efficiently [15] [16].

Radiology, also known as Medical Visualization, creates, stores, processes, and saves images [17]. Visualization devices work through the use of computer technology and data process techniques and help doctors to reach proper diagnosis and to prepare disease diagnosis and a treatment plan [18].

E-Prescription provides digital input, storage, and transmission of prescription information electronically among institutions. The era of writing prescription on paper has come to an end due to switching to the E-Prescription System. With the system, doctors write prescriptions on digital environment and pharmacists can see which doctor prescribed which medicines online. Being supported simultaneously by smart card, this system ended health certificates and referral notes, thus all transactions passed upon digital environment [19].

Nursing Informatics System contains systems on which information and communication systems focuses on procedures and fields about nursery. The system makes information process and management easier [5] [12].

Telemedicine provides distant patient treatment services with the help of technology [20].

E-Information Services is one of the services that the Ministry of Health delivers. With this procedure, service can be received via double sided, sound-video transmitting, interactive screen located in the patient's house which provides communication between healthcare staff and the patient.

Biometric Authentication has been developed to identify individuals by recognizing their physical and behavioral characteristics features [21]. The most important feature of biometric systems is developing personal features. These features provide such security that it cannot be transferred to another individual.

IV. HISTORICAL DEVELOPMENT OF THE E-HEALTHCARE SERVICES IN TURKEY

E-Healthcare service works has started with the projects of the Ministry of Health with the help of the World Bank in 1991 and the Healthcare Information Systems started in 1995. The studies in the field of healthcare information systems have been improved with the Ministry of Health Project in Healthcare Project (CHP) which started in 2003 to create a Health Information System (HIS) that covers every aspect of the healthcare sector. Studies for this are called E-Healthcare Project. Healthcare ministry undertook the coordination of E-Healthcare Work Group in the extent of "E-Transformation Turkey Project", created and executed a Schedule in 2006. It includes projects like E-healthcare Project, Central Hospital Appointment system (E-appointment), E-prescription, Electronic Referral system (E-referral), Family Practice, Electronic Identity Card, and Tele-Medicine. The Healthcare Informatics Congress from 2006 and the Healthcare Informatics Congress from 2007 were held to discuss this matter. "E-Healthcare System in Turkey Project" has been improved by holding E-Healthcare/Tele-Medicine Congress in the extent of Informatics Summit in 2008 [22] [23].

V. METHODS

The research was conducted between the dates of 1 of June 2013 and 31 of August-2013 in Ankara Private Sanatorium Health Center. The basis of the research is created total 5000 patients who had applied to receive medical service. The sampling of the study consists of 656 patients.

The research is a descriptive, cross-sectional study. Data were gathered via public survey form. The public survey consists of 19 questions and among them, there are questions to measure participants' sociodemographic status along with the ones to evaluate participants' awareness of E-healthcare services, usage of services and satisfaction level of these services, opinions about E-healthcare services protecting participants' privacy, information sources about application of the services and problems occurred using the services.

The surveys were done in the waiting room while the patients were waiting for examination. They usually lasted about 5 minutes. Participation in the survey is completely voluntary. Likert Scale 5 Point is applied to the poll. During data analysis, analysis was done via combining the participants that gave the answers of “bad” and “very bad” with the ones gave the answers of “good” and “very good”. The data which had been gathered by poll results was analyzed via SPSS 18.0 package program.

VI. RESULTS

60.4% (n=396) of the patients are female, 39.6 % (n=260) are male. 30.6% (n=201) of the patients are elementary school graduates, 10.2% (n=67) are middle school, 28.7% (n=188) are high school graduates, 8.5 % (n=56) have two-year degree, 19.7% (n=129) have bachelor’s degree, 1.5% (n=10) have master’s degree, 0.8% (n=5) have doctorate. 74.7% (n=490) of the participants are married, 21.3% (n=140) are single, 0.9% (n=6) are divorced, 3% (n=20) are widower.

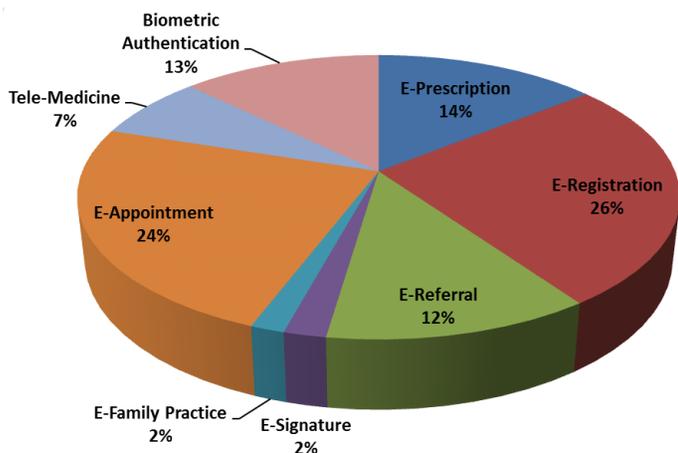


Figure 1. Participant’s Awareness Status Of The E-Healthcare Services E-Healthcare Application

It can be seen on the figure that the service patients are aware of most is E-Registration 26.0 %, with E-appointment following with the second highest ratio of 24.0 % (Figure 1).

While 51.8% (n=340) of the participants encountered problems about E-Healthcare procedures, 9.8% (n=64) of them did not. While 17.7% (n=116) of the participants pointed out that there has been no difference regarding services after E-Healthcare procedures took effect, 20.7% (n=136) of them have no idea about the matter.

TABLE I. SATISFACTION AND USAGE STATUS OF THE PARTICIPANT ABOUT E-PRESCRIPTION, E-APPOINTMENT AND E-REGISTRATION SERVICES

	Poor		Good		Excellent		No Usage	
	n	%	n	%	n	%	n	%
E-Prescription	41	6.2	42	6.4	257	39.2	316	48.2
E-Appointment	171	26.1	111	16.9	295	45.0	79	12.0
E-Registration	64	9.7	78	11.9	477	72.8	37	5.6

While 39.2% of the participants are satisfied with E-prescription services, satisfactory ratio of E-registration services is 72.8%. 26.1% of the participants are dissatisfied with E-appointment services (Table 1).

Among the patients who use the E-prescription system 40.1% pointed out that they think that the system is secure in terms of protecting personal privacy, 31.3% are indecisive, and 28.7% pointed out that the system is insecure in terms of protecting personal privacy. It is observed that 61.4% of the patients who participated in the research use E-registration system in registration before examination, 13.1% occasionally use it, and 25.5% of the patients do not use it. When it is analyzed that if electronic registration system makes procedures easier in the hospitals, according to the participants, 66.6% of them think the system makes it easier to benefit from medical services, while 14.3% thinks otherwise. According to the 10.7% of the participants, even with the help of E-registration system there is no difference, while 8.4% are indecisive.

TABLE II. SOURCES OF THE PROBLEMS IN E-HEALTHCARE SERVICE PROVISION ACCORDING TO THE PARTICIPANT

Sources Of The Problems*	n	%
Healthcare Staff	432	66.0
Software and Substructure Inadequacy	521	79.0
Lack of Information	499	76.0
Healthcare Policies	234	36.0

According to the participants, most of the problems about the E-healthcare services mostly occur because of software and substructure inadequacy 79.0% (Table 2).

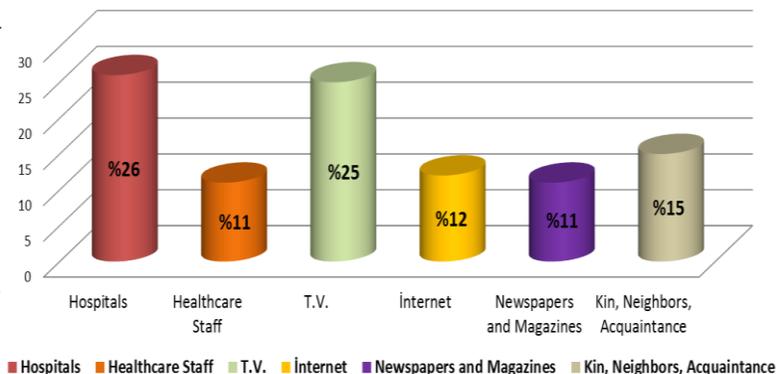


Figure 2. Information Sources Of The Participant About The E-Healthcare Practices

Hospitals (26.0%) and Television (25.0%) are at the top of the information sources which are for E-healthcare practices (Figure 2).

VII. CONCLUSION AND FUTURE WORK

Healthcare sector is affected by the changes and innovations which are brought by technology. Each passing day new treatment methods and products become available. These days, intense usage of technology in healthcare sector makes the usage of E-healthcare services more important, and it is of great importance for serving these services more efficiently, more effectively and of higher quality. It is obvious that generating information, reaching information and using information with the help of technology has great importance to the healthcare institutions and to the individuals who want to make use of these institutions' services.

The main objective of this study is the evaluation of the services that are provided in healthcare institutions based on the patients' opinions. We also discuss the usage status of these services. We surveyed patients about their awareness of the E-healthcare services, usage ratio of the services, satisfaction level, problems about the services, information sources about the services, and problem sources of the patients.

In conclusion, these can be suggested:

- It is observed that with respect to telemedicine practices, healthcare information systems usage ratio is not enough. Because of this, hospitals should try improving R&D activities.
- Aspects like data transfer, data transfer security, adaptation convenience, access convenience, response time, determines E-healthcare services' quality. Improving these aspects will improve the satisfaction level and usage ratio of these services.
- Healthcare Ministry should raise awareness about the importance of informatics systems on general healthcare systems.

ACKNOWLEDGMENT

We are thankful for the help received from Başkent University that participated in this study.

REFERENCES

[1] G. Eti İçli, F. Eti Aslan and S. Kuşoğlu Importance of computer usage and computer based registration system in the healthcare institutions that are service business , Trakya University Journal of Social Science, vol.2 2005, pp. 33-45.
 [2] M. Öztürk, Information management's contribution to the productivity in healthcare management, 2003, pp. 197-201.
 [3] A. Köksal and E. Esatoğlu, Analysis of electronic the information systems that are used in private and university hospitals in the province of Ankara, Ankara University Journal of Dikimevi Vocational School of Health, vol.7 2005, pp.53-65.
 [4] M. Özata Effects of e-healthcare projects that are conducted by the ministry of health and social security institution on healthcare services, Journal of Azerbaijani Studies 2009, pp.444-464.

[5] F. Ay, International electronic registration systems, nursery practices and computer relation , Gulhane Medical Journal , vol.51 2009, pp.131-136.
 [6] E.A. Sargutan, Healthcare Technology Management, Hacettepe Journal of Health Administration, vol.8 2005, pp.113-144.
 [7] H. Moghaddasi ,F. Asadi , A. Hosseini and Z. Ebnehoseini, "E-health: a global approach with extensive semantic variation" , J Med Syst vol. 36 2012 , pp.3173-3176.
 [8] Z. Onay, Information systems in healthcare sector, Dokuz Eylül University Journal of EAS vol.13 1998, pp. 35-46.
 [9] Mary-Louise J. and Karla L. Acceptance of Swedish e-health services, Journal of Multidisciplinary Healthcare, vol.3, 2010,pp.55-63.
 [10] F.G. Altın, Application of information Technologies in the healthcare sector; Example Izmir, Süleyman Demirel University Institute of Social Sciences of Department of Business Administration, Thesis of Master, Isparta, 2008.
 [11] M. Yılmaz, and A.E. Demirkan, Hospital management and evaluation of the utility of the information system, Journal of Informatics Technology, vol.5 2012, pp.19-28.
 [12] M. Rezai-Rad , R. Vaezi, and Nattagh , F. "E-Health readiness assessment framework in Iran", Iranian J Publ Health vol.41 2012, pp. 43-51.
 [13] V. Bal, The measurement of information systems' effects on the healthcare institutions via data envelopment method, the research in Turkey, Süleyman Demirel University Institute of Social Sciences of Department of Business Administration, Thesis of PhD. Isparta, 2010.
 [14] http://www.ailehekimligi.gov.tr/index.php?option=com_content&view=article&id=760:aile-hekimlii-bilgi-sistemi-ahbs-nedir&catid=88:personel-cin-&Itemid=227
 [Accessed: 21-April-2013].
 [15] B. Şahin, Hospital Management processes and healthcare management information systems, Kadir Has University, Institute of Social Sciences of Department of Business Administration, Thesis of Master, İstanbul, 2010.
 [16] T. Yua, and H. Hob, " the design and development of a physician-oriented pacs for the enhancement of e hospital facilities", International Journal of Medical Informatics vol.77 2008, pp.836-847.
 [17] U. Şeno1, A. Aktaş and O. Saka, Radiology information system Academic Enformatics IX Academic enformatics conference notices, 2007, pp. 431-433.
 [18] S. Taşdemir, The evaluation of the computer system integration that are existed in the healthcare ministry hospitals in Ankara and the Ministry of Health healthcare informatics system projects, Hacettepe University, Institute of Health Sciences, Department of Healthcare Management, Thesis of Master, Ankara, 2005.
 [19] R. Latifi "International virtual e-hospital" The Balkans Journey, Current Principles and Practices of Telemedicine and E-Health 2008, pp. 3-20.
 [20] <http://www.saglik.gov.tr/SBSGM/belge/1-15487/tele-tip.html>
 [Accessed: 4-April-2013].
 [21] M. Akçay, H. Çetinkaya, New biometric systems that are used in campuses, Academic informatics, XIII Academic Informatics Conference Notices, 2011, pp. 8-52.
 [22] S. Ertek, Tele-health and tele-medicine applications in endocrinology, Acibadem University, Journal of Health Sciences vol.2 2011, pp.3.
 [23] R. Akdağ, Progress report, transformation in health program of Turkey, Ministry of Health in Turkey Publishing, Ankara, 2008.

Studies on the Use of Electrolyzed Water as a Disinfectant at Home Care

Koichi Umimoto, Aki, Kamada, Masahiro Miyata,
Syunji Nagata

Department of Biomedical Engineering
Osaka Electro-Communication University
Osaka, Japan

umimoto@isc.osakac.ac.jp, kmd.aki080707@gmail.com
ce_miyata@yahoo.co.jp, narasinagataschunji@yahoo.co.jp

Junichiro, Yanagida

Department of Medical Technology
Kobe Tokiwa University
Kobe, Japan
jyanagida@kobe-tokiwa.ac.jp

Abstract—The prevention of opportunistic infection for the elderly is important in home care and the hygiene management for infection is required. When water containing sodium chloride is electrolyzed, electrolyzed water with strong bactericidal ability due to the available chlorine (AC) is generated on the anode side. Slightly acidic to neutral electrolyzed water (SANEW, pH 5.0 to 7.5) is physiological pH and is suitable for biological applications. For producing SANEW simply and at a low cost, the container has electrolysis cell in a cylindrical shape having a sidewall without membrane partition and the sidewall serves as a cathode in the electrolyzer device. The graphite rod was used as the anode. As a result, the pH and AC concentration were 5.6 and 13.7 ppm, respectively. SANEW was obtained directly by this experimental device and this water showed a strong bactericidal activity. This device is useful for producing SANEW as a disinfectant to employ at home care, when considering economic and environmental factors, since it returns to ordinary water after use.

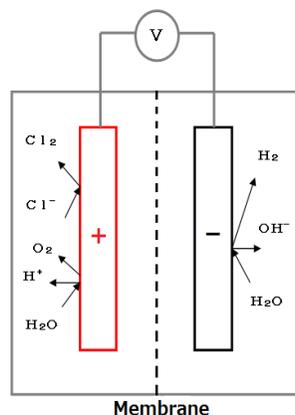
Keywords- Home care; Electrolyzed water; Bactericidal activity.

I. INTRODUCTION

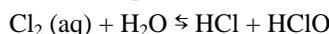
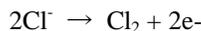
The prevention of opportunistic infection due to a reduction in resistance or physical strength of the elderly is important in home care and the hygiene management for infection is required. Electrolysis is known as a method of separating an ionic substance by way of a chemical reaction. A device for achieving electrolysis requires certain components, such as an electrolyte containing an ionic substance, a pair of electrodes (an anode and a cathode), a diaphragm and a direct electric current supply. In the electrolysis process, water containing sodium chloride (NaCl) is electrolyzed, resulting in the production of strongly acidic electrolyzed water (SAcEW, pH 2.2 to 2.7) on the anode and strongly alkaline electrolyzed water (SAIEW) on the cathode side (Fig.1). SAcEW contains an available chlorine (AC) such as hypochlorous acid (HClO), which is known to have a strong bactericidal action and shows an instantaneous bactericidal activity [1] [2]. SAcEW reverts to ordinary water again after use. Therefore, recently this water has attracted considerable interest in a medical field.

However, the activity does not persist. In addition, SAcEW stimulates the oral mucous etc. because of its strong acidity, and is therefore unsuitable for biological applications [3][4]. On the other hand, in slightly acidic to neutral electrolyzed water (SANEW, pH 5.0 to 7.5), since the activity persists and its pH is physiological levels, it can be applied to various uses. However, the production of SANEW requires electrolysis of hydrochloric acid itself or use of hydrochloric acid as a pH adjuster. Thus, the production is too complicated to perform in domestic homes.

In this study, we developed a simple device to produce SANEW directly for home care without use of hydrochloric acid and evaluated the bactericidal activity of this solution.



Anode side



Cathode side

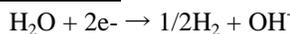


Figure 1. Principle of producing electrolyzed water with two electrolytic cell

This paper is structure as follows. Section II describes the device used as well as the approach to measure

bactericidal activity. In Section III, we present the results. In Section IV, we discuss the relevance of the results. Section V concludes the paper.

II. METHODS

A. Device

The most expensive in the electrolyzer device is an electrode which is coated by platinum for the protection against corrosion. In order to reduce the cost, the container was electrolysis cell in a cylindrical shape having a sidewall without membrane partition. The sidewall was made of stainless steel and was operatively connected to a DC power supply so that the sidewall serves as a cathode in the electrolyzer device. The graphite rod was used as the anode. As the graphite rod was arranged as the anode in the vicinity of a center of the container, the anode was surrounded by the cathode at a constant distance, and thereby the strongly alkaline electrolyzed water will be obtained at the vicinity of the sidewall of the container (Fig. 2).

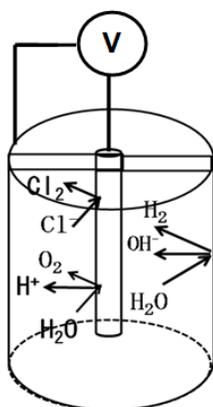


Figure 2. Principle of producing electrolyzed water with a cylindrical shape

B. Measurement

Using an experimental device, 1L of 0.1% NaCl solution was put into a container and electrolysis is performed by applying a DC 20 voltage for 30 minutes. The values of the pH and AC concentration of the electrolyzed water were measured with diethyl-p-phenylenediamine by a spectrophotometer.

C. Bactericidal activity

Two strains of bacteria (*S.aureus* and *B.cereus*) were prepared to investigate the bactericidal activity of electrolyzed water. The bactericidal activity was examined as follows. These bacteria were cultivated at 37°C for 24 hours under aerobic-culture in petri dishes. After cultivation, each one colony was incubated with 10% povidon iodine,

70% isopropyl alcohol, SAcEW and SANEW, also this solutions were added onto the fresh petri dishes and were cultivated for 48 hours. The colony of bacteria in the petri dish was counted and the bactericidal activity was judged.

III. RESULTS

The obtained measurement results, the levels of pH and AC concentration of the extracted electrolyzed water at 30 minutes after the start of the electrolysis are listed in Table 1. The levels of pH of those water were from 5.5 – 5.9 and those of AC concentrations were from 11.1 – 13.7 ppm. SANEW was obtained directly by this experimental device.

The results of bactericidal activity of chemical disinfectants and electrolyzed water are shown in Table 2. There were many colonies of *S. aureus* and *B.cereus* in each petri dish as controls, while there was no colony of bacteria after added SANEW as same as other solutions.

TABLE I . THE LEVELS OF PH AND AC CONCENTRATION OF ELECTROLYZED WATER

	pH	AC concentration (ppm)
Electrolyzed water	5.9	11.2
	5.6	13.7
	5.6	13.0
	5.5	11.1

TABLE II. BACTERIAL ACTIVITY OF ELECTROLYZED WATER

Solutions	<i>Bacteria</i>	<i>S.aureus</i>	<i>B.cereus</i>
Control (Sterilized water)		16.6×10 ⁶	67×10 ⁵
CFU/ml			
10% povidon iodine		0	0
70% isopropyl alcohol		0	0
SAcEW		0	0
SANEW		0	0

IV. DISCUSSION

Generally, in an electrolyzed water generator having a membrane, equal amounts of acidic water and alkaline water are generated in the respective electrolytic chambers with the same capacities on both sides of the membrane. Consequently, SANEW cannot be directly produced. Alternatively, a system for producing SANEW by a method using hydrochloric acid as a pH adjuster with a membrane-less system suffers from the problem of handling hydrochloric acid.

SANEW has strong bactericidal activity against *E.coli* and *B.cereus* similar to chemical disinfectants and also, it has an advantage that its bactericidal activity stably persists for a long time, making it useful for sterilization, disinfection and cleaning as same as SAcEW with pH 2.2 [5]. Accordingly, it is applicable to electrolyzed water generators producing bactericidal water that can contribute to killing bacteria on equipment and utensils in food factories, sterilization of instruments in medical-related departments, care homes for the elderly, cleaning toilets and the interiors of buildings, and cleaning bathrooms. Furthermore, since bactericidal water can be simply generated and returns to ordinary water when discarded, the present study is easy to use for improving public hygiene.

The present study is characterized in that electrolysis cell in a cylindrical shape having a sidewall serves as a cathode, and does not need to maintain for membrane replacement. The structure is a simple one that does not need any special tool. This apparatus can be made at a low cost about 1/10 times as compared with conventional apparatus using hydrochloric acid [6]. Therefore, this device is useful for producing SANEW as a disinfectant to employ at home care. However, as a disadvantage, the graphite rod elutes very slightly during electrolysis by DC 20 V and needs to be replaced with long term use. And also, the quantity of SANEW production is 1L/30 min because of a batch type specification, which is rather low compared to the conventional apparatus of flowing water type (5L/min). Further research is necessary to make an improvement in this apparatus.

V. CONCLUSION

We made a simple electrolytic device in cylindrical shape having a sidewall and succeeded to produce SANEW with strong bactericidal ability as a disinfectant. SANEW can be produced from a saline solution and at a low cost in this system. This device is useful in home care.

ACKNOWLEDGMENT

This research was supported in part by a Grants-in-Aid for Scientific Research from Japan Society for the Promotion of Science.

REFERENCES

- [1] K. Hotta, K. Kawaguchi, K. Saito, K. Ochi, and T. Nakayama, "Antimicrobial activity of electrolyzed NaCl solution: effect on the growth of *Streptomyces* spp.," *Actinomyatologica* vol. 8, pp. 51-56, 1994
- [2] K. Kumon, "What is functional water?," *Artif. Organs*, vol. 21, pp. 2-4, 1997
- [3] K. Umimoto, Y. Emori, H. Fujita, and K. Jokei, "Evaluation of strong acidic electrolyzed water for the

disinfection," *IEEE-EMBS, APMBE, Proceedings CD-ROM*, 2003

- [4] K. Umimoto, Y. Kanno, T. Kawabata, and K. Jokei, "Characteristics of strong acidic electrolyzed water," *IFMBE Proceedings* vol. 8, APCMBE, PA-2-01, 2005
- [5] K. Umimoto, H. Kawanishi, Y. Tachibana, N. Kawai, S. Nagata and J. Yanagida, "Development of automatic controller for providing multi electrolyzed water," *IFMBE Proceedings* vol. 25, pp. 306-009, 2009
- [6] Purester Morinaga Milk Industry. Co. LTD.
URL: <http://www.morinagamilk.co.jp/products/purester/product/2014.06.30>

Timeline-based Clinical Case Manager

Cristian Taslitchi, Florica Moldoveanu, Alin Moldoveanu, Alexandru Egner

Faculty of Automatic Control and Computers

University Politehnica of Bucharest

Bucharest, Romania

e-mails: cristian.taslitchi@gmail.com, florica.moldoveanu@cs.pub.ro,
alin.moldoveanu@cs.pub.ro, alexandru.egner@cs.pub.ro

Abstract— The main purpose for visualizing medical data in Clinical Information Systems (CISs) is to convert the medical data in relevant information about the patient's health status. The process of conversion from single disparate data into useful information considers as relevant input datasets the known clinical problems and their clinical pathway, the already collected medical data and the social, demographic and administrative data. Visualization of the medical data represents the operational decision support system at point of care. The concept presented in this paper is a potential solution to the existing CISs' shortcomings, through the extent of the timeline-based social networking experience to medical software, and at the same time, by applying the industry standard of business process modeling, Business Process Modeling Notation (BPMN) 2.0 in encoding the clinical pathways and administrative processes. The primary goal of the Timeline-based Clinical Case Management System (TCCMS) is to give a comprehensive picture of patients' condition, both real-time as well as historically, using textual and graphic means, and to sustain, in a task-oriented approach and based on advanced decision support algorithms, the application of accurate treatment plans and actions. This paper presents a data visualization concept that hides under a simple temporal relation all the complexity of medical field, into a familiar Graphical User Interface (GUI), promoted by social networks in the last years, finally giving the chance to healthcare IT to become completely paperless.

Keywords—Medical data visualization; clinical pathways; timeline; case management; BPMN.

I. INTRODUCTION

"The Electronic Health Record (EHR) is a longitudinal electronic record of patient health information generated by one or more encounters in any care delivery setting. Included in this information are patient demographics, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data and radiology reports." [1]

A large majority of the existing CISs emphasizes the need for separating between accessing medical history and the operational user interface.

The current CISs' market covers most of the healthcare provider operational needs in regard to clinical services with some degree of support for point of care clinical decisions. The GUI for documenting clinical cases is centered usually on patient and patient banner in order to help the medical

personnel to easily identify the current patient clinical context.

This ensures a comprehensive standard-based approach in regards to CISs functionalities, which is regulated by the world's leading medical informatics organizations: HL7 EHRs [2], CCHIT [3], Eurorec [4] / Prorec [5], etc.

In this context, in order to analyze the current state of the art, we need to structure the existing knowledge in three domains: clinical pathway visualization, relevant medical data visualization (medical and administrative) and the combination of these two - medical data in clinical context.

Clinical pathway visualization should be considered from two points of view: from the point of view of clinical pathway encoder or designer, and from the point of view of the one who is executing the patient current clinical pathway requested actions. Projects/solutions like Protégé [6], Tallis Toolset [7], GUIDE [8], GLARE [9], VisiGuide [10], AsbruView [11], etc., are suitable for encoding and/or execution of a clinical pathway, but with limited adoption by the healthcare providers.

Not necessary in relation with the clinical context, projects like Graphical Summary of Patient Status [12], Time Lines and LifeLines [13], PatternFinder [14], KNAVE and KNAVE-II [15], VISITORS [16], VIE-VISU [17], Interactive Parallel Bar Charts (IPBC) [18], Gravi++ [19], and others moved in the direction of visualizing the medical relevant data.

There are also very few combined approaches of medical data in clinical context: Guideline Overview Tool (GOT) [20], Midgaard [21], CareVis [22], NHS Common User Interface [23], Visual-D [24], but most of them failed to be widely adopted.

The barriers in CISs' adoption are mainly generated by the GUI complexity through the magnitude of change perceived by medical personnel accustomed to work with paper documents. The CISs usually ignore their practices and their social, communication and professional context and this is reflected in unified browsing experience for heterogeneous data and inefficient decision support at point of care.

The potential solution to the previously mentioned CISs' shortcomings consists in extending of the timeline-based social networking experiences to medical field by hiding under a simple temporal relation all the complexity of medical field with benefits especially in user adoption and learning curve.

The paper structure, section by section, is presented below:

Section II describes the challenges experienced in conversion of medical data into relevant information about the patient's health status,

Section III describes the concept and the elements of novelty of such a system in the Electronic Health Record (EHR) context,

Section IV describes the main set of functionalities required for the concept implementation and

Section V presents the way forward in concept implementation.

II. MEDICAL DATA VIZUALIZATION

The main purpose of medical data visualization in patient-centric CISs is to convert the medical data in relevant information about the patient's health status. The process of conversion from disparate data into useful information should be analyzed at least from several perspectives: communication, computer science (and GUI) and healthcare domain (especially, clinical context and clinical pathway).

The relevant input datasets which are used by the data visualization process could be grouped in three categories: known clinical problems and their clinical pathway, the already collected medical data and the social, demographic and administrative data.

Basically, the medical data visualization in a CIS should represent the operational decision support system at point of care and at the same time a Clinical Case Management System (CCMS).

It is essential to visualize the current clinical problem and its corresponding clinical pathway; also, to know what are the active problems (including chronic clinical problems), what the medical history is, what the recent objective observations are, what the social, demographic and administrative details are, etc. The progress observed in the patient treatment, the definitions of the clinical pathways with specific actions, stages, conditions and so on and nevertheless the best practices of the clinical problem (to treat the health problem) should be accessible.

It is obvious that the level of adoption of industry standards in terms of functionality it's quite limited and the main barrier in adopting comes from the fact that implementation does not take into account the end user practices and their context.

Medical personnel are accustomed to work with paper documents and previous attempts to create paperless solutions have failed due to the magnitude of change perceived by the often non-technical end users mainly because of GUI complexity.

So, the medical professionals need a Clinical Case Management System, developed around their current social, communication and professional context, able to manage operational processes and, at the same time, to provide an efficient point of care decision support.

III. TIMELINE-BASED CLINICAL CASE MANAGEMENT SYSTEM

The concept presented in this paper is a potential solution to the previously mentioned shortcomings in order to extend the timeline-based social networking experiences to medical software and at the same time to introduce the industry standard of process modeling, BPMN [25], in encoding the clinical pathways. The primary goal of the Timeline-based Clinical Case Management System (TCCMS) is to offer a comprehensive picture of patients' condition, both real-time as well as historically, using textual and graphical means, and to sustain, in a task-oriented approach and based on advanced decision support algorithms, the application of accurate treatment plans and actions.

Furthermore, using clinical protocols and timelines, in combination with the visualization of patients' relevant medical data, dramatically improves the point of care decision support.

Another important characteristic of TCCMS is the fast development and reusability of medical templates, achieved through an external component, part of a Business Process Management Solution (BPMS) [26] also used to execute clinical protocols and guidelines that encode and organize the decisions and action tasks for the medical personnel.

A BPM-based case management solution in healthcare offers the benefits of configurable workflows for both the medical areas (clinical pathways) as well as the administrative areas (Admission, Discharge and Transfer). An example of BPM implementation of administrative processes (outpatient encounter) is presented in Figure 1. The presented process allows the basic management of the outpatient encounter, managing also the exceptions like encounter reactivation, automatic checkout or canceling the encounter. The notifications are also part of the process definition by the fact that the process can be started based on a received message from the appointment system, and also, the process contains a throw notification event designed in fact for the communication with inpatient encounters systems.

Based on the medical documents associated with a patient and on a complex array of business rules as a part of the current clinical pathway, relevant alerts regarding a specific patient (e.g., allergies, high cardiovascular disease risks etc.) will be triggered. Moreover, the alerts must suggest recommended actions to be taken as a consequence.

During clinical pathway encoding, using the clinical pathway development environment as a collection of workflows designer, advanced business rules designer, process simulators and execution engine, the clinical pathway encoder has the possibility to define customized alerts based on a patient conditions, in order to generate at runtime all sorts of critical patients' status notifications.

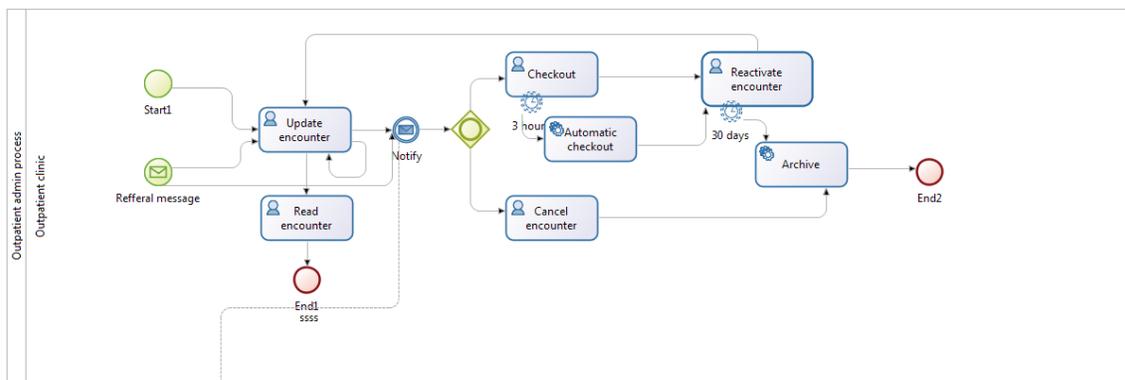


Figure 1. TCCMS - Simple BPMN representation of outpatient encounter

TCCMS overcomes the problem raised from the unavailability of easily interpretable clinical guides within existing medical applications and takes the recording of clinical information beyond historical and statistical reasons, by being a proactive solution that is giving a strong decisional support to the medical personnel. As a concept, TCCMS targets directly any type of healthcare provider.

The central piece of this approach is the Clinical Timeline, representing a historical view of clinical documents disposed along a vertical time axis as thumbnails, which offers a clear and actionable insight into the patient’s clinical history, as presented in Figures 2 and 3.

Figure 2. TCCMS - Timeline view with entries grouped by event dates (concept)

IV. TCCMS KEY FEATURES

There are few core features implemented by the proposed system:

Visualization

Medical documents displayed as thumbnails along a vertical timeline;

Problem management

Capability to initiate, activate or inactivate a new episode of illness;

Encounter management

Capability to execute administrative actions like admission, discharge and transfer;

Documentation and actions

Case-level actions;

Document-level actions;

Document-level comments that can generate actionable alerts;

Possibility to attach unstructured documents;

Capability to also view the documents added directly by the patient through the PHR;

Filtering

Filtering records by medical staff, problems/diagnoses, types of medical documents;

Filtering records by administrative events/medical encounters;

Integration

Integration with diagnostic departments (laboratory, radiology, functional explorations, etc.);

Integration with local or national e-Health services (e-Referral, e-Prescribing, national EHR, etc.) and reflected by specific actions (e.g., dispatching a referral);

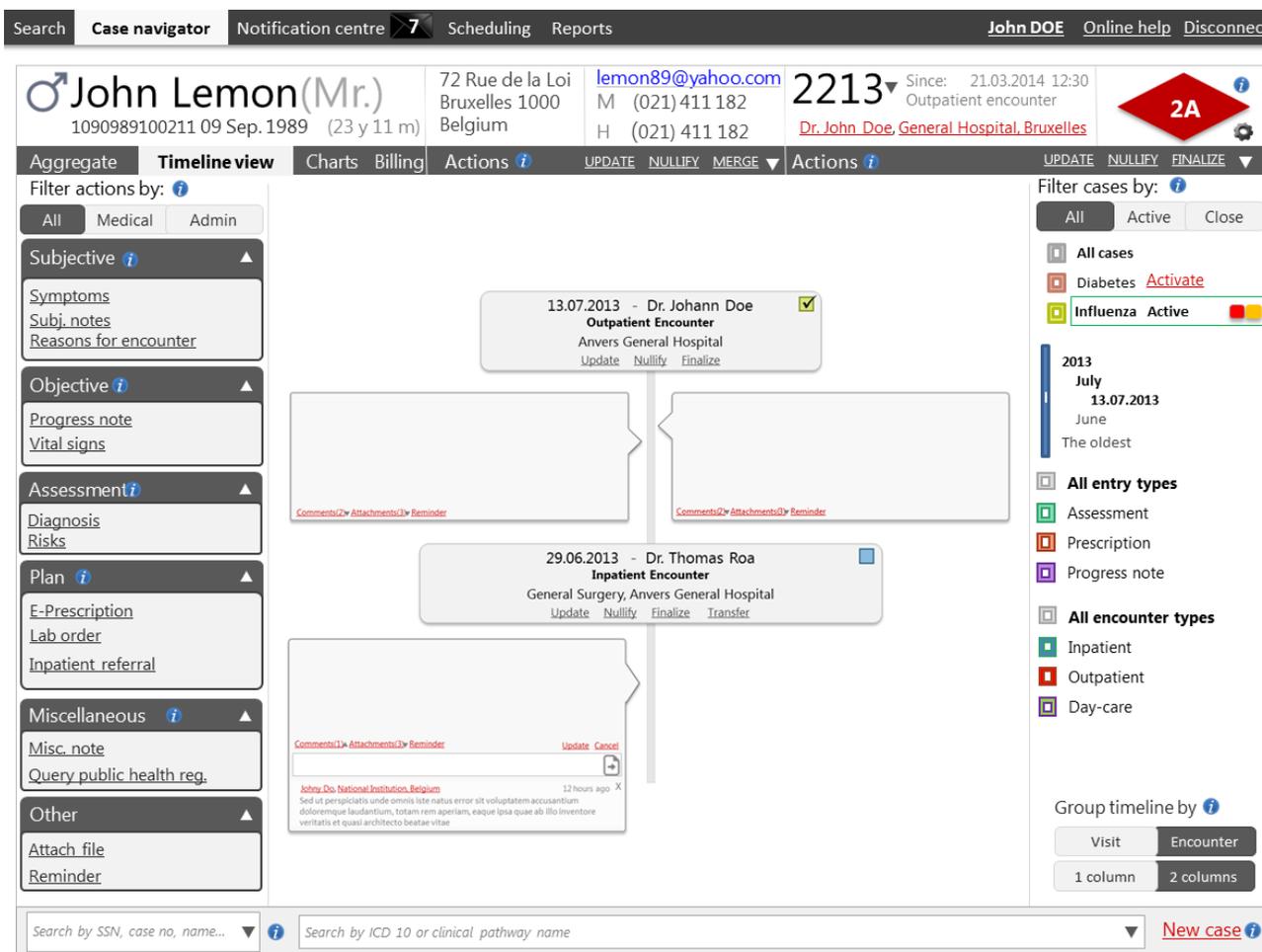


Figure 3. TCCMS - Timeline view with entries grouped by encounters

As medical data sit at convergence the episode of care (the administrative sequences, usually collection of encounters) and episodes of illness (the medical events that are performed for treatment of a clinical problem), a comprehensive view of a patient’s case must include both these interrelated aspects. Moreover, complex clinical workflows and treatments available today lead to the collection of patient-centric information in the form of series of numbers (often representing analyses results), medical documents, images and videos, all coming from different equipment at different points in time. As such, one of the main benefits of this approach, when compared with the tried and proven patient encounter-based interfaces, is represented by the possibility of dynamically loading a large volume of data that is time-sorted, meaning that most recent analyses and results will be shown first, allowing physicians to have a quick overview of the patient’s situation. Moreover, the clinical timeline provides a unified browsing experience for a volume of heterogeneous data that was collected at different points in time and using a wide range of medical equipment.

The pervasiveness of computing platforms and their wide-scale adoption has led to the emergence of several new methodologies for user interface design that have been widely embraced by the public. One of the relatively new means of data presentation is the timeline. In order to provide a gentle learning curve and natural grouping of information, TCCMS GUI concept presented in Figure 4, is developed around familiarity gained from social networking services like Facebook and suitability of this approach to the medical domain, and therefore embraced the established graphical presentation patterns.

While not a new idea with regards to the presentation of medical information [29], timelines have been embraced with the advent of widely used social networks that popularized them. As such, they can be considered an already mature and well-known mean for data presentation, significantly reducing the steepness of the learning curve.

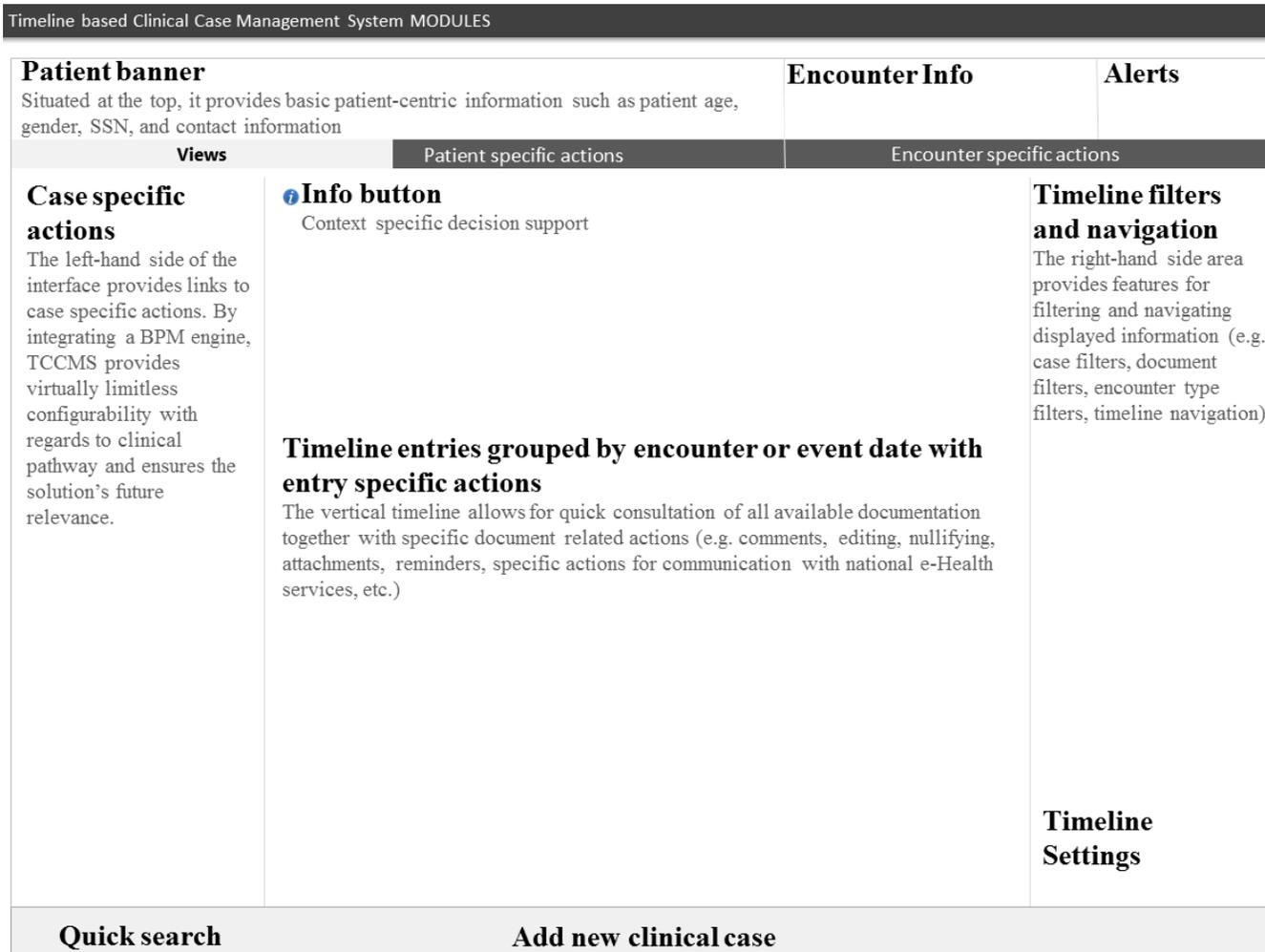


Figure 4. Conceptual layout description (concept)

V. CONCLUSION AND FUTURE WORK

Despite the fact that EHR Systems are widely used, the paperless CISs are still a desideratum and the previous attempts failed due to the magnitude of change perceived by the often non-technical end users.

The last decade has created a new paradigm in which users have realized the need for systems that do not need or have very little need of training. This paradigm is based on user habits and their knowledge field.

Basically, the concept of Timeline-based Clinical Case Management System presented in this paper hides under a simple temporal relation all the complexity of medical field, the complexity of clinical pathways and administrative protocols and the decision support into a familiar Graphical User Interface, promoted by social networks in the last years, finally giving the chance to healthcare IT to become completely paperless.

Part of the concept described above is implemented in a Personal Healthcare Record solution [27] since 2012 and in 2013 was tested on small scale healthcare professionals' pilots on two verticals: oncology and family doctors. All the implementations proved significant benefits in user adoption and learning curve.

Currently TCCMS is under industrial implementation as a multitenant/cloud solution and the underlying development technologies are: Bonita BPM [28], Node.js [29] and AngularJS [30].

REFERENCES

- [1] HIMSS Resource Library – Electronic Health Records, retrieved: April, 2014 (<http://www.himss.org/library/ehr/?navItemNumber=13261>).
- [2] HL7 Electronic Health Record-System (EHR-S) Functional Model, retrieved: April, 2014 (<http://www.hl7.org>).
- [3] Certification Commission for Healthcare Information Technology, retrieved: April, 2014 (<http://www.cchit.org>).
- [4] European Institute for Health Records, retrieved: April, 2014 (<http://www.eurorec.org>).
- [5] Romanian Association for Electronic Medical Record - PROREC Romania, retrieved: April, 2014 (<http://www.prorec.ro/>).
- [6] Protégé - open-source ontology editor and framework for building intelligent systems, retrieved: April, 2014 (<http://protege.stanford.edu/>).
- [7] Tallis PROforma Primer, Advanced Computation Laboratory part of Cancer Research UK, retrieved: April, 2014 (<http://www.cossac.org/tallis>).
- [8] GUIDE, Laboratorio di Informatica Medica Università di Pavia, retrieved: April, 2014 (http://www.openclinical.org/gmm_guide.html).
- [9] GLARE, Università del Piemonte Orientale Amedeo Avogadro, retrieved: April, 2014 (http://www.openclinical.org/gmm_glare.html).
- [10] VisiGuide - multi ontology guidelines browser, BGU Medical Informatics research center, Ben-Gurion University, retrieved: April, 2014 (http://medinfo.ise.bgu.ac.il/medlab/ResearchProjects/RP_visiGuide.htm#).
- [11] The ASGAARD Project, AsbruView, Vienna University of Technology, Faculty of Informatics, Institute of Software Technology and Interactive Systems, retrieved: April, 2014 (<http://www.asgaard.tuwien.ac.at/asbruvew/index.html>).
- [12] S. Powsner and E. Tufte, "Graphical Summary of Patient Status", 1994, retrieved: April, 2014 (http://www.edwardtufte.com/tufte/lancet_p1).
- [13] T. D. Wang, C. Plaisant, A. Quinn, R. Stanchak, B. Shneiderman, and S. Murphy, "Aligning Temporal Data by Sentinel Events: Discovering Patterns in Electronic Health Records. Time Lines and LifeLines", 2008, retrieved: April, 2014 ([http://z3.aq.gs/papers/Aligning%20Temporal%20Data%20by%20Sentinel%20Events,%20Discovering%20Patterns%20in%20Electronic%20Health%20Records%20\(2008\).pdf](http://z3.aq.gs/papers/Aligning%20Temporal%20Data%20by%20Sentinel%20Events,%20Discovering%20Patterns%20in%20Electronic%20Health%20Records%20(2008).pdf)).
- [14] C. Plaisant et al., "Searching electronic health records for temporal patterns in patient histories: A case study with Microsoft Amalga", Technical Report HCIL-2008-13. College Park, MD: University of Maryland, 2008, retrieved: April, 2014 (<http://www.cs.umd.edu/hcil/patternFinderInAmalga/UMD-AMIA08-v17finalsubmitted-forweb.pdf>).
- [15] KNAVE and KNAVE-II, BGU Medical Informatics research center, Ben-Gurion University, retrieved: April, 2014 (http://medinfo.ise.bgu.ac.il/medLab/ResearchProjects/RP_KNAVE.htm).
- [16] D. Klimov, Y. Shahar, and M. Taieb-Maimon, "VISITORS, Intelligent visualization and exploration of time-oriented data of multiple Patients", 2008, retrieved: April, 2014 (<http://cs.uwaterloo.ca/~jchampai/papers/5235880526386162235.pdf>).
- [17] W. Horn, C. Popow, and L. Unterasinger, "Metaphor Graphics to Visualize ICU Data over Time. Intelligent Data Analysis in Medicine and Pharmacology, VIE-VISU", 1998, retrieved: April, 2014 (<http://www.ifs.tuwien.ac.at/~silvia/wien/vu-infovis/articles/Horn-idamap98.pdf>).
- [18] L. Chittaro, C. Combi, and G. Trapasso, "Data mining on temporal data: A visual approach and its clinical application to hemodialysis", Journal of Visual Languages and Computing, Interactive Parallel Bar Charts (IPBC), 2003, retrieved: April, 2014 (http://www.cieffeweb.com/franz/hcilab/media/k2/attachments/DataMining_JournalVisualLanguages03.pdf).
- [19] K. Hinum et al., "Gravi++: Interactive Information Visualization of Highly Structured Temporal Data", Journal of Universal Computer Science, Special Issue on Visual Data Mining, Gravi++, 2005, retrieved: April, 2014 (http://publik.tuwien.ac.at/files/pub-inf_2884.pdf).
- [20] W. Aigner, "Guideline Overview Tool (GOT)", Vienna University of Technology, Institute of Software Technology and Interactive Systems, 2001, retrieved: April, 2014 (<http://ieg.ifs.tuwien.ac.at/techreports/Asgaard-TR-2001-4.pdf>).
- [21] R. Bade, S. Miksch, and S. Schlechtweg, "The MIDGAARD Project, Connecting Time-Oriented Data and Information to a Coherent Interactive Visualization", retrieved: April, 2014 (<http://ieg.ifs.tuwien.ac.at/projects/midgaard.html>).
- [22] W. Aigner and S. Miksch, "The CareVis Project, Interactive Visualization Methods to Support Protocol-Based Care", retrieved: April, 2014 (<http://ieg.ifs.tuwien.ac.at/projects/carevis/>).
- [23] Microsoft Corporation, Microsoft Health Common User Interface, retrieved: April, 2014 (<http://www.mscuri.net/Default.aspx>).
- [24] Patient data visualization for facile medical assistance process management, retrieved: April, 2014 (<http://www.visual-d.ro/>).
- [25] Business Process Model and Notation, retrieved: April, 2014 (<http://www.bpmn.org/>).
- [26] Business Process Management, retrieved: April, 2014 (http://en.wikipedia.org/wiki/Business_process_management).
- [27] Medipedia, Personal Healthcare Record solution, retrieved: April, 2014 (<http://www.medipedia.ro>).
- [28] Bonita BPM, retrieved: June, 2014 (<http://www.bonitasoft.com>).
- [29] Node.js, retrieved: June, 2014 (<http://nodejs.org>).
- [30] AngularJS, retrieved: June, 2014 (<http://angularjs.org>).

The Implementation of Teledentistry for Pediatric Patients

Rodrigo Mariño^{*}, David Manton^{*}, Parul Marwaha^{*}, Kerrod Hallett[†], Ken Clarke[‡]

Matthew Hopcraft[§], Michael McCullough^{*}, Ann Borda[¥]

^{*}Oral Health CRC, Melbourne Dental School

University of Melbourne

Melbourne, Australia

rmarino@unimelb.edu.au, djmanton@unimelb.edu.au, pmarwaha@unimelb.edu.au,

m.mccullough@unimelb.edu.au

[†]Royal Children's Hospital Melbourne

Melbourne, Australia

kerrod.hallett@rch.org.au

[‡]Institute for a Broadband-Enabled Society

University of Melbourne

Melbourne, Australia

clak@unimelb.edu.au

[§]Australian Dental Council Ltd.

Melbourne, Australia

Matthew.Hopcraft@adc.org.au

[¥]Health and Biomedical Informatics Centre

University of Melbourne

aborda@unimelb.edu.au

Abstract—The present study tested a prototype teledentistry system in which regional Community Health Centers are linked to the Melbourne Dental School or the Royal Children's Hospital in Melbourne (RCH). Three general dental practitioners (GDP) working in community dental clinics in the Australian state of Victoria were trained to manipulate an intraoral camera and to use existing ICT infrastructure to communicate with a dental specialist at RCH and transmit video images for remote assessment. Participants were recruited from the RCH's patient database for cleft lip and palate (CL&P) and orthodontics, living in the selected rural locations. Patients/parents of patients participating in the study completed a questionnaire to assess their experiences with the program. Forty-two assessments/consultations were conducted; 26 CL&P patients, and 16 in orthodontics. For most patients, the outcome of the consultation was the avoidance of trips to the centrally located RCH for initial assessment and/or follow-ups. This field trial provided initial evidence on how teledentistry might improve access to specialist care; identified broader community benefits for both the family and the services providers. From the RCH perspective, the potential reduction of inappropriate referrals with the concomitant reduction of waiting lists for specialist consultation, were important advantages of teledentistry.

Keywords—oral health; teledentistry; intraoral camera; cleft lip and palate.

I. INTRODUCTION

In the last few decades, the implementation of teledentistry has been widely witnessed by various institutions and organizations concentrated mainly in the United States and Europe, but such trials also occur in many other parts of the world. A recent review of the teledentistry literature concluded that most reports referred to pilot projects, and the remainder concentrated on experimental

stages and short-term outcomes, and were descriptive in nature. Despite these limitations, these trials prove that this technology can be successfully implemented in different health settings [1]. The positive outcomes and positive health professional-patient experiences described are very encouraging and clearly indicate that teledentistry works by delivering practical solutions [1] [2].

Teledentistry is particularly well suited for children. Using teledentistry, children's teeth were screened for early childhood caries, during which it was reported that all children liked seeing their teeth on the computer screen [3]. Dental imaging was seen as a game by them, rather than as a dental examination. Moreover, as no instruments are used and the camera head does not need to be inserted far into the child's mouth to obtain dental images, there was less risk of uncooperative behavior by the very young child or toddler than that posed by a conventional dental examination. Child comfort is also increased when the teledentistry examination is conducted in a familiar environment, as opposed to a clinical environment. This resulted in children being more enthusiastic and co-operative during the imaging and recording procedures [3]. In addition, parents and children do not have to take time off work or school for travel, and a child can be tracked easily to determine whether treatment has been rendered, or if an emergency evaluation is needed.

In the state of Victoria, Australia, general dental services are provided by the State to all school children and those adults from lower socioeconomic groups, with strict eligibility criteria and waiting times of up to 18 months [4]. Thus, to see a dentist specializing in pediatric dentistry, access in remote areas is limited, and often there is a long waiting list for both consultation and treatment, especially for specialist care.

Teledentistry has advantages as a method of providing oral specialist services [5]. For example, there are clear advantages if patients could be examined by a dentist/dental therapist with links to a centralized pediatric dentistry specialist, who could provide support with diagnosis and treatment planning and prioritization via tele-consultation and the use of intraoral cameras. Rural community clinics and isolated dental practices are likely to benefit most from this approach. More patients could receive assessment and treatment, since patient care would be effectively triaged at the community level for future care in a specialist centre. For patients, it would reduce the cost of treatment and the need to travel to Melbourne to be seen by the specialist, because their problems were previously identified and planned via teledentistry.

From a public health perspective (i.e., Royal Children's Hospital), if this system is implemented, this screening would save considerable time and decrease waiting lists [6]. Specialists might conduct the teleconsultations from a computer in a dedicated room, this would mean that the time in the clinic could be used entirely to treat patients [7]. The result would be a more productive use of clinical time and resources.

The present project builds on a University of Melbourne Institute for a Broadband Enhanced Society (IBES), Project Seed Grant, which tested the technology under laboratory conditions (proof of concept) and developed the instructional material for non-oral health professional operators [8]. The validity of the teledentistry approach was also investigated and there was no loss in quality compared to face-to-face examinations [8]. Thus, results demonstrate that the proposed teledentistry approach for oral health screening using an intraoral camera is feasible and reliable as an alternative to traditional oral health consultation.

This paper is organized in six sections. The first Section provides the foundation for the need for teledentistry in this population. The second Section is concerned with the aims and objectives of the paper. Section 3 describes the methodology used in this field trial of teledentistry. Section 4 describes the results of the trial, including interviews with personnel and responses from parents of the children involved in the program. Sections 5 and 6 discuss the results of the trial and conclude on its findings, respectively. Further steps are also discussed in last section.

II. AIMS AND OBJECTIVES

The specific objectives of this study were to: assess the feasibility of using teledentistry for pediatric teleconsultation in children and adolescents living in rural and remote areas of the Australian state of Victoria; and to assess the participants' (patients and dental practitioners) views about the structure, content and delivery of the program.

The working hypothesis of this study is that an initial assessment by a consultant, using teledentistry, would decrease the number of long-distance trips needed by patients located in remote areas to visit the RCH to see a specialist (i.e., orthodontist, pediatric dentist), thereby avoiding disruption and reducing costs. In addition, the use

of teleconsultation as a method of screening patients would help to categorise treatment priority avoiding the need for unnecessary referrals and for the patient to travel to an often distant centre for additional assessment.

Additionally, as there is some tension between the increased need for oral health care and a financial climate which limits the oral health budget, the study included an evaluation of whether this innovative oral health care program could be implemented under current financial arrangements.

The plan was to conduct remote assessments/consultations in three specific specialist service areas:

- 1) Cleft lip and palate (CL&P). Support for the timely management of CL&P conditions, which have involvement of pediatric dentistry as part of the multidisciplinary team.
- 2) Dental trauma. Support for the management of oro-facial trauma in rural or remote Community Health Centers, and isolated practices. Patients who present with a trauma can be imaged by trained personnel, a pediatric dental consultant views the case from a remote place and a rapid response is obtained [9].
- 3) Orthodontics. Malocclusions remain untreated due to lack of (or restricted access to services) (barriers include financial, geographic, access to specialist).

It was considered that this assessment would provide initial understanding of the implementation challenges and associated issues to aid decision making in expanding those services to other underserved populations and locations.

III. METHODS

Three community dental health clinics in rural areas of Victoria were recruited to participate in this project. These clinics were located in Rosebud, Shepparton and Geelong, and worked in partnership with the University of Melbourne's Melbourne Dental School and the Royal Children's Hospital of Melbourne, which acted as the central site.

Training was provided for the staff involved in the project and an instruction was manual prepared to assist with use of the intraoral camera. Three general dental practitioners (GDPs) working in community health centers at each of the three remote locations manipulated an intraoral camera. They used existing ICT infrastructure to communicate with the dental specialist at the Royal Children's Hospital of Melbourne (RCH) and uploaded and distributed the images to the pediatric dentist at the RCH for remote assessment.

For the purposes of this trial, assessment of fifty patients was considered to be adequate to meet the specific objectives of this study. The study included children that would generate payment for general consultation and for specialist consultation. Thus, participants were recruited from the RCH's cleft lip and palate (CL&P) and orthodontics patient database who also lived in the selected locations.

Patients were introduced to the study by the local GDP. When the patients, or their primary carers, expressed interest

in participating, each received a Plain Language Statement describing the study and a Consent Form. Once informed consent was obtained, patients underwent an oral health assessment. Patients/parents of patients participating in the study completed a questionnaire to assess their experiences with the various aspects of the program. This included satisfaction, acceptance and practical issues of the teledentistry approach and participants were also invited to discuss any concerns associated with the project.

In the present study, a teledentistry installation was organized using a SOPROLIFE® [10] intra-oral camera (Acteon, France) to capture video and transmit both audio and videos in a high definition software platform (i.e., GoToMeeting®) over the Internet. Additionally, each GDP was sent a web camera (Logitech) to connect to his/her computer. Mpeg4 audio was also transmitted at 128kbit/s along with the images via the use of Clear One Chat 50 model microphone/speaker units also connected via USB cables. This allowed excellent quality audio communications between the patient and clinician nodes. The RCH has an excellent review system available for teleconsultation as a two-way interactive consultation [11], however, it had been rarely used for dentistry prior to the present study.

Rather than arranging video conferencing in an ad-hoc basis, it was thought to be more effective if the consultant would be available during a set time each week. Teleconsultations were organized once a week on Fridays afternoon.

The trained GDP obtained the reason for the consultation, manipulated the intraoral camera and recorded findings for each participant. The remote pediatric dentistry/orthodontic consultant, in collaboration with the local GDP, recorded findings for each participant. An off-site pediatric dentistry consultant and orthodontist located at the RCH, performed the 'virtual dental assessments' and was available to discuss the case with the GDP in real-time teleconferences. Treatments needs were determined by the specialist and the specialist also evaluated whether a referral to the RCH was required.

The remote examiner assessed the patient's needs and provided advice and follow-up to the GDP on how to manage the condition either locally or by referral for specialist care (e.g., orthodontics, pediatric dentistry) as required. They could also organize a specialist consultant at the RCH or Royal Dental Hospital of Melbourne. Additionally, the remote examiner provided advice to the health staff at the local Community Health Centre, or to the parents of the child.

Data collection extended between August and December 2013. At the end of the cycle GDPs who collected the information were sent a summary evaluation form in which they reflected on their acceptance of the practice, and their experience as a whole. The utility of the instructional training kit and any other issues associated with the project were also assessed. The evaluation form consisted of statements that participants rated on a five 5-points likert scale, depicting their level of agreement with the statement (1 'Strongly agree'; 3 'Neutral'; 5 'Strongly disagree'). The summary evaluation also contained four open-questions, so

participants could include their thoughts about their experience and critiques.

Because of the small sample size, the analysis will only include basic descriptive information on the distribution of selected socio-demographic and outcome variables, and parents' views about the format, content and delivery of the teledentistry program. In some cases, categorical and ordinal data were analyzed utilizing Chi square analysis (χ^2) to compare results between different oral conditions and distribution of socio-demographic and outcome variables. To complement this quantitative description and to obtain a better understanding of the usefulness of this approach, from the perspectives of the users (i.e., parents), a qualitative process evaluation was organized to offer new insights.

Ethical approval to conduct this study was sought and obtained from the University of Melbourne.

IV. RESULTS

Three general dental practitioners were recruited for this project. Recruitment of patients took longer than expected as many did not want to participate. The most common answer was that they would come to Melbourne anyway. At the end of data collection, the three GDPs conducted assessments/consultations in two specific specialist service areas; 26 CL&P patients, and 16 in orthodontics. Additionally, one patient presented with Cohen's syndrome. Trauma could not be assessed because no case with orofacial trauma presented during the period of data collection. The analysis that follows does not include the patient with Cohen's syndrome.

Seventeen examinations were conducted in Shepparton, thirteen in Geelong and another twelve in Rosebud. Mean age was 8.6 (4.2) years (See Table I) with significant difference in mean age by oral condition ($p < 0.01$) and by location ($p < 0.05$). CL&P were younger than orthodontics patients (7.2 vs. 10.9 years, respectively). By location, participants from Geelong were younger than those from the other two locations (6.1 vs. 9.3 and 10.3 years). Ages ranged from 1 year and 11 months to 18 years of age. The largest group of participants (41.9%) was between 4 and 8 years of age. The majority of participants (60.1%) were males, with no significant differences by location or oral condition.

For most participants, the outcome of the consultation was the avoidance of trips to the centrally located RCH, for initial assessment and/or follow-ups. For 7.3% of the cases, the follow-up consultation would occur in the three months following the teleconsultation. In about half of the teleconsultations (48.8%), the advice from the consultant was the need for a follow-up visit, which would occur within 6 to 12 months. Another 7.3%, were advised to arrange an appointment at the Dental Department of RCH. For 17.1%, the consultant requested additional information (e.g., radiographs), or the type of general dental treatment that would be required (e.g., restorations, extractions, oral hygiene instructions, etc.) and were referred to their local clinic. For the remaining 20% ($n = 8$), the patient was not eligible for treatment at public clinics, and in those cases advice was provided on alternative treatment avenues for

initial evaluation (e.g., the Royal Dental Hospital of Melbourne or local specialists). This proportion would represent inappropriate referrals to the RCH. Inappropriate referrals represented 44% of the orthodontics consultations.

TABLE I. PARTICIPANTS CHARACTERISTICS AND OUTCOME OF THE TELECONSULTATION BY ORAL HEALTH CONDITION

	Oral condition		
	Cleft lip and palate	Orthodontics	Total
Age (mean and s.d.)	7.2 (4.3)	10.9 (2.6)	8.6 (4.2)
Sex	n (%)	n (%)	n (%)
Male	18 (69.2)	8 (50.0)	26 (61.9)
Female	8 (30.8)	8 (50.0)	16 (38.1)
Location			
Shepparton	10 (38.5)	7 (43.8)	17 (40.5)
Geelong	13 (50.0)	- (0.0)	13 (31.0)
Rosebud	3 (11.5)	9 (56.2)	12 (28.5)
Outcome	a		
Review next 3 months	3 (12.0)	- (0.0)	3 (7.3)
Review at 6 months	10 (40.0)	- (0.0)	10 (24.4)
Review at 12 months	8 (32.0)	2 (12.5)	10 (24.4)
Referral to CL&P/Ortho/RCH ^b	3 (12.0)	4 (25.0)	7 (17.1)
Referral local clinic	- (0.0)	3 (18.8)	3 (7.3)
Referral other	1 (4.0)	7 (43.7)	8 (19.5)
Total	26	16	42

a. Figures do not add due to missing values

b. Cleft lip and palate and orthodontic clinics at the Royal Children’s Hospital of Melbourne

When parents were asked about their level of satisfaction with remote dental assessment, amongst those parents who answered the question (n=33), the majority was either strongly satisfied (82%) or slightly satisfied (12.0%). Another 5% of parents were neutral about the remote assessment (See Table II). Parents described the service provided in these ways:

“I believe this is a valuable service for rural communities” (Rosebud-2).

“They did give us instructions on hygiene and checked up on our upcoming appointment at the RCH”. ...“This was our first experience and we were very impressed” (Shepparton-5).

The majority of parents (75.6%) commented that the most valuable element of the remote dental assessment was the avoidance of travel to the city to visit a dental specialist which caused disruption to family routines, and was often difficult and expensive to organize. Parents commented:

“Not needing to take the day off to drive to Melbourne for five minutes appointment” (Shepparton-9).

“... the advantage of not having to travel to Melbourne is great, plus money saving” (Shepparton-2).

Parents considered the teleassessment as appropriate and would ‘strongly recommend’ or ‘recommend’ the practice to other people (97%). One parent (3%) slightly would not recommend remote examinations to other parents. No reason was given for that opinion.

The majority of parents (90%) found it very easy/easy to understand the instructions received from the remote examiner. One parent indicated: *“Amazing that they can consult this way”* (Rosebud-8). On the other hand, four parents (10%) were neutral about understanding of instructions received from the remote examiner.

TABLE II. PARENTS’ RESPONSES TO TELEDENTAL ASSESSMENT QUESTIONNAIRE (%)

1. How satisfied were you with the remote dental examination? ^a				
Strongly satisfied	Slightly satisfied	Neutral	Slightly dissatisfied	Strongly dissatisfied
82.0	13.0	5.0	-	-
2. If remote examinations were available for patients, would you recommend them to other people?				
Strongly recommend	Slightly recommend	Neutral	Slightly not recommend	Strongly not recommend
86.0	11.0	-	3.0	-
3. Were instructions from the examiner in the remote examination clear and easy to understand?				
Very easy	Slightly easy	Neutral	Slightly difficult	Very difficult
69.0	21.0	10.0	-	-
4. How satisfied were you with the review of your dental needs by the remote dentist?				
Strongly satisfied	Slightly satisfied	Neutral	Slightly dissatisfied	Strongly dissatisfied
74.0	21.0	5.0	-	-
5. How appropriate was the format of the remote dental examinations?				
Very appropriate	Slightly appropriate	Neutral	Slightly inappropriate	Strongly inappropriate
74.0	20.0	3.0	3.0	-

a. N= 39

When parents were asked about how satisfied they were with the review of oral health needs, the majority was either strongly satisfied (74%) or slightly satisfied (21%), two CL&P’s parents (5%) were neutral.

The majority considered the format of the remote dental examination to be either very appropriate (74%) or slightly appropriate (20%). On the other hand, one parent (3%) was neutral about its format and another (3%) considered remote dental examination to be slightly inappropriate. No reason was provided for that view, but they were a child with CL&P’s parents.

No statistically significant differences were present in the parents’ evaluations by oral conditions. The exception was the level of satisfaction with the review, where CL&P parents tended to be more “Strongly satisfied” than orthodontics case’s parents (84% vs. 57%, respectively; p<0.05).

The GDPs recruited were able to operate the camera, conduct intraoral examinations and transmit the information accurately. They provided feedback on the training material presented (i.e., a hard-copy, on-line manual and demonstrations). There was general agreement that the material presented was clear and relevant to the purposes of this project and that the information provided in the manual

and in the training was helpful in providing the necessary step-by-step information to conduct the oral examination, operate the camera, send the information, etc. However, they were neutral regarding the length of the material. GDPs considered that the manual provided less relevant and sometimes unnecessary information to oral health professionals, (e.g., dental anatomy).

On the question about the training received, the GDPs indicated that they may need more practice before starting examinations outside the study. One GDP commented about the need of more practice time to manipulate the intraoral camera, in particular, to get good images of the maxillary arch.

When asked about the relevance of the teledentistry model in their workplace, they indicated that the technology could be expanded to other areas in dentistry, for example dental trauma, dental emergencies, and the provision of treatment to those who cannot travel.

V. DISCUSSION

The main aim of the present study was to address key priorities (i.e., “*Children and Adolescents*”, “*Improving services to rural communities*” and “*Potential benefits of technological innovations in dentistry*”) established by Australia's National Oral Health Plan 2004-2013 [12]. The study targeted children and adolescents living in regional and remote locations, and proposed the use of teledentistry to provide an additional step in closing the gaps in the provision of sustainable oral health care services to underserved areas of the country (e.g., rural areas). Rural and regional Australia has major access to oral health workforce shortages, in particular oral health specialists (e.g., oral medicine, pediatric dentistry, maxillo-facial surgery).

The major outcome of the present study was the successful trial of an alternative model for pediatric oral health service provision in remote and underserved areas via a teledental diagnosis and teleconsultation model. The trial provided general and specialist oral health care support to local facilities to assist in regular and timely oral health checks using a GDP in the first instance, and subsequent specialist dental services when the required treatment was identified. In so doing, the trial showed that pediatric teledentistry is a viable solution, in terms of time, stress, and money saved for parents and children who were able to avoid travel to the city for consultation. Furthermore, the concept of teleconsultation was well received by parents and patients and by the GDPs. However, this support must be evaluated with caution in view of the sample size.

Teledentistry can be a highly effective method for enhancing early diagnosis and referral for patients who otherwise might not receive timely care. Additionally, today's high resolution and reliable digital and online technology makes it possible to be connected for distant oral health promotion, education, and assessment, transcending social and geographic barriers.

Findings would indicate that this is a valid, efficient and time saving method for clinical screening. This teledentistry study via teleconsultation was successfully in improving accurate diagnosis and appropriate referrals. It was also

extremely valuable in providing feedback to patients, for example, about the need to bring radiographies or about the eligibility of services.

More specifically, in this project, there were reductions in costs to patients. This reduction of costs on the patients/parents side was achieved without increasing costs to the oral health provider. In this telehealth project, both the community health centres and the RCH, charged the services provided within current financial arrangements. Nonetheless, despite these arrangements, GDPs, and to a lesser degree the specialists, put a significant amounts of in-kind time to self-train and setting up the teledentistry installation. However, these must be considered as research driven costs.

While acceptability and cost saving of the study, from the patient perspective, was established, a societal perspective should be the preferred one. From a public health perspective, the evaluation of the success of the proposed model of care and its sustainability will be dependent on the ability to clearly demonstrate service and economic benefits from the services provider's perspective. Supportive business cases, to a large extent, have not been captured by earlier telehealth projects.

The Australian government established funds to provide financial incentives for health teleconsultation with a specialist, consultant physician, etc. to provide teleconsultation to a range of health professionals (i.e., medical practitioners, nurse practitioners, midwives, psychiatrists, and Aboriginal health workers), but that did not include the provision of financial incentives for oral health services or teleconsultations. This incentive ceased on the 30 of June 2014 [13].

Results have been presented in a simple and descriptive fashion and therefore some limitations should be acknowledged when interpreting these findings. Firstly, as with any voluntary study, there is the possibility of a bias in self-reporting of information. Secondly, with respect to sampling, the sample was small in terms of numbers of respondents and not all CL&P or Orthodontics patients registered with the RCH or local community health centers participated in the study. The questionnaire data lacked, in some instances, the necessary depth for a detailed analysis of the overall clinical experience and its context.

Despite these limitations, this field trial provided initial evidence of how teledentistry might improve access to and efficiency of specialist care in various ways; it showed a pathway to improvements in the quality of access and provision of oral health care; it identified potential broader community benefits such as the level of convenience for both the family and the dental specialist; and it provided evidence of the generally excellent levels of acceptance of the virtual examination by patients, parents, and oral health professionals. In the example of teledentistry presented in this paper, oral health screenings were performed by GDPs at distant sites, thus reducing the need for patients and dentists (or dental specialists) to travel to health care facilities, particularly those located in rural areas. Participants were practically unanimous in their satisfaction

with, and appreciation of, the various benefits of the teledentistry services delivered to them.

From the RCH perspective, the potential reduction of inappropriate referrals with the concomitant reduction of waiting lists for specialist consultation, are important advantages of teledentistry, which are clinically important and also have budgetary implications.

Nonetheless, a significant shortcoming of the current oral health system is its failure to take advantage of innovations in health promotion and e-technologies. This failure is also impacted by the paucity of research information informing oral health practices and identifying innovative ways to use e-health and m-health to make preventive and care intervention programs more accessible, particularly for those living in rural Australia. Findings from this study also add valuable information to the discussion about the value and feasibility of this technology, particularly where unmet needs for dental services among children and young people are high and accessibility is low. It is suggested that teledentistry can make a valuable contribution to the delivery of dental care in both the private and public dental settings.

The project could easily be extended as an integrated part of the general adoption of telemedicine/ telediagnosis. Further research will be required to undertake economic and clinical outcome modeling to determine if the teledentistry approach is cost-effective and leads to a similar or better level of care being provided in comparison to the traditional model of oral health assessment. This will lead to more advanced stages of teledentistry implementation, including larger samples, multi-State community-based trials of longer duration of the technology, which will lead to sustained outcomes.

VI. CONCLUSIONS

Findings suggest that teledentistry may be an important public health measure to improve access to oral health specialist services for populations where referral to specialists is not possible or feasible. Real-time consultation with oral specialists could provide a new avenue for socially disadvantaged children (Poor, rural, immigrants) to receive these services. At present, these malocclusions remain untreated resulting in oral health inequalities.

An important challenge for future trials would be to ensure that tele-oral health models and programs are maintained in a community for a length of time that is sufficient to achieve the stated goals. These trials would necessarily have a highly collaborative, partnership approach, with a strong academic base in rural health issues

to ensure that the results of the present study can be further developed and implemented.

ACKNOWLEDGMENT

This project was funded by a grant from Google/Institute for a Broadband-Enabled Society, The University of Melbourne. We would also like to acknowledge the pediatric dental consultants, the general dental practitioners and the parents and patients involved in this study.

REFERENCES

- [1] R. Mariño, and A. Ghanim. "Teledentistry: a systematic review of the literature." *J Telemed Telecare*. 2013;19:189-194.
- [2] S. W. Chang, et al., "Teledentistry in rural California: a USC initiative. *J Calif Dent Assoc* 2003;31:601-608.
- [3] D. T. Kopycka-Kedzierawski, R. J. Billings, and K. M. McConnochie, "Dental screening of preschool children using teledentistry: a feasibility study." *Pediatr Dent* 2007;29:209-213.
- [4] Dental Health Services Victoria. Average waiting times. (<https://www.dhsv.org.au/patients-and-public/waiting-lists>). [retrived: June, 2014].
- [5] N.A. Mandall, K.D. O'Brien, J. Brady, H.V. Worthington, and L. Harvey, "Teledentistry for screening new patient orthodontic referrals. Part 1: A randomised controlled trial." *Br Dent J* 2005;199:659-662.
- [6] J. Cook, C. Mullings, R. Vowles, R. Ireland, and C. Stephens, "Online orthodontic advice: a protocol for a pilot teledentistry system." *J Telemed Telecare* 2001;7:324-333.
- [7] E.D. Bednar et al., "Application of distance learning to interactive seminar instruction in orthodontic residency programs." *Am J Orthod Dentofacial Orthop*. 2007;132:586-594.
- [8] R. Mariño, et al., 'A teledentistry approach for oral health screening in nursing homes.' Available at: <http://www.slideshare.net/ifa2012/3-mariooral-health-if-apresentation29may2012>. [retrived: June, 2014].
- [9] D. T. Kopycka-Kedzierawski, and R.J. Billings. Teledentistry in inner-city child-care centres. *J Telemed Telecare* 2006;12:176-181.
- [10] SOPROLIFE: Light Induced Fluorescence Evaluator. <http://www.soprolife.com>. [retrived: June, 2014].
- [11] S. Jury, A. M. Walker, and A. J. Kornberg, "The introduction of web-based video-consultation in a paediatric acute care setting." *J Telemed Telecare* 2013;19: 383-387
- [12] Australian Health Ministers' Advisory Council, Healthy mouths healthy lives. Australia's National Oral Health Plan 2004-2013. South Australian Department of Health, 2004.
- [13] Department of Human Services. Telehealth. <http://www.medicareaustralia.gov.au/provider/incentives/telehealth/> [retrived: June, 2014].

Introducing a Patient-Centered e-Health Record Over the Cloud

Konstantinos Koumaditis, Marinos Themistocleous, George Vassilacopoulos, Andriana Prentza, Flora Malamateniou, Dimosthenis Kyriazis, George Pittas
 Digital Health Services Laboratory (DHSL)
 Department of Digital Systems
 University of Piraeus
 Piraeus, Greece
 e-mail: {konkoum,mthemist,gvass,aprentza,flora,dimos,gpittas}@unipi.gr

Abstract— The aim of this paper is to highlight the Patient-Centered e-Health (PCEH) concept, introduce its importance and demonstrate a multidisciplinary project that combines advanced technologies. The project combines several aspects of PCEH functionality, such as: (a) homecare telemedicine technologies, (b) e-prescribing, e-referral, e-learning and (c) state-of-the-art technologies like cloud computing and Service Oriented Architecture (SOA), will lead to an innovative integrated e-health platform that delivers many benefits to the society, the economy, the industry and the research community. This paper provides insights of the PCEH concept and the current stages of the project. In doing so, we aim to increase the awareness of this significant work and disseminate the knowledge gained so far through our effort.

Keywords-Personal Healthcare Record; Cloud Computing; Healthcare Information Systems Integration.

I. INTRODUCTION

Healthcare Information Systems (HIS) integration has been associated with various aspects, amongst others: strategic, social, and/or organisational [1]. In this respect, there is a common trend to address HIS integration by an overall approach, seen as integrated patient centered care [2]. Integrated patient centered care reflects on integrated HIS (with elements as e-health services) requiring coordination across professionals, facilities, support systems that is continuous over time and between patient visits [3]. This approach is observed on national healthcare strategies that encourage patient involvement in their healthcare treatment. Moreover, in the USA and Europe, online personal health records that allow patients to manage their health data have emerged [4]. For example, in Finland, this integration trend can be observed in a legislation that allows citizens to access and interact with their own Electronic Healthcare Records (EHRs), ePrescriptions and audit-logs via the Internet [5].

Following similar legislative opportunities worldwide, patients increase their involvement with HIS. This is a growing involvement, seen in parallel with mechanisms for the collection of information (obtained by mobile and other

sources) in order to develop an enhanced, complete and integrated view of citizens health status. The latter is reflected in EHRs and Personal Health Records (PHRs), which are being enriched and exploited by different actors and stakeholders (i.e., health and care professionals, citizens, nutrition experts, hospitals, etc.) in the health ecosystem. Three general PHR models have been proposed [6]: a) the stand-alone model, b) Electronic Health Record (EHR) system, and c) the integrated one, which is an interoperable system providing linkage with a variety of patient information sources, such as EHRs, home diagnostics, insurance claims etc. The main types of health information supported by PHRs are problem lists, procedures, major illnesses, provider lists, allergy data, home-monitored data, family history, social history and lifestyle, immunizations, medications and laboratory tests [7][8]. Widely known PHR platforms in terms of centralized web-based portals include Dossia and Microsoft Health Vault platforms. Many systems presented in literature offer integration with already established PHRs platforms [9][10]. Early experiences from the adoption of PHR-based systems have been found to be positive, showing that such systems can be feasible, secure, and well accepted by patients [11]. Nonetheless, today's EHRs and PHRs are far from being what the citizens consider as of value to their health, since for the public view, health means more than being disease-free.

Following this trend for patients' empowerment, academics, practitioners and patients advocate in favor of the patient centered healthcare systems. Still the aforementioned advocates have not yet reached a concise definition of Patient-Centered e-Health (PCEH) that is shared across the research disciplines that focus on health and Information Technology (IT) [12]. The lack of consensus can be attributed, amongst other, (a) on the number of challenges that are involved in transitioning healthcare delivery to a more patient-centered system and (b) the lack of proof-of-concept through well-documented and effective PCEH projects.

Healthcare is unique and complex ecosystem that poses several challenges on developing PCEH [13]. The healthcare ecosystem consists of several networking organisations that constantly interact with each other, but also differentiate amongst them. The differentiation can be noted in issues, such

as: (a) medical specialisations, (b) socio-technical and IT capacities, (c) organisational cultures, (d) structures, (e) actors and (f) business process [1]. More precisely, healthcare tasks are distributed between several actors (physicians, nurses, residents, and other clinical support staff) and artefacts (information technology, healthcare specific machines, paper notes) [14].

Thus, the challenge to integrate and redesign existing healthcare systems towards a more patient-centered exists [2]. This challenge is emphasized when integration efforts as the PCEH projects try to leverage the different actors and their sub-sequential attributes. Apparently, the professional healthcare actors with their many years of training, qualifications and expertise have much more medical knowledge than their patients. As a result, a paternalistic system has evolved where physicians expect, and patients expect them, to make the decisions about, or at least recommend, an appropriate course of treatment [15]. Therefore, an integrated system of personal healthcare information that is governed by the patient him/herself contradicts the established norms and highlights new challenges (e.g., validity and royalty of medical data, decision making culture etc.). For example following a more shared decision making or interpretation of the enclosed data, as the PCEH entails, requires (a) a plethora of the necessary medical data integrated in an easily accessible and comprehensible platform adequate for decision-making and (b) the physicians' arbitration to support or contradict those decisions. This requires well-developed sophisticated systems with clear boundaries on decision-making, responsibilities and availability of data.

Regardless the challenges, moving toward patient-centeredness is important [12]. To this end, this paper aims to introduce: (a) the main concepts surrounding the PCEH and (b) a PCEH project utilizing cloud computing. These are depicted in the following sections.

II. PATIENT-CENTERED E-HEALTH (PCEH)

Most developed countries are facing important overall problems regarding health care services, such as: (a) aging population with increased demand on specialized health care services (e.g., Chronic diseases), (b) need for increased efficiency with limited financial resources (e.g., Staff /bed reduction), (c) requirements for increased accessibility of care outside hospitals (e.g., home care) to name a few. To these problems, advances in information and communication technologies have provided considerable assistance in the form of EHRs [6]. Yet, it seems that traditional EHRs, which are based on the 'fetch and show' model, provide limited functionality that does not cover the spectrum of the patients' needs. Therefore, new solutions as the PHRs appeared to narrow this gap. In more detail, PHRs' data can come from various sources like EHRs, health providers (e.g., e-

Prescribing, e-Referral), and/or directly from the patient him/herself – including non-clinical information (e.g., exercise habits, food and dieting statistics, etc.) [16].

The PCEH concept is a new multidiscipline area of research, with crucial aspects as it deals with the wellbeing of patients.

However, due to the length limitations of this paper we briefly present up-to-date research on the field, with the intention to fully present and analyse our rigorous research in a future publication. In this paper, we focus mainly on Wilson's *et al.*, (2014a) views. In more detail, Wilson *et al.*, (2014b) depicts that the PCEH should integrate three themes:

- **Patient-focus** - In many cases, e-health developers have created systems designed for patients' use that is not patient-focused but rather focused on healthcare organizations' objectives. Patient-focus requires PCEH strategies to be centered first and foremost on the requirements and perspectives of patients. To this extent if the patient require e-health services tailored to their needs, developers need to accommodate these needs. For example, young web-savvy patients expect their e-health applications to be responsive to their medium of choice (mobile, tablet, etc.), while more unexperienced elderly patients require a more user friendly environment.
- **Patient-activity** - Patient-activity requires comprehensive, interactive input by patients in providing data about themselves and representing their own perspectives as well as consuming information of interest to them. Yet, achieving high patient-activity in other e-health services may require reconceptualization of healthcare processes and information flows in order to provide opportunity to patients to add information they perceive to be relevant. The PHR is an example of such an e-health application.
- **Patient-empowerment** - in a technological perspective the empowerment happens through information-sharing, offering the patients a visual overview of their course of treatment, letting the patients take their own measurements, and letting them provide verbal and written inputs. From the PCEH perspective, however, patient-empowerment centers on providing similar levels of control via e-health that exist for patients in other modes of interaction with their healthcare providers.

The value of the three introduced characteristics is to ascertain the generalizability and abstraction properties of patient-focus, patient-activity, and patient-empowerment to the theoretical domain and to explore relationships among the PCEH characteristics [17]. Although at an early stage Wilson *et al.*, (2014b) arguments provide helpful guidance in the emerging issue of patient-centered e-health and can be of value in the development, design and evaluation of PHRs. These issues are included in our research agenda as well.

To this end, we introduce in this paper our own practical involvement with a PHR project and provide a brief introduction in the following section.

III. PROVIDING INTEGRATED E-HEALTH SERVICES FOR PERSONALIZED MEDICINE UTILIZING CLOUD INFRASTRUCTURE (PINCLOUD)

PINCLOUD seeks to integrate different application components, leading to the provision of an end-to-end personalized disease monitoring and medical data service “anytime, anywhere”, which ensures an independent living regardless of age [18].

The scenario upon which PINCLOUD is based, as seen in Figure 1, is a patient governs his/her PHR that can be remotely monitored by a physician located either at a hospital or at an individual medical office. Complementary to the PHR’s stored information the doctor monitors the patient using a home care platform that receives and analyses patient’s medical data. The proposed home care platform will include among others the following services: (a) Asthma or Chronic Obstructive Pulmonary Disease (COPD) disease management; (b) Hyper-tension disease management; (c) Diabetes monitoring; (d) Electrocardiogram (ECG) monitoring; (e) Video/ Audio Access to physicians for remote consultation; (e) Remote picture and text archiving and communication service (back-up/long term archiving complementary to infrastructure operated by hospitals) and (f) Fall Prevention and Detection Services. The doctor can access the patient’s PHR on-line through a cloud computing service. The latter can support the doctor in decision making and results in better quality of health service. In more detail, the doctor retrieves and updates the patient’s medical data and can also use the proposed on-line system to: (a) prescribe a new medicine; (b) fill in an e-referral for specific exams (e.g., blood test); (c) inform and advise his/her patient or (d) ask the patient to visit the hospital. Following the doctor’s advice, the patient visits a pharmacy, or a diagnostic centre or a hospital. At the final stage, the healthcare service providers (doctors, hospitals, diagnostic centres) and pharmacies interact with the health insurance organisation to compensate all outstanding orders and medical actions.

Currently, PINCLOUD [19] is in its implementation phase, upon which the various components, such as: (a) PHR platform, (b) e-prescribing and e-referral, and (c) homecare applications, are being developed and tested.

PinCloud Architectural Approach



Figure 1. Providing Integrated e-Health Services for Personalized Medicine utilizing Cloud Infrastructure (PINCLOUD)

IV. MAIN IDEAS

Service and data availability is crucial for healthcare providers who cannot effectively operate unless their applications are functioning properly and patients’ data are available in a consistent manner. This is also the case for PINCLOUD. PINCLOUD’s services (e.g. E-Prescription, E-Referral, Home-Care and PHR) ought to be available continuously with no interruptions or performance degradation since they will be used for decision making regarding the patients wellbeing.

New research projects, as PINCLOUD need to reinsure service availability to the participating healthcare providers and other organizations. In addition, hardware and software installations, upgrades, and reconfigurations have to be managed and maintained without any service interruptions that may cause problems. In order to achieve the availability in a cost efficient way the use of Cloud-Computing seems to be the appropriate solution and thus the PINCLOUD was designed based on its features. These features as cost-saving, agility, efficiency, resource consolidation, business opportunities and Green IT are relevant and applicable to the healthcare sector.

Besides, PINCLOUD potentially will be responsible for the governance of a big volume of medical data. The protection and integrity of such data is vital for both the patients’ privacy and their wellbeing. At this stage of the project the protection of these data is achieved with a Private Cloud delivery model. A Private Cloud model is operated by a single organization. In the private cloud, the technology resides within an organization’s own data center and the resources are deployed as needed to the different departments. In our project, a private IT company which is part of the consortium has provided the Private Cloud’s infrastructure. Thus, the developers can overcome the

challenges associated with other Cloud models (e.g., Public, Hybrid) since the ability to manage and control sensitive patient data remains within the organization.

PINCLOUD is based on the well-known Cloud-Computing three service models' structure, namely: (a) Software as a Service (SaaS), (b) Platform as a Service (PaaS) and (c) Infrastructure as a Service (IaaS). Respectively, PINCLOUD provides the user interaction through SaaS. In theory, SaaS is the capability provided to the consumer to use the provider's applications running on a cloud infrastructure. The applications are accessible from various client devices through either a thin client interface, such as a web browser (e.g., web-based email), or a program interface. PINCLOUD offers four applications, such as (a) E-prescription, (b) E-referral, (c) Home-Care and (d) PHR. These applications provide the main functionality required and are being consumed by End-Users (e.g. Patients, Doctors, Hospitals/Labs and Insurance Bodies). All these users access the PINCLOUD through user interface provided as a service. For example, a PINCLOUD registered user can have access to his/her medical record online.

In addition, PINCLOUD takes advantage of PaaS service model. Literature presents PaaS as the capability provided to the consumer to use and or deploy into the cloud infrastructure consumer-created or acquired applications created using programming languages and tools supported by the provider (NIST). Accordingly, it takes advantage of the PaaS model and provides open source components as Web-Services and Application Programming Interfaces (APIs) that facilitate the integration with third (3rd) parties (e.g., Medical Data Providers, Hospitals). For example, when a hospital decides to be integrated in the PINCLOUD system, it can allocate and consume the Web-services' API created.

The processing and storage capability of PINCLOUD is based on IaaS model. IaaS is the capability provided to the consumer to provide processing, storage, networks, and other fundamental computing resources while the consumer can deploy and run arbitrary software, which can include operating systems and applications. PINCLOUD takes advantage of the IaaS and provides data processing and storage of medical data. IaaS consists of multiple Virtual Machines (VM), Medical Data Base and Network Infrastructure. In the given case, multiple VMs are utilized with each one dedicated to one service (e.g. Database, Access Control, Backup).

V. EXPECTED BENEFITS

The project shall build a reliable, secure and extensible platform warranting stakeholder collaboration and enjoying public trust. The expected benefits for all participant organizations include amongst others: (a) the development of integrated healthcare services that improve quality of service and reduce costs; (b) business process reengineering, improvement, simplification and integration; (c) enhanced decision making for health organizations and significant reductions to medical errors; (d) standardization, automation,

synchronization, better control and communication; (e) improved coordination, management and scheduling of specific health supply chains and services; (f) development of monitoring systems that improve quality of care of patients at home; (g) establishment of an infrastructure that provides up-to-date information; (h) development of an innovative organizational environment for the participating hospital using horizontal processes instead of the traditional hierarchical organization; (i) implementation of an extensible and maintainable infrastructure that can be enriched with other medical services; (j) development of an appropriate, sustainable technological framework that can be deployed and applied in other relevant situations and environments; (k) investigation of state-of-the art technologies and novel research that extends the body of knowledge; (l) significant research outcomes and publications of excellent quality; (m) production of new platforms, infrastructures and solution that can be further exploited, (n) knowledge and expertise gained can lead to competitive advantage and (o) production and export of technical know-how for all the participants.

The results of the proposed project are of great importance for the businesses that deal with the medical/health sector as they will gain the potential to gain competitive advantages through the project. The area of healthcare is significant and the need for advanced and innovative IT solutions in this area is apparent too. Thus, the participant enterprises will have the opportunity to: (a) develop an integrated platform that can be used by other organizations in the future; (b) better understand and analyze the complexities of the Greek healthcare environment; (c) experiment and implement innovative integrated solutions that can be turned into products; (d) gain expertise and know-how on a complex area; (d) sell these products and know-how at national and international level since PINCLOUD seeks to develop an innovative solution; (e) obtain and reinforce experiences that can be used for the development of other network-oriented systems and (f) extend their business activities.

The benefits for both healthcare organizations include among others: (a) specifications of processes for the management of healthcare processes; (b) simplification and acceleration of business processes; (c) better management of healthcare tasks; (d) personalized disease monitoring and cost calculation; (e) more efficient operation and (f) economies of scale.

The academic institutions' participation in the project is equally important and include benefits, such as: (a) knowledge exchange and transfer; (b) engagement in innovative research; (c) investigation of state of the art technologies; (d) opportunity to publish research articles of high quality; (e) prospect to conduct applied research and combine theory and practice.

PINCLOUD will deliver the following benefits to the national economy and society: (a) enhancement of occupation and working activities for the participating partners; (b) the reinforcement of scientific research; (c) improved delivery of healthcare services at reduced cost; (d) patients' and next of

keen satisfaction; (e) the development of innovative and state of the art healthcare systems; (f) more efficient allocation and management of computing resources; (g) the development of new products and jobs; (h) reduction of medical errors and consequently the amount of people that are affected or die due to them; (i) the reduction of the cost as an immediate effect of the reduction of medical errors; (j) technical, scientific and research benefits; (k) reduction of the amount of prescriptions and referrals and the associated cost; (l) improvement of the quality of life of people who live in islands or rural areas.

VI. CONCLUSIONS AND FUTURE RESEARCH AGENDA

This paper introduces a Patient-Centered e-Health (PCEH) conceptual aspects alongside a multidisciplinary PHR project that combines state of the art technologies like cloud computing, Service-Oriented-Architecture (SOA), homecare telemedicine technologies, e-Prescribing, e-referral and e-learning in healthcare environment. The aim of the project is to create an integrated PHR platform that delivers many benefits to the society, the economy the industry and the research community. To this end, various technologies (e-health, cloud, etc.) and healthcare issues (e.g., complexity, PCEH, etc.) were presented. Additionally, our intentions on the way we propose to address and combine these issues were explained and depicted. In the previous section the benefits of such an endeavor alongside the steps taken so far to realize the implementation of a secure and reliable system, were analyzed. Yet, further research is required both in the testing and evaluation of our design and implementation.

To this end, the Research and Development (R&D) team engineered several mechanism to test and evaluate PINCLOUD and its components. For example, a proof-of-concept test will be implemented to check the communication of various sensors with the main PHR. The results of this test will be examined by healthcare professionals and provide initial evaluation of the technologies used. Additional, testing mechanism have been designed for other components (e.g., e-prescribing and e-referral) as well. Besides, PINCLOUD will be implemented in two different cloud IaaS providers so as to study the interoperability in two different settings. The results of this test will again provide insights into the utilized technologies and if needed reconfigurations and adjustments will be implemented. The authors expect the results of this test to be the subject of our next publication.

REFERENCES

- [1]. D. Finnegan and K. Hamid, Information systems (IS) integration approaches in healthcare: a critical review, in *Integrating Healthcare With Information and Communications Technology*, W. Currie and D. Finnegan, Editors. 2009, Radcliffe Publishing: London. pp. 35-63.
- [2]. T. Leventhal, P. K. Taliaferro, C. Wong, S. Hughes, and S. Mun, The Patient-Centered Medical Home and Health Information Technology. *Telemed J E Health.*, 2012. 18(2).
- [3]. S. Singer, et al., Defining and measuring integrated patient care: promoting the next frontier in health care delivery. *Med Care Res Rev*, 2011. 68(1): pp. 112-127.
- [4]. A. D. Black, et al., The Impact of eHealth on the Quality and Safety of Health Care: A Systematic Overview. *PLoS Med*, 2011. 8(1): pp. e1000387.
- [5]. P. Ruotsalainen, A. Iivari, and P. Doupi, Finland's strategy and implementation of citizens' access to health information. *Stud Health Technol Inform.*, 2008. 137: pp. 379-85.
- [6]. D. Detmer, M. Bloomrosen, B. Raymond, and P. Tang, Integrated personal health records: transformative tools for consumer-centric care. *BMC Medical Informatics and Decision Making*, 2008. 8: pp. 45.
- [7]. P. Tang, J. S. Ash, D.W. Bates, J.M. Overhage, D.Z. Sands Personal Health Records: Definitions, Benefits, and Strategies for Overcoming Barriers to Adoption. *Journal of the American Medical Informatics Association*, 2006. 13(2): pp. 121-126.
- [8]. J. Halamka, K. Mandl, and P. Tang, Early Experiences with Personal Health Records. *Journal of the American Medical Informatics Association*, 2008. 15(1): pp. 1-7.
- [9]. S. R. Reti., H.J. Feldman, and C. Safran, Governance for Personal Health Records. *Journal of the American Medical Informatics Association*, 2009. 16(1): pp. 14-17.
- [10]. F. Zhou, Mobile Personal Health Care System for Patients with Diabetes, in *Aging Friendly Technology for Health and Independence*, Y. Lee, et al., Editors. 2010, Springer Berlin Heidelberg. pp. 94-101.
- [11]. P. Jennett and M. Watanabe, Healthcare and Telemedicine: Ongoing and Evolving Challenges. *Disease Management & Health Outcomes*, 2006. 14(1).
- [12]. V. Wilson and D. Strong, Editors' Introduction to the Special Section on Patient-centered e-Health: Research Opportunities and Challenges,. *Communications of the Association for Information Systems*, 2014a. 34(15).
- [13]. K. Koumaditis, M. Themistocleous, M. Mantzana, and K. Souliotis, A Proposition of Critical Success Factors Influencing SOA Implementation in Healthcare, in *European Conference on Information Systems 2012*: Barcelona, Spain.
- [14]. T. Kannampallil, Schauer, G., Cohen, T., & Patel, V. Considering complexity in healthcare systems. *Journal of Biomedical Informatics*, 2011. 44(6): pp. 943-947.
- [15]. S. A. Sherer, Patients are Not Simply Health IT Users or Consumers: The Case for 'e-Healthicant' Applications. *Communications of the Association for Information Systems*, 2014. 34(17): pp. 351-364.
- [16]. V. Koufi, F. Malamateniou, and G. Vassilacopoulos, An Android-Enabled PHR-based System for the Provision of Homecare Services. *International Journal of Measurement Technologies and Instrumentation Engineering (IJMTIE)*, 2013. 3(2): pp. 1-18.
- [17]. E. V. Wilson, W. Wang, and S. D. Sheetz, Underpinning a Guiding Theory of Patient-Centered E-Health. *Communications of the Association for Information Systems*, 2014b. 34(16).
- [18]. M. Themistocleous, K. Koumaditis, and G. Vassilacopoulos. Providing Integrated e-Health Services for Personalized Medicine utilizing Cloud Infrastructure. in *European, Mediterranean & Middle Eastern Conference on Information Systems 2013 (EMCIS2013)*, October 17-18. 2013. Windsor, United Kingdom.
- [19]. Lab of Medical Informatics. Providing Integrated eHealth Services for Personalized Medicine utilizing Cloud Infrastructure. 2014 [cited 2014 17th April]; Available from: <http://pincloud.med.auth.gr/en>.

Sono-Contrast Spectroscopy for Cancer Virtual Biopsy in LMIC Settings

Yan Yu

Department of Radiation Oncology
Thomas Jefferson University
Philadelphia, U.S.A.
Yan.Yu@Jefferson.edu

Lydia Liao

Department of Radiology
MD Anderson Cancer Center at Cooper University Hospital
Camden, NJ, U.S.A.
Liao-Lydia@Cooperhealth.edu

Abstract—We present an initiative to adapt, optimize and productize a multimodal breast cancer detection technology, termed “Sono-Contrast Spectroscopy” (SCS), for use in Low- and Middle-Income Countries (LMIC) to facilitate point-of-care early detection of breast cancer. The prototype SCS scanner was developed from proof-of-concept in vivo preclinical research and subsequently through a first-in-human pilot clinical study. Quantitative evaluation with histopathology data from tissue biopsy of the interrogated lesions as ground truth demonstrated that the SCS technique achieved very high discriminating power as measured by sensitivity, specificity and Receiver Operating Characteristics (ROC) analysis; the Area Under the Curve (AUC) ranged from 0.90 to 0.95 in racial/ethnic subgroup analysis, and was equal to 0.91 over the entire study group of 66 subjects. Particularly of relevance to global health applications in the LMIC settings, the SCS technique does not require clinical subspecialty interpretation, is easy to deploy and operate, has no disposable or consumable parts, reports diagnostic results instantaneously, and potentially offers an effective alternative to expensive and invasive large-core vacuum-assisted needle biopsy followed by subspecialty pathology evaluation, all of which may be inaccessible in LMICs. Significant steps towards global health deployment in these settings are outlined.

Keywords—cancer diagnosis; spectroscopy; biopsy; near infrared; focused ultrasound.

I. INTRODUCTION

According to the World Health Organization, breast cancer is the top cancer in women in the developing world, and its incidence is increasing due to increases in life expectancy and urbanization; furthermore, the majority of breast cancers that develop in Low- and Middle-Income Countries (LMICs) are diagnosed in very late stages [1]. Therefore, early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control. Population-based cancer screening is a highly complex public health undertaking. Mammography screening is very costly and is cost-effective and feasible only in countries with good health infrastructure that can afford a long-term organized population-based screening program. Breast cancer survival rates vary greatly worldwide, ranging from 80% or over in North America, Sweden and Japan to around 60% in middle-income countries and below 40% in low-income countries [2]. The low survival rates in less developed countries can be

explained mainly by the lack of early detection programs, resulting in a high proportion of women presenting with late-stage disease, as well as by the lack of adequate diagnosis and treatment facilities [1].

Early detection of breast cancer has been proven to reduce mortality by about 20% to 35% [3]. Histopathological examination is considered to be the “Gold Standard” for definitive diagnosis of cancer but requires adequate tissue samples that are collected through biopsy procedures capable of sufficient tissue retrieval. Of the two major approaches for breast biopsy, needle biopsy and open excisional biopsy, needle biopsy is the most commonly practiced standard in affluent countries because it is less traumatic, produces little or no scar, allows quicker recovery, and is less expensive.

Relative to LMIC resources, however, these techniques can be prohibitively expensive (e.g., *disposable* large-core needle), requires tissue transfer to pathology facilities and expert review (not always available or timely), and results in patient call-back (often impractical in remote/rural settings). Open excisional biopsy suffers from these same drawbacks, and results in greater trauma and postsurgical care. At the same time, it is well known that current methods for breast cancer surveillance including breast self-exam (BSE), clinical exam, mammography, ultrasound and even Dynamic Contrast-Enhanced (DCE) MRI lead to high proportions of unnecessary biopsies (on average, only 1 in 3 to 4 biopsies results in a cancer diagnosis even in highly subspecialized breast care centers). In less affluent healthcare environments, some or many of these proven diagnostic modalities may be unavailable or not uniformly affordable by all patients. Clearly, there is a severe unmet need in LMICs for realizing adequate and accessible diagnosis of treatable early stage breast cancer.

We have successfully developed and validated a breast cancer diagnosis tool using combined Near Infra-Red (NIR) Diffuse Reflectance Spectroscopy (DRS) and Low-Intensity Focused Ultrasound (LIFU) modulation of blood flow in vivo. We have shown, first in preclinical animal models and recently in a pilot clinical study, that focused ultrasonic pulses create different blood flow and tissue oxygenation signatures depending on whether the tissue being interrogated is malignant or normal; these differences can be markedly discriminated via NIR spectroscopy, with pronounced contrast in spectral parameters. Thus we termed the technique sono-contrast spectroscopy (SCS). Importantly, this technique overcomes a prevailing problem

in using noninvasive optical tissue interrogation methods, i.e., the spatial or targeting certainty becomes highly degraded due to NIR light propagation in tissue. Numerous physical, mathematical or multimodal hardware devices have been applied to solve this fundamental “ill-posed” problem in biomedical photonics. Here we deploy the fundamental solution that the acoustic sonication is focused on the target lesion unequivocally; any change in spectrophotometric values before, during and after sonication is characteristic of the lesion being interrogated. Thus there is no need for multiple expensive source/detector arrays, inverse solutions, a priori multimodal information or multimodality encoding, leading to a simple, low-cost and somewhat elegant device.

Importantly, the SCS *in vivo* scans are completely noninvasive: both the ultrasonic and NIR light intensities needed are well below U.S. Food and Drug Administration (FDA) recommended safety levels. Additionally, computer-aided discrimination of cancerous vs. normal findings can be made instantly, following a 2-min. or less sonication and light illumination/spectral acquisition time. If proven sufficiently accurate for breast cancer diagnosis, the proposed technique can be considered “*virtual biopsy*” with real-time reporting of study results offering rapid turnaround in busy LMIC breast clinics.

There is no disposable component in the SCS exam; only routine cleaning/disinfecting is needed after each patient’s visit. In the long run, focused ultrasonic transducers (note: these are *not* sonographic probes), low-power NIR lasers and photodiodes can all be mass assembled from off-the-shelf components; RF signal generation can be achieved in software and dedicated amplification circuitry. Data transmission, analysis and diagnostic algorithm updates can make use of wireless technology (e.g., Bluetooth), consumer electronics (e.g., Smartphone apps) and cloud computing. Thus, it is entirely feasible that the fully productized device will be low-cost, battery-driven, and usable by non-specialists.

We envision that the eventual SCS device will be handheld, reports examination results instantly in two mode: (a) simple – such as green, yellow and red LEDs for benign, needing further interrogation and highly suspicious of malignancy; (b) comprehensive user-configurable interface where patient-specific factors such as age, racial/ethnic group, Body Mass Index (BMI), cup size, and other relevant health/lifestyle parameters can be associated with the diagnostic finding. The globally deployed SCS device will use cloud-computing and massively distributed learning paradigms to improve its diagnostic accuracy and adapt to new LMIC environments or racial/ethnic settings. The overall goal of this initiative is to push breast cancer diagnosis progressively earlier, so that low-cost treatment regimens such as surgery alone, or breast-conserving surgery plus simple whole breast tangential radiation, are still effective in eradicating the disease.

Even in LMIC communities where breast ultrasound and/or mammography is accessible to patients, there is still a large gap between a suspicious imaging finding and positive diagnosis by surgical excision. In affluent countries, this gap is being closed by improved accessibility of DCE MRI,

Contrast-Enhanced Spectral Mammography (CESM), 3D/tomosynthesis, and ultimately large core needle biopsy with tissue histology diagnosis and biomarker profiling. Absent of such expensive technologies, patients in LMICs are faced with the choice of surgical excision with high probabilities of negative result, or delayed diagnosis of cancer. The proposed SCS technology can be used as a low-cost method to close this gap by identifying suspicious lesions that are associated with high likelihood of malignancy.

Accurate surgical excision also requires technology guidance. In affluent countries, this is achieved by wire localization under stereoscopic imaging, ultrasound and MRI, or radioactive seeds. In LMIC communities where facilities or patient logistic does not permit such complicated precision guidance, the SCS technology may become a useful tool for the surgeon to identify the tumor extent/location immediately prior to incision. The standard of care for breast cancer treatment in the U.S. and many developed countries is lumpectomy plus radiation (or mastectomy). When radiation therapy is inaccessible in LMICs, the standard care is relatively unclear; however, anecdotal evidence suggests that limited excision/lumpectomy alone sometimes represents the entire treatment. In such cases, arming the surgeon with a real-time cancer delineation tool like the SCS probe can potentially change the probability of local control vs. recurrence.

In affluent countries, modern standard of care consists of large-sample tissue histology diagnosis plus biomarker profiling. In LMICs, however, even the cost of large core sample retrieval can be prohibitive. The decision for open surgical excision biopsy is considerably more difficult because of its invasiveness. Through added diagnostic value in using the SCS technology, we hope to inform the patient more effectively before undergoing highly invasive and costly procedures that may be unnecessary, thus the concept of “*virtual biopsy*”.

At the same time, the cancer screening initiative we plan to implement would serve as early sentinel events pointing to the need for comprehensive diagnostic workup in patients with highly suspicious breast lesions. In LMIC settings, low-cost surgical excision (mastectomy or wide-excision lumpectomy) may be an accessible option. Radiotherapy may or may not be accessible; chemotherapy or targeted biologics may be out of reach. Early diagnosis of localized, non-metastatic breast cancer could be an important demarcation between curative vs. palliative treatment plans.

In short, in the SCS technology we hope to achieve the complementary goals of eliminating unneeded invasive interventions and discovering breast cancer before it becomes expensive or impractical to treat.

II. SONO-CONTRAST SPECTROSCOPY PRECLINICAL STUDIES

In 1971, Dyson *et al.* reported that stationary ultrasound waves caused stasis of red blood cells *in vivo* [4]. In 2006, we reported our initial animal study, supported by NCI R21 CA107860, in which this effect was first used to differentiate

tumor from normal leg muscle tissue in mice [5]. Under normal physiological conditions, oxygen dissociates from hemoglobin molecules in red blood cells to replenish the oxygen supply in tissues as blood flows through the vessels. When standing wave ultrasound is used to slow or stop the blood flow, the ratio of oxy- vs. deoxy-hemoglobin content decreases, which can be measured using NIR spectroscopy. We hypothesized that the effect of this acoustic radiation force on blood flow and stasis would be different in normal vessel network morphology vs. malignant, angiogenic morphology (lack of directionality, chaotic network, leaky vessel walls, etc.). The “*sono-contrast*”, i.e., changes in spectroscopic parameters due to administration of ultrasound acoustic force, was indeed found to be strong in normal vasculature and absent in tumors, thus serving as an excellent discriminator of benign vs. malignant vascular morphology in the *in vivo* model [6].

TABLE I. PANEL OF SPECTROSCOPIC PARAMETERS WITH STATISTICALLY SIGNIFICANT CORRELATION WITH IMMUNOHISTOCHEMICAL PARAMETERS

Dependent Variable	Statistically Significant ($p < 0.05$) Predictors from Regression Analysis	p value
Percentage of perfused vessel area in analysis area	Maximum minus minimum of the ratio signal with baseline trend subtracted	0.031
	Standard deviation of the ratio signal with baseline trend subtracted	0.015
Average distance between all vessels in analysis area	Maximum minus minimum of the ratio signal with baseline trend subtracted	0.008
	Standard deviation of the ratio signal with baseline trend subtracted	0.005
Mean EF5 intensity for all vessels	Difference between the endpoint values of the baseline trend line	0.013
Mean EF5 intensity for perfused vessels	Difference between the endpoint values of the baseline trend line	0.012
Standard deviation of average distance for all vessels	Maximum minus minimum of the ratio signal with baseline trend subtracted	0.023
	Standard deviation of the ratio signal with baseline trend subtracted	0.014

To study the physiological differences between normal vasculature and tumor vasculature, immunohistochemical studies were then conducted on the mouse muscle tissue and tumor samples following imaging and cryostat sectioning. Results of regression analyses showed that certain spectroscopy signals are significantly ($p = 0.005$ to 0.013) correlated with immunohistochemistry analysis of a panel of variables including percent area of perfused vessels, total number of vessels, mean distance between vessels (both total and perfused), and EF5 intensity (see Table 1) [5]. These

findings further support the hypothesis that SCS is a functional reporter of vascular microenvironmental variability, and strongly suggest that SCS may be used to characterize tumor neoangiogenesis, proliferation and aggressiveness.

III. SONO-CONTRAST SPECTROSCOPY PILOT CLINICAL STUDY

A. Instrument Design

Based on the encouraging animal study results, we designed a human breast SCS scanner [7][8] and conducted a pilot clinical study to evaluate the diagnostic accuracy of this multimodal detection method. The scanhead was designed to deliver focused acoustic radiation fields up to about 2.4 cm deep in tissue. Two 1 MHz focused transducers (Channel Industries, Santa Barbara, CA) were aligned orthogonally inside the scanhead to create a focal area at the intersection of the axes. A commercial ultrasound probe (Philips L12-5, Valhalla, NY), located in the same plane as the focused transducers, was used for image co-registration with the NIR spectroscopy information, tissue density information and blood flow information. The ultrasound probe and focused transducers have two degrees-of-freedom, so that the focal zone can be scanned in tissue depth-wise and laterally. Three force sensors (Honeywell model 53, Morristown, NJ) were incorporated on the lower concave compression plate of the scanhead to measure the force exerted on the breast.

The optical spectroscopy system consisted of 18 customized 15-foot long and 2.5-mm diameter fiber bundles terminating at the concave bottom plate of the scanhead. Out of these 18 fiber bundles, 6 were used as sources and 12 were used as detectors. The 6 sources were illuminated by two laser diodes (LG-Laser Technologies, Germany) through a multichannel optical switch (O/E land Inc., Canada) that had 2 input channels and 6 output channels. Diffuse reflectance signals were collected by the 12 detectors, amplified by 12 avalanche photodiodes (APD) (Hamamatsu C5460-01, Bridgewater, NJ), and then transmitted through 1 multi-channel data acquisition card (National Instrument, Austin, TX) to the computer for analysis.

The ultrasound imaging probe was connected to a commercial ultrasound system (Philips iU22, Valhalla, NY) for image co-registration. The focused ultrasound transducers were driven by a function generator (Agilent 33250A, Santa Clara CA) connected to an RF amplifier (Amplifier Research 25A250A, Souderton, PA). During the operation, the forward and reverse power level was monitored via a directional coupler (Amplifier Research DC3010, Souderton, PA) using an oscilloscope (Tektronix TDS 2022, Richardson, TX), for ensuring electrical safety. A mobile hydraulic cart was used to host the instruments.

According to ANSI Z136.1 (1993) Safe Use of Lasers, for wavelength 0.647-0.905 μm , the maximum permissible exposure (MPE) to skin is 0.2-0.5 $\text{W}\cdot\text{cm}^{-2}$. We selected 0.2 $\text{W}\cdot\text{cm}^{-2}$ as the threshold. Two Continuous Wave (CW) laser diodes were used in the spectroscopy system: one had a wavelength of 685 nm with the maximum output of 50 mW; the other had a wavelength of 830 nm with the maximum output of 110 mW. The power output for the two laser systems can be adjusted using the knob in the front panel. The threshold laser output at the source terminals was calculated to be 9.8 mW for the two laser units. A laser power meter system (Coherent LabMax, Santa Clara, CA) was used to calibrate and mark the corresponding threshold positions on the two units.

Based on the FDA guideline, the derated global maximum acoustic output of the diagnostic ultrasound equipment should not exceed Pre-amendments acoustic output exposure levels, i.e., derated Spatial Peak Temporal Average Intensity $I_{\text{SPTA}} \leq 0.72 \text{ W}\cdot\text{cm}^{-2}$. We calibrated the acoustic radiation fields to ensure that it was within the limit. The acoustic focal spot having the maximum peak-positive voltage signal on the oscilloscope was found at about 2 cm below the bottom plate, which is the designed intersection of the axes of the two focused transducers. The I_{SPTA} was determined to be 0.4 $\text{W}\cdot\text{cm}^{-2}$, below the FDA ultrasound limits of 0.72 $\text{W}\cdot\text{cm}^{-2}$. The focal spot was then registered in the ultrasonography system for image guidance during the pilot clinical study. This calibration established the baseline of the dual-transducer focused acoustic radiation field. A Quality Assurance (QA) protocol was formulated based on the same procedure.

B. Clinical Study Results

Clinical study was carried out under an Institutional Review Board (IRB) approved protocol at Cooper University Hospital, NJ. The intended patient populations were those who present with a solitary mass in the breast that required ultrasound-guided tissue biopsy to rule out malignancies. The study was scheduled to be performed on the same day as biopsy. Once the patient signed the consent form for participation, the SCS scanning procedure would first be performed. After completing SCS scanning, the patient would be re-prepped using sterile technique for the standard needle biopsy procedure. Usually 3-4 core biopsy specimens were obtained for the same mass using large core biopsy needle. The approximate location of each core would be documented. Based on our clinical experience, the time taken from prep to first tissue removal was approximately 10 min. This time interval should be sufficient for the reversible process of vascular compression by LIFU to recover fully to the original state [4,9]. Tissue histology was obtained for all patients from the standard pathology reports. This information served as ground truth for developing the Computer-Aided Diagnosis (CAD) algorithm and validating its effectiveness.

The collected data stream consists of LIFU signals and NIR diffuse reflectance spectroscopy signals together with time stamp. They are first synchronized and segmented into 12 channels (corresponding to the 12 detectors). The diffuse

reflectance spectroscopy signals are first processed using moving average technique to remove the noise and smooth the data. Discrete wavelet analysis is then used to further process the data, which involves using filters of different cutoff frequencies to analyze the signal at different scales.

A total of 66 patients were enrolled with informed consent under the IRB-approved protocol. Subsequent biopsy of each index lesion revealed 14 histologically-proven cancers (8 IDC, 4 ILC, 1 metastatic adenocarcinoma in lymph node, 1 invasive mammary carcinoma with ductal and lobular features; final staging 1A to 4). Using histology gold standard as ground truth, the predictive accuracy of SCS incorporating sophisticated wavelet analysis was evaluated [10]. Results of this human study corroborated the animal study. By exploiting the sono-contrast differences and imaging features, we have developed a panel of spectral and imaging biomarkers that demonstrates high discriminating power. It was found that this methodology predicted cancer vs. non-cancer with sensitivity of 93% at specificity of 81%; the area under the ROC curve ("area under the curve", or AUC), was determined to be 0.91 [11]. In comparison, reader-averaged AUC for mammography has been generally reported to be 0.70 [12]. Furthermore, additional subgroup analysis revealed that certain spectral and imaging biomarkers in the panel could discriminate between ductal and lobular cancer subgroups ($p=0.022$), and between HER2 negative 0 vs. 1+ subgroups ($p=0.044$) [11]. These subgroup analysis results further reveal that SCS may be used to interrogate and characterize breast cancers. This first-in-human trial clearly demonstrated the effectiveness of SCS as an *in vivo probe* of invasive breast cancers.

We also performed secondary analysis of the clinical study data by racial/ethnic groups including "White" (non-Hispanic), "Hispanic" and "African American" subgroups [13]. While the pilot study was not powered to generate definitive conclusions, it was found that subgroup-specific tuning of the diagnostic algorithms may lead to incremental improvements to diagnostic accuracy. For example, AUC was 0.95 for "White", 0.92 for "African American", and 0.90 for combined "African American"+"Hispanic" subgroups, respectively. Bootstrap resampling method was applied to overcome the data limitation; thus, these results should be regarded as suggestive of potentially even more improved efficacy in LMIC-specific racial/ethnic populations.

IV. SYSTEM ADAPTATION FOR LMICS

A. Low-power, Portable Configuration

The early generation instrument was tested with attenuated intensities in both the optical and the ultrasonic subsystems. The clinical data revealed that substantially low-powered optical and ultrasonic modules would be effective in eliciting contrast in blood flow/oxygenation between benign and malignant masses. Additionally, as few as one well-selected light detector channel (out of 6) was sufficient for diagnostic data collection. Thus, we have identified significant opportunities to eliminate over-designs to achieve a modular system with portable ultrasonic generator,

miniaturized transducers and off-the-shelf optical bench. Furthermore, the original design incorporated an imaging ultrasound probe in the scanhead for image guidance. Considering the likelihood that sonographic equipment may not be readily available in LMIC clinics as well as the viable alternatives found in the pilot clinical study (such as using a standalone imaging probe to mark the location and depth of interrogation), the imaging probe has been eliminated from the second-generation device design. Also eliminated are all scanning mechanisms in the lateral and depth directions; probes with sonication depths of 0–1, 1–2, 2–3, and 3–4 cm will be selectable, with appropriate standoff bolus as needed. Thus the new device design is predominantly “point-and-shoot” in operation. Together with near real-time CAD reporting of results, this design will offer a point-of-care virtual biopsy assay for cancer detection in low-resource healthcare environments.

B. Smart Diagnostics and Cloud-based QA Repository

Quality control of SCS clinical measurement data is critically important for diagnostic algorithm self adaptation and distributed learning (see Section C, below). The opportunity for non-expert or minimally trained healthcare providers to use a simple and noninvasive “point-and-shoot” device on patients further highlights the need for built-in QA surveillance. Excessive movement of the handheld probe during a point data acquisition period (which lasts for 105 sec. in our initial clinical study and is reducible to 36 or minimally 24 sec. in the second-generation) will cause signal breaks or noise in DRS, and may perturb LIFU sonication pulses. Such unwanted movement will be detected using built-in accelerometer chip with associated user warning/guidance and, if necessary, repeat data acquisition. Poor acoustic field contact can potentially lead to false positive findings; thus it is important to ensure consistent probe-tissue coupling. This will be monitored using built-in hydrophone circuit at the probe side. Similarly, NIR light-tissue coupling is essential for adequate illumination and DRS signal detection. Smart diagnostics on the collected spectral signal will be carried out in real-time to detect poor probe-tissue contact by analyzing the reflectance above ambient background signals, and communicated through simple user interface on the device.

In addition to the self-diagnostic functionalities built into the device to prevent erroneous use or data collection, anonymized study data from each examination can be transmitted to centralized QA repository using modern wireless technology. To achieve best interconnectivity for these purposes, integrate wireless capabilities (Bluetooth, WiFi) and Smartphone/tablet compatibility will be incorporated in the final product. Where the device is not used in online mode (e.g., in rural settings where WiFi or wireless connection is off), the data transmission will occur when the system is docked with online connection after field use or in charge mode. These data will include: sonication pulse heights and widths at both input amplifier and hydrophone receiver ends, reference optical wavelength intensity received, the full spectral signal, and accelerometer

signals, all synchronized to the same timeline. From these data, nearly every scenario in the data acquisition sequence can be reconstructed. More sophisticated cloud-based QA diagnostics algorithms can then be developed by aggregative analysis of signal deviations.

C. Large Scale Distributed Learning to Improve Cancer Predictive Accuracy

Another design consideration is to include a touch screen interface to give the user limited access to software configuration such as entering racial/ethnic profile (or complexion), age range, breast density estimate, cup size, BMI, etc. Although some of the patient-specific factors currently do not enter the diagnostic model, they are potentially useful in later software release/updates as additional algorithm self-training codes are developed. For example, if a false-positive or false-negative diagnosis is generated, the user will be able to enter the correct diagnosis and force the algorithm to learn from the data. Similarly, correct diagnosis can be used by the self-learning codes in conjunction with patient-specific factors to discover statistically significant influence factors for increased diagnostic accuracy. In the future, if users consistently enter patient-specific factors and definitive tissue diagnoses associated with the SCS exam data, it is possible to improve the diagnostic accuracy continually by aggregating this information from multiple devices in the field. De-identified data can be transmitted to cloud-based applications that aggregate and disseminate statistically significant data to generate refined diagnostic models. Alternatively, if transmitting patient data to central repositories is culturally or administratively unacceptable, then downloadable “app” can be developed for the user to run model extraction algorithms. The app can be designed to bring in collective knowledge from other downloaded apps (i.e., app on other SCS devices in the field), extract and abstract diagnostic features, spectral fingerprints, etc., that may be significant in model building, and upload the abstracted data (not the patient data) to cloud-based servers.

Similarly to other large-scale distributed learning paradigms, it is anticipated that the predictive accuracy will continually improve with the frequency and variety of use. Importantly, it is envisioned that the SCS system be *adaptive* to population-specific signatures of cancer assay, with the ultimate goal of becoming a diagnostic and screening tool for global health.

V. CONCLUSION AND FUTURE WORK

Sono-contrast spectroscopy has been shown in preclinical and clinical studies to confer high discriminating power for diagnosing malignant breast masses. An adaptation strategy has been outlined to produce a portable device with uncompromised performance characteristics suitable for LMIC deployment. Additional use of modern wireless, cloud computing and large-scale distributed learning technologies will enable unprecedented cancer diagnosis algorithm’s self-learning/adaptation and population-based tuning capabilities.

To further meet the cancer burden needs in LMICs, it is envisioned that a set of end-firing and side-firing probes incorporating the SCS technology will be developed for detecting cancers of the cervix, prostate and rectum. Pilot clinical studies will be designed to evaluate the effectiveness of SCS as either adjunct or primary detection technology in the presence/absence of standard screening tests.

ACKNOWLEDGMENT

The preclinical in vivo study and the pilot clinical study described in Sections II and III were carried out under the support of U.S. NIH/NCI grants R21 CA107860 and R33 CA107860, respectively.

REFERENCES

- [1] <http://www.who.int/cancer/detection/breastcancer/en/> World Health Organization webpage, accessed on March 24 2014.
- [2] M. P. Coleman, M. Quaresma, F. Berrino, et al. "Cancer survival in five continents: A worldwide population-based study (CONCORD)". *Lancet Oncol.*, vol. 9, August 2008, pp. 730-56.
- [3] J. G. Elmore, K. Armstrong, C. D. Lehman, and S. W. Fletcher, "Screening for breast cancer". *Journal of American Medical Association*, vol. 293, October, 2005, pp. 1245-1256.
- [4] M. Dyson, B. Woodward, and J. B. Pond, "Flow of red cells stopped by ultrasound". *Nature*, Vol. 232, 1971, pp. 572-573.
- [5] B. A. Winey, V. Mistic, L. Laio, K. Parker, B. M. Fenton, and Y. Yu, "In vivo cancer diagnosis with optical spectroscopy and acoustically induced blood stasis using a murine MCA35 model". *Med Phys.*, vol. 33, June, 2006, pp. 1623-33.
- [6] V. Mistic, B. Winey, H. Liu, L. Liao, P. Okunieff, K. Parker, et al., "Tumor detection in vivo with optical spectroscopy". *Conf. Proc. IEEE Eng. Med. Biol. Soc.*, vol. 5, May, 2005, pp. 4708-11.
- [7] K. Yan, T. Podder, K. Huang, Y. Yu, and L. Liao, "A noninvasive multimodal sono-contrast NIR spectroscopy system for breast cancer diagnosis". *BioInformatics and BioEngineering (BIBE)*, IEEE International Conference, 2010, pp. 285-286.
- [8] K. Yan, T. Podder, K. Huang, L. Liao, and Y. Yu, "A multimodal sono-contrast NIR spectroscopy system for breast cancer diagnosis: System design and safety considerations". *3rd International Conference on Biomedical Engineering and Informatics (BMEI)*, 2010, pp. 1386-1390.
- [9] F. L. Lizzi, D. J. Coleman, J. Driller, L. A. Franzen, and M. Leopold, "Effects of pulsed ultrasound on ocular tissue". *Ultrasound Med. Biol.*, vol. 7, March, 1981, pp. 245-252.
- [10] K. Yan, Y. Yu, and L. Liao, "A non-invasive multimodal sono-contrast NIR spectroscopy system for breast cancer diagnosis". *4th Int. Conf. Biomed. Eng. Informatics*. 2011, pp. 1034-1037.
- [11] K. Yan, Y. Yu, E. Tinney, R. Baraldi, and L. Liao, "Clinical study of a noninvasive multimodal sono-contrast induced spectroscopy system for breast cancer diagnosis". *Med. Phys.*; vol. 39, 2012, pp. 1571-8.
- [12] K. M. Kelly, J. Dean, S. J. Lee, and W. S. Comulada, "Breast cancer detection: Radiologists' performance using mammography with and without automated whole-breast ultrasound". *Eur Radiol.* vol. 20, 2010, Nov., pp. 2557-64.
- [13] K. Yan, Y. Yu, and L. Liao, "Multimodal sono-contrast NIR spectroscopy for breast cancer diagnosis: Cancer characterization modeling and subgroup study". *IEEE ICSP2012 Proceedings* October, 2012, pp. 2144-7.

New Approach to Information Extraction from X-ray Plates

High Quality Digitalization

Ivan Evgeniev Ivanov, Vesselin E. Gueorguiev

Technical University Sofia
Sofia, Bulgaria
e-mail: {iei,veg}@tu-sofia.bg

Desislava Valentinova Georgieva

New Bulgarian University
Sofia, Bulgaria
e-mail: dvelcheva@nbu.bg

Abstract—This article aims at solving one of the most important issues of computer-based interpretation of medical images for diagnosis purposes – obtaining the maximum authentic image, which then can be processed by computer-assisted diagnosis methods. The article offers a new approach to the problem of the X-ray plate digitalization – namely increasing the quality and the quantity of information obtained from the X-ray plate by creating a model of the plate illumination while an X-ray image is being created. The implementation of the presented method is based on the theory of high dynamic range images. Increase and enhancement of human perception of X-ray plates and possibilities to diagnose more precisely many sicknesses are the final result of this work.

Keywords—*medical imaging; X-rays; HDR-images; image digitalization.*

I. INTRODUCTION

In the era of computer-based medical applications, the requirements for the diagnostic process quality are directly related to the quality of the computer generated data/information used by physicians. This follows to the requirement for generation new approaches for data acquisition, data storage and data/information processing. On the medical images processing tools market this led to the development of many new solutions. For example, the desire for increasing the quality of generic images led to the fast progress in the hardware and software development of digital X-Ray machines, CT, MRI, ultra-sound apparatuses, and the possibility to control the image-taking process. The need to store these images without any loss of information and without any reduction of the quality leads to changing the standards for image processing as well as the standards for image archiving – the best example is the changing of the DICOM standard in the last 10 years.

One of the most important characteristics of the diagnosis process is the need to track patient's status over time. In the area of automated and semi-automated methods and systems for detection and diagnosis of diseases and changes in tissues, this required to define the concept of "equality" and "comparability" of medical images. Now, this term is used to define how the physicians' evaluation of the sameness of the two images coincides with the computer evaluation. This is a very serious problem, because tracking of a disease evolution

is assessed depending on how the patient's organs and tissues have changed. This is based on images which were taken at different times, on different systems and under different conditions. Although some digital X-ray machine manufacturers have software for images obtained from various X-ray apparatus from their product list [12], this problem has not yet been solved when using images obtained by the apparatus of different manufacturers.

An additional factor, complicating the process of automated tracking of the disease, is the need to use X-ray images stored on plates and films. This requires the plates with X-ray images to be digitized with the quality and characteristics that allow computer-based comparison with images obtained by digital X-ray apparatus. From a technical point of view, this issue is much more complex than the problem of images portability between digital X-ray apparatus, due to the use of different physical phenomena in the process of obtaining digital images:

- The digital X-ray apparatus uses a digital sensor, which takes the X-ray photons and converts them into an optical picture depending on the sensor calibration – the process uses an additive type of lighting system because photo-photons, which are used for optical image generation, are generated by the emitting material, most commonly selenium. The resulting image is a medical image, which is displayed on a display and interpreted by radiologists. Therefore, in the same stream of X-ray photons radiologists can get different optical pictures depending on the sensor calibration and the sensor linearization [3][4]. This is used by radiologists for improving the quality of the final digital image.
- The digitization process of X-ray plates/films is an optical information conversion from an analog form (recorded on the plate) to a digital form to be displayed - this is a subtractive type of image generation, because the digital image is generated by measuring changes of luminosity when the light passes through the plate. This is a totally different class of problems, since the main limitation is the inability to obtain additional information to be used for the correction of deficiencies in the analog image. For example, it is necessary to use different type of methods and techniques for correcting

the nonlinearity and the constraints of a digitizing system.

Since the final image quality is the result of three different groups of characteristics – the quality of the recorded image on the plate, the way the X-ray plate is stored, and the quality of the digitalizing system – the development of new digitalizing methods and techniques requires the use of more diverse hardware and software tools. The classic solution in this case is the use of a very small size laser beam, which allows high accuracy of measurement of the luminosity change, low degree of influence of the diffuse lighting over the luminosity change, and the well-known apparatus architecture [8][9]. A major drawback of this approach is the fact that digitization cannot compensate for the change in the final image quality due to deterioration of the image quality with improper storage or because of an incorrect process of image creating on the plate [14][15][16].

The present paper describes a new approach to the process of X-ray image digitalization from the plate, which allows for compensating the reduction of image quality due to deterioration in the characteristics of the plate. At the same time, this approach allows you to compensate the reduction in the final image quality, resulting from the overexposed/ underexposed X-ray image recording. Also, this approach allows to preserve all the necessary characteristics of the radiographic image such as resolution, dynamic range, contrast, sharpness, etc. This is achieved through an image pre-processing technique which resembles the characteristics of the X-ray-image-creating process by modern digital X-ray apparatuses.

This present paper is structured as follows:

- Section II background of the new digitalization method
- Section III describes the HDRI-based digitization method for X-ray plates
- Section IV includes the analyses of the results
- Section V is the paper conclusion.

II. BACKGROUND OF THE NEW DIGITALIZATION METHOD

X-ray imaging utilizes the ability of high frequency electromagnetic waves to pass through soft parts of the human body largely unimpeded. With classical X-ray apparatus, X-rays are usually generated in vacuum tubes by bombarding a metal target with high-speed electrons. The X-ray images are produced when the radiation passed through the body is absorbed by a photographic plate or digital X-ray sensor to produce a radiograph [17]. The resulting X-ray images show the parts of your body in different shades of black and white because different tissues absorb different amounts of radiation:

- Calcium in bones absorbs X-rays the most, so bones look white;
- Fat and other soft tissues absorb less and look gray;
- Air absorbs the least so lungs look black.

The quality of the digitalization process of such images will be measured with the difference between the information stored on the image and the one read from it.

From the perspective of optics an X-ray plate represents a type of material that fully corresponds to the laws of the physics of semi-transparent materials. This allows a much more flexible approach to be used for digitalization of the X-ray image plate in order to extract the fullest possible information for the optical picture recorded on the plate. One of the benefits of the computer system in this case, compared to the human vision system, is the fact, that the computer system does not have features like "visual weight" and "approximation of the color consistency". At the same time, the computer system does not have different perception sensitivity for color and grayscale images, which is a well-known characteristic of human vision.

Analyses showed that the plate with a recorded X-ray image on it has the behaviour of a multilayer structure. This is due to several factors: the different photo-photons penetration into the material corresponding to their energy in the process of image creation; the different distribution of the light-sensitive elements (often silver) in the plate material; and the different penetration of chemical reagents when handling the plate after capture. Therefore, the change in the different plates when exposed to the same constant light is different. In terms of optics, this characteristic of the plate material causes the effects of the subsurface scattering – the effect strongly depends on the spectrum and the energy of the light flux passing through the plate. Thus, the resulting optical picture after passing the light through the plate is some kind of averaging of recorded illumination in the different levels of the plate. This means that if the plate is illuminated for a short period of time with light having constant spectrum and intensity, we cannot obtain all the information stored in the plate. This defines the main difference between X-ray scanner manufacturers using laser beam lighting - the choice of the beam spectrum and energy results in a different amount of loss of recorded information. These differences are particularly visible when scanning overexposed or underexposed X-rays. Another reason for the search of a new approach is the characteristic of human vision which allows manifold increase of its dynamic range. When a person has long been watching the same image or scene for a prolonged period of time he gradually starts perceiving its elements in a much different way from the initial perception.

This is due to the fact that the human dynamic range increases through the gradual light accumulation in the photoreceptors – mainly, this is a chemical process. In computer science the idea that comes closest to this one is the idea of creating and using the so-called HDR images.

Limitations in the dynamic range of photo-sensors require to look for new methods and approaches to solve this problem.

Different approaches were developed – from increasing the dynamic range of photo-sensors to methods based on the

merging of information from photo-sensors with different photosensitivity.

Today a combined approach – photo-sensors with wider dynamic range and control of the sensitivity range is mostly used.

Thus, combining information obtained in different ranges it is possible to create an image with a much wider dynamic range. The most well-known and used method today is the High Dynamic Range Imaging (HDRI) [12].

HDRI, in photography and imaging, includes a set of techniques for obtaining and reproducing a greater dynamic range of luminosity (the difference between the brightest and darkest parts of the image) than when using standard photographic and imaging techniques [13]. Thus, HDR-images can present more accurate intensity levels of light for real scene. So, the HDR-image does not store pixels intensity values – it stores the information for the illumination in logarithmic form or as a real number without a fixed presentation of individual color channels [12]. Therefore, the use of HDR-images in the X-rays plate digitalization process allows the creation of a model corresponding to the illumination which has created the original image. In this way, by using lighting with different exposures, we can obtain information about the light flow which generated changes in the different levels of the plate. The only problem in this case is the number of exposure levels and the exposure value for these levels.

III. THE HDRI-BASED DIGITIZATION METHOD FOR X-RAY PLATES

Based on the research results of existing systems and technologies for X-ray plates digitization and using quality criteria for digital images from digital X-ray apparatus described in [1][5][6][7], the following primary requirements to develop a new method for digitization of chest X-ray images have been defined:

- The method should make it possible to obtain images with resolution at least 600 dpi (5 LP/mm).
- Digitized images should be grayscale images with at least 12 bits depth (4096 gray levels).
- The method should make it possible to obtain images with at least 120 dB dynamic range.
- The method should control the final image quality, similar to the pre-processing in digital X-ray apparatus.
- The method does not generate medical artifacts in digitization images.
- The method should allow compensating the reduction of image quality due to changes in the X-ray plate resulting from improper storage.
- The method should allow the digitization of all sizes of radiographic plates while maintaining the same quality.

The idea of the method is to create the illumination model (the HDR-image) which has led to the grayscale image stored on the X-ray plate. This idea is implemented by capturing the sequence of images with different exposures

(these images are images with low dynamic range – LDR-images). Thus, the information about tissues and organs with different X-ray density would be obtained in great detail.

To achieve the above requirements a method for X-ray plates digitization based on a "photo-camera" type of scanner has been developed [10][14]. The main difference between those methods and the presented in the paper new one is in the way how the information in X-ray plates is extracted and in the quality of the digitalization X-ray images.

The method has the following main characteristics: digitalization of segments and bracketing over segmented image, remote calibration of the digital photo-sensor, stitching multiple images' segments and the HDR-image generation, pre- and post-processing of digital image.

The proposed new digitalization method uses the following steps to achieve its goal:

- Step 1. Photo-sensor calibration to reach the biggest possible dynamic range according to plate's quality.
- Step 2. Determining how many segments are needed to digitalize the processed X-ray plate.
- Step 3. Segment by segment digitalization of the X-ray plate following pre-defined scanning path and using bracketing.
- Step 4. Using segments stitching for simultaneous rendering of all the layers of the full image (captured with different exposures).
- Step 5. HDR image generation.
- Step 6. Image pre-processing and LDR-image generation.
- Step 7. Post-processing and rendering of the final digitalized X-ray image.

The goal of the first stage of the method is a selection of photo-optical characteristics of the photo-sensor. This allows obtaining the largest possible amount of information about the luminance recorded on the plate.

These characteristics are sensitivity of the photo-sensor, optical zoom, focal length, shutter speed and white balance. To determine the optimal values of these parameters a procedure has been developed which is based on a comparison of the average exposure of the image and the exposure of the image in the brightest and darkest areas (the aim is to have difference between the brightest and darkest areas not bigger than 4.0-4.5 EV). The procedure is iterated till an appropriate value of the average exposure and exposure range of change between the darkest and brightest areas is found. The same settings of the sensor system are used for the processing of all segments [8][9][10]. This increases the final image quality because it reduces medical artefacts.

The second stage of the method requires to determine the number of segments (rows and columns) which the image should be broken down into. The selected algorithm includes the size of the X-ray plate, the required final image resolution, image size according to the selected values for the focal length and optical zoom, and the degree of overlap for the particular class of images (underexposed plates, overexposed plates, plates with loss of brightness, etc.). For

chest X-ray plates, it was found that the best quality is obtained with an overlap between 35% and 45%, i.e., about 40%. Thus, for a plate size 43/40 cm a 5×4 matrix is used, while for 30/35 cm the matrix is 3×3.

The third stage is capturing plate segments using the bracketing procedure. In the initial versions of these photo-camera-based scanners, filming of the entire image was used, which determined the low resolution of the resulting image. The resolution of the resulting image is the CCD/CMOS sensor resolution. This limits the quality of the final image. The method uses technology based on digitalization of an X-ray plate as a set of ordered segments to meet the requirements for digitization of all sizes of X-ray plates and to achieve the necessary resolution of the final images (Figure 1).

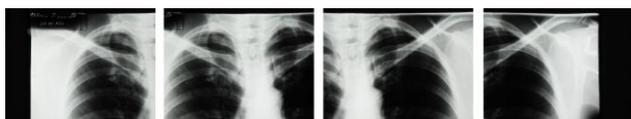


Figure 1. Digitalized X-ray - one row of image segments.

The method uses technology based on capturing of each segment by a bracketing procedure (our method uses 5 LDR-images with different exposures). To achieve the dynamic range value requirement all individual images are captured and stored with a 12-14 bits depth (when using images with 8-bits depth, the maximum value of the dynamic range does not exceed 60-65 dB); see Figure 2.



Figure 2. X-ray image bracketing with exposures 0 EV, -2 EV, +2 EV.

The fourth stage task is to generate an integral image from the segments - the image segments are stitched into one, and thus a total final image is obtained. The stitching procedure is done simultaneously for different exposure segments and this allows a physical and geometric homogeneity of the final images (one per selected exposure of image capturing) to be achieved. Of a particular importance for the quality of the processing at this stage are the settings of the photo-sensor and the capturing procedure of each plate segment. The reason for this is that lung X-rays have a great number of “looking similar” areas which frequently results in wrong stitching. To solve this problem a methodology for software stitching tool evaluation and selection was developed which can be used in the presented area of application (medical images) without generation of artifacts with diagnostic importance. The methodology includes 10 comparison parameters which allows to estimate the possibilities to work with sensor raw data, homogenization of luminosity between segments, working

with different overlapping, simultaneous stitching of layers with different exposures, etc.

The next stage is the generation of a luminance model for the X-ray plate. To achieve this goal a 32-bits HDR-image using the Tone Mapping Algorithm is generated. The selected exposure values for individual LDR-images allow the required final image quality to be obtained for all radiographic densities. The result of this stage is an image which is analogous to the raw data obtained from the X-ray digital sensor.

Digital image pre-processing is the 6th stage – this stage has tasks similar to those addressed at the pre-processing stage of the digital X-ray apparatus, i.e. various operations are performed to correct the quality of the digitalized image. Most often these operations include the level of detail adjustment, local and global contrast changes, structures sharpness selection, eliminating the ‘halo’ effect, dynamic range adjustment (Figure 3). At the final stage of processing, the HDR-image is converted to the 16 bits per channel grayscale LDR-image. This is the final image after X-ray plate digitalization.

The last stage is the post-processing of the final image – as an additional stage in our method we propose the possibility to use methods for digital post-processing of the displayed final image. In this case the radiologist selects different values for brightness, contrast, level-of-details – this additionally improves the quality of the digitalized images. This stage is not obligatory and can be replaced by any product for medical images post-processing.

The main problem when using HDRI-based technology to produce high quality medical images is the choice of the exposure values for LDR- images that will be used to create the HDR-image. The classic technique requires using 3 LDR-images in which the base image is chosen so that there is an optimal presentation of the scene objects. The additional exposures are made at ‘+2 EV’ and ‘-2 EV’, which makes it possible to reach improved level of details and contrast in the brightest and darkest areas [11]: 1 EV corresponding to a standard power-of-2 exposure step. Experiments demonstrated that for the purposes of chest X-ray plate digitization the presented above set of exposure values is not applicable. The reason is that the X-ray image does not have great homogeneity of the pixels color and intensity distribution in the entire range, because there are various well-defined radiographic densities, which lead to strictly defined grey levels. Therefore, the method is oriented to take 5 LDR- images with the following exposures: ‘0 EV’, ‘+1.67 EV’, ‘+2 EV’, ‘-1.5 EV’, ‘-2 EV’. In this way the quality of the HDR-image is a function of the correct photo-sensor calibration to create a base image (the image with 0 EV) – the goal of Stage 1.

IV. ANALYSIS OF THE RESULTS

The experiments with the proposed method for digitization of chest X-ray plates, validated by physicians with over 20 years’ experience from hospitals at the Medical

University of Sofia, have led to the following conclusions on the applicability of the method:

- The possibility to control the number of segments used to capture the plate, makes it possible to receive the digitized image with a resolution better than the grain of the plate. This allows the correction of the digitalized image which does not generate medical artifacts. The only problem is the increased digitalization time when the final image resolution is increased.
- The creation of the illumination model (the HDR-image) allows one, much more correctly, to choose the values for the different characteristics of the final image (dynamic range, contrast, sharpness, level of details, etc.). This significantly improves the final image quality compared to other digitization techniques.
- Classic X-ray plate scanners use constant exposure for the image capturing. In the case of images with a pronounced bimodal histogram this creates significant image readability problems. The proposed digitization method makes possible to avoid the appearance of this type of image histogram, due to the ability to manage the process of transformation from an HDR-image to the final LDR-image.
- In medical images with a small dynamic range, after digitalization, the image histogram has a narrow stretch and a very large peak in it. This creates serious problems for quality enhancement methods, which very often lead to the intrusion of medical artifacts. Examples of such images are underexposed images: they have small dynamic range and large peak in white area. The proposed digitalization method makes it possible to create images with a unimodal histogram with a normal (Gaussian) distribution of intensities.
- In overexposed X-ray images most often the histogram has a bimodal nature. The approach used in the proposed digitalization method allows to create an image with a unimodal (or similar in nature) histogram because the created illumination model (the HDR-image) makes it possible to minimize the peaks in the dark area (the user has control over the mapping process between the HDR-image and the final LDR-image). This significantly improves the image quality and the possibility for using automated methods of digital image processing.

Some results of the presented digitalization method are shown in Figure 4 and Figure 5.

V. CONCLUSION

The proposed X-ray plates digitalization method is highly adaptable depending on the condition and quality of the X-ray plate, and some specific needs. The possibilities to manage sensor settings and the presence of a pre-processing stage substantially improve the quality of digitalized images. Comparability of results for different types and different sizes of X-ray plates show that when a correct adjustment of

the digitalization system is set the captured images have higher quality, or at least similar to that captured by classical X-ray scanners. In several cases, the presented method has allowed to diagnose or exclude the occurrence of diseases that until now could not unambiguously be interpreted only using the original X-rays.

ACKNOWLEDGMENT

This work is funded partially by Bulgarian NSF under DO02/113 and DRNF02/3 projects.

REFERENCES

- [1] Frost and Sullivan Institute. "Growth Partnership Service: Medical Imaging", Frost & Sullivan's Medical Imaging Research and Consulting practice, March 2011, available from: <http://www.frost.com/prod/servlet/svcg.pag/HCIM>. last accessed 12.June.2014
- [2] R. Koenker, "Improved conspicuity of key X-ray findings using advanced postprocessing techniques: Clinical examples." *MedicaMundi*, 2005;49(3):11.
- [3] E. Krupinski et al., "Digital Radiography Image Quality: Image Processing and Display", *J Am Coll Radiol* 2007, 4:389-400.
- [4] M. Williams et al., "Digital Radiography Image Quality: Image Acquisition", *J Am Coll Radiol* 2007, 4:371-388
- [5] ICRU. "Medical Imaging - The assessment of image quality", ICRU report 54, International Commission on Radiation Units and Measurements, 1996.
- [6] EUR. "European guidelines on quality criteria for diagnostic radiographic images", Report EUR 16260 EN Luxembourg, Office of official publication of the European Communities; 1996.
- [7] ICRU. "Image quality in chest radiography", Report 70, Journal of the ICRU, Vol. 3 No.2; 2003.
- [8] V. N. Misale, S. Ravi and R. Narayan, "Digital Radiography Systems Techniques and Performance Evaluation for Space Applications", Proceedings of the National Seminar & Exhibition on Non-Destructive Evaluation, NDE 2009, December 10-12, 2009
- [9] B. Barbero and E. Ureta, "Comparative study of different digitization techniques and their accuracy", *Computer-Aided Design*, vol. 43, issue 2, Feb. 2011, pp. 188-206
- [10] P. Krogh, "Camera Scans – Using a Digital Camera as a Film Scanner", 2009, available from: <http://dpbestflow.org/camera/camera-scanning> [last accessed: 12.June.2014]
- [11] D. Nightingale. "Practical HDR: A complete guide to creating High Dynamic Range Images", 2nd ed., ISBN 978-0240821221, 2011
- [12] E. Reinhard, W. Heidrich, P. Debevec and S. Pattanaik. "High Dynamic Range Imaging: Acquisition, Display, and Image-Based Lighting", 2nd ed., Morgan Kaufmann, ISBN 978-0123749147, 2010
- [13] F. Banterle, A. Artusi, K. Debattista and A. Chalmers. "Advanced High dynamic Range Imaging: theory and practice". AK Peters/CRC Press, ISBN 978-156881-719-4, 2011
- [14] V. Gueorguiev and I. Ivanov. "Digital cameras as low-cost tools for telemedicine and e-health: opportunities and constraints". In proceeding of: 4th International Joint Conference on Biomedical Engineering Systems and Technologies (HEALTHINF2011); Rome, 2011, pp. 608-613
- [15] V. Gueorguiev, D. Georgieva, M. Nenova and I. Evgeniev. "Advancing in digitalized x-ray images post-processing". In proceeding of: eTELEMED 2013: The Fifth International

Conference on eHealth, Telemedicine, and Social Medicine, Nice, France, Feb - Mar 2013, pp. 234 – 239

[16] D. Georgieva, V. Gueorguiev and I. Evgeniev. "Problems in the digitalization of x-ray, ultrasonic and Doppler machine images". In proceeding of: 6th Annual International Conference on Computer Science and Education in Computer

Science 2010 (CSECS 2010), Fulda, Germany, June, 2010.

[17] IOP Institute of Physics. "X-ray imaging: Teaching Medical Physics", Lecture notes, 2012, url: http://www.iop.org/education/teacher/resources/teaching-medical-physics/xray/file_56282.pdf [last accessed: 12.June.2014]

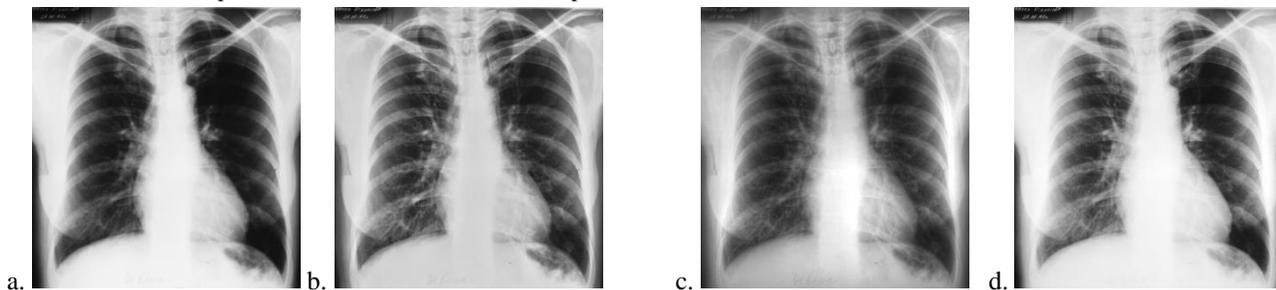


Figure 3. Images after different pre-processing operations: (a) the basic image; (b), (c), (d) corrected images.

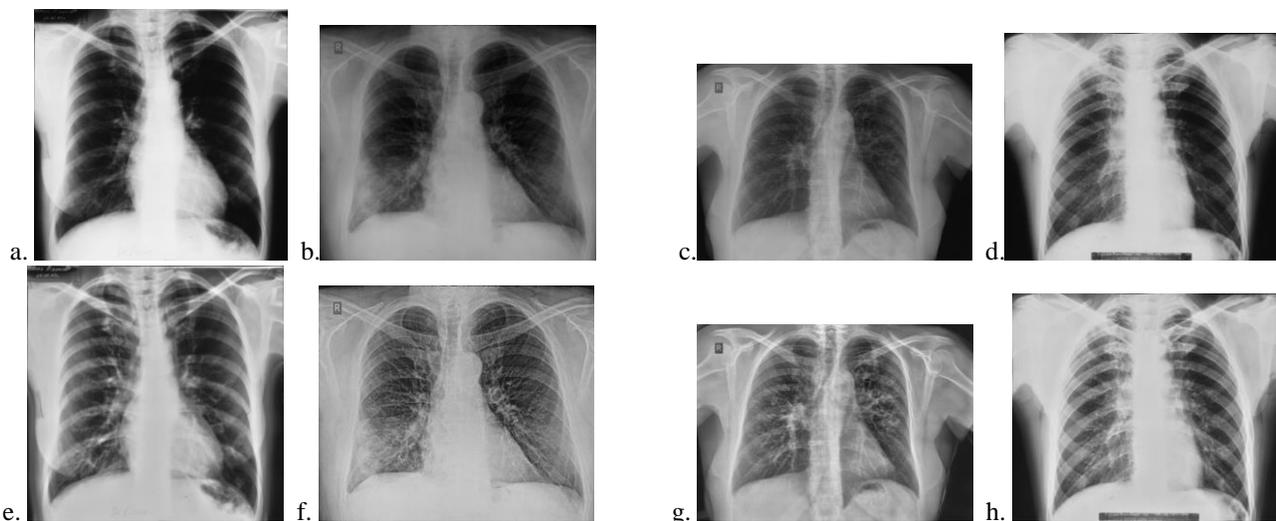


Figure 4. Comparison between classical digitalization method and presented HDR-based digitalization: (a)(b)(c)(d) digitalization by classical method; (e)(f)(g)(h) digitalization by the presented HDR-method.

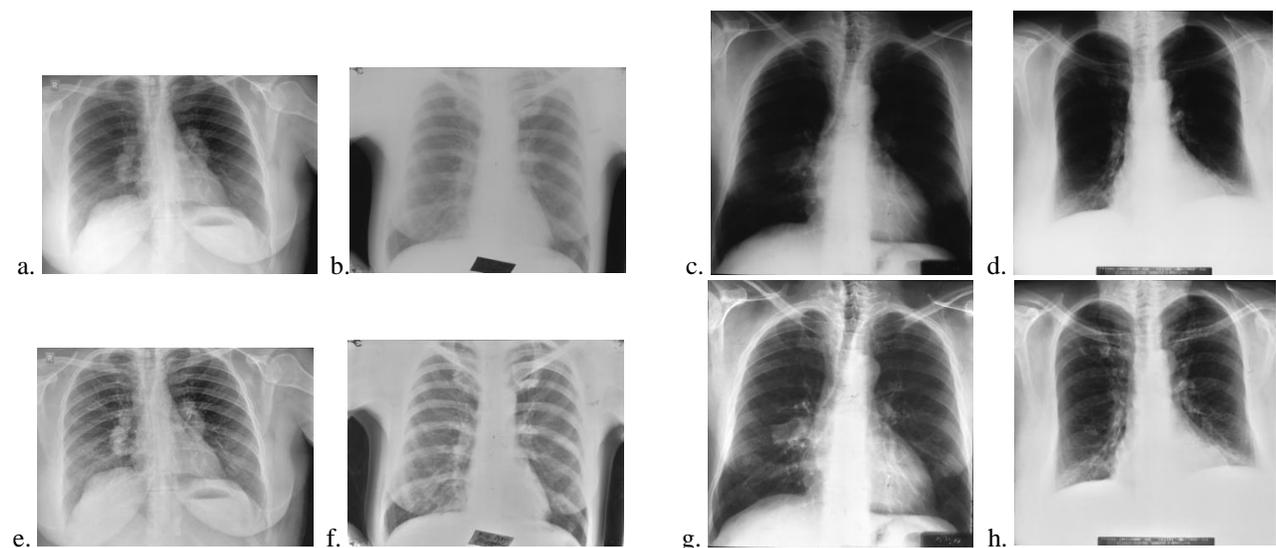


Figure 5. Comparison between classical digitalization method and presented HDR-based digitalization: (a)(b)(c)(d) digitalization by classical method; (e)(f)(g)(h) digitalization by the presented HDR-method.

A Future Strategy Towards Smoking Cessation: Persuasive Multimedia Application (PMA) in Strengthening Motivation towards Smoking Prevention and Cessation

Wan Ahmad Jaafar Wan Yahaya, Rosli Che Din, Munira Hashim
Centre for Instructional Technology & Multimedia,
Universiti Sains Malaysia, 11800 Penang, MALAYSIA
Emails: {wajwy@usm.my, roslichedin@gmail.com, niera_hashim@yahoo.com}

Abstract—Smoking cessation or successful quitting depends a lot on one of its identified crucial factors - motivation. The PRIME Theory of Motivation has listed five motivation domains in the human motivational system. These are Plans, Responses, Impulses, Motives and Evaluations. For the purpose of this study, Persuasive Multimedia Application (PMA) has been produced and used as a learning and persuasion approach through the use of Persuasive Technology. PMA has adopted a cause-and-effect principle from Persuasive Technology as a learning strategy at the macro-persuasion level, and Multimedia and Redundancy principles draw from Mayer's Multimedia Learning Principles as a design strategy at the micro-persuasion level. A total of 54 respondents have been selected and have undergone a 2x2 quasi-experimental research design experiment. Considering the limitations of this study, only three selected PRIME domains in the form of Plans, Evaluations and Motives were measured by using an instrument adapted from the PRIME questionnaires and later analyzed using IBM SPSS 20. The results of the study prove that the PMA developed by using the cause-and-effect principle, specifically one in the Multimedia and Redundancy mode (Mode B), has produced a significant impact on motivation towards smoking cessation, especially in terms of the evaluations domain.

Keywords-*Persuasive Technology; Captology; Persuasive Multimedia Application (PMA)*

I. INTRODUCTION

Teenagers or adolescents are defined as individuals in the 10 – 19 year age group according to the World Health Organization (WHO) and the Canadian Paediatric Society [1]. WHO [13] added that there are more than 1.1 billion adolescents worldwide, and 85% of them live in developing countries. Heikkinen et al. [4] stated that smoking is associated with other types of unhealthy behaviours such as alcohol consumption. Thus, all efforts to control smoking are worthwhile, especially when intervention programmers have not paid attention to smoking cessation among adolescents [4].

In the United States, tobacco use remains the leading cause of death, although its use is voluntary [12]. Research has proved that smokers, who quit, live longer than those who continue to smoke and those who receive intensive treatment receive a mortality benefit.

The article is structured as follow: Section 2 will discuss the related research. Section 3 will define and discuss the concept of a behaviour and motivation support system. Section 4 will discuss the methodology employed in the research. Section 5 will present the data analysis. Section 6 will discuss the

finding. Section 7 will discuss the research implications. Finally, section 8 will suggest the future research directions.

II. BACKGROUND TO THE PROBLEM

In their official website the World Health Organization (WHO) has also said that 80,000 and 100,000 children worldwide start smoking every day, and roughly half of them are from Asia [6]. About 50 teenagers in Malaysia below the age of 18 start smoking everyday according to a survey conducted by the Malaysia Ministry of Health (MOH) (2003) even after the 'Tak Nak' (Say No) campaign.

In 2003, the United States Center for Disease Control and Prevention (CDC) found that motivation and readiness to quit smoking are among predictors of successful quitting. They have also found from self-reports that 41% of current smokers (20.2 million) had tried to quit smoking for 1 or more days within the previous 12 months. Many smokers who try to quit cite a desire to improve their health as the main reason.

Parkinson et al. [8] also stated that beliefs about smoking are important predictors of smoking behaviour among youth. West [9] has also stated that human being's motive for doing something (including smoking) depends on his/her beliefs, or what he refers to as the 'Evaluations' domain in PRIME Theory.

Therefore, developing innovative and effective approaches to control tobacco use among youth, through both prevention and cessation strategies, remains a high public health priority [6]. Parkinson et al. [8] also suggested that anti-smoking media may be an important means of targeting beliefs about smoking among youth, especially when they often respond defensively to messages that threaten their lifestyle, attributes and prospects [5].

III. SIGNIFICANCE OF THE STUDY

Persuasive Technology is defined as any interactive computing system designed to change people's attitudes or behaviours [3]. Therefore, it has created a space for the development and the implementation of a Persuasive Multimedia Application which aims to increase motivation with regard to smoking prevention and cessation among teenagers.

Previous studies that have used this technology showed that Persuasive Technology is capable of changing people's attitudes or behaviour in terms of the expected attitudes or

behaviour. Hence, this study will produce a persuasive multimedia application that will contribute to the current efforts of the Malaysia Ministry of Health (MOH), the Malaysia Ministry of Education (MOE), the Malaysia Ministry of Youth and Sports and, especially, parents and teenage smokers themselves.

This PMA has been designed and developed based on Multimedia Learning Principles [7] and Persuasive Technology [3]. The finding will help to enlighten other researchers about which of the multimedia presentation elements (words, images or both) and Persuasive Principles work best in increasing teenagers' motivation with regard to smoking cessation, and then impacting on their smoking behaviour after gaining enough knowledge and motivation through persuasion.

IV. THEORETICAL FRAMEWORK

Two theoretical foundations of this study are the design and development of the PMA, which is based on Persuasive Technology [3], and Multimedia Learning Principles [2] and the use of PRIME Theory [10][11] to explain human motivational systems.

The theoretical foundations can be interpreted in terms of the following conceptual framework (Fig. 1):

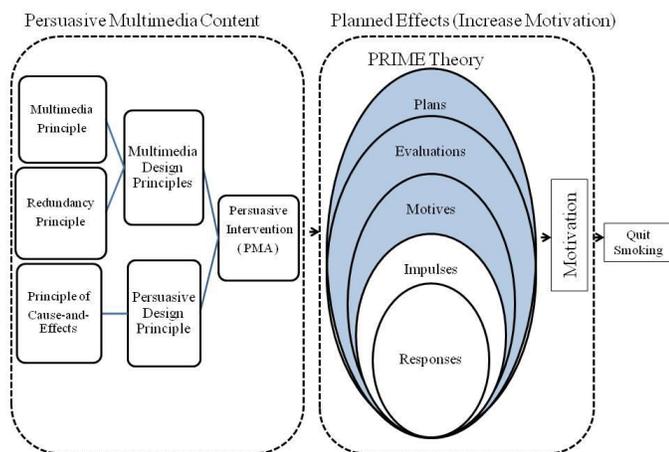


Figure 1. Conceptual Framework

Persuasive Multimedia Application (PMA) has been developed by using the principles in Persuasive Multimedia Content. In the Planned Effects (increase motivation), the motivation is called intrinsic motivation and it is based on the satisfactions of behaving "for its sake." This intrinsic motivation depends on what is known as internal environment in PRIME Theory [11].

V. LIMITATIONS OF THE STUDY

There are more principles related to Persuasive Technology and multimedia learning principles than can be dealt with in this study in order to maximize the full potential of Persuasive Technology. However, due to the limitations of the

timeframe, only one principle from Persuasive Technology (cause-and-effect), two from multimedia learning principles (Multimedia and Redundancy) and three domains of PRIME theory (Plans, Evaluations and Motives) are used in this study.

Finally, due to these limitations, this study could only focus on the proof of the persuasive multimedia model with the factors that foster intrinsic motivation based on three elements in PRIME Theory on the selected participants in the school's multimedia lab.

VI. METHODOLOGY

The main purpose of this study is to design and develop a persuasive multimedia application based on Persuasive Technology principles and Multimedia Learning Principles in order to increase teenagers' motivation in terms of smoking prevention and cessation in such a way as to enable them to quit smoking. The study also suggests an appropriate way to evaluate its effectiveness.

A. Method and design

It is suggested that the study employed a 2 x 2 quasi-experimental design in which two groups of participants will be tested twice using pre-test and post-test experiments with regard to a particular exposure to different modes of treatment as indicated by the following Table 1:

TABLE 1. RESEARCH DESIGN.

	Phase 1	Phase 2	Phase 3
Treatment 1 Group #1	Baseline motivation test (Pre-test) -using questionnaire adopted from PRIME theory	Persuasive courseware (PMA Mode A- Multimedia Principle) Treatment #1	Post motivation test (Post-test) -using questionnaire adopted from PRIME theory
Treatment 2 Group #2	Baseline motivation test (Pre-test) -using questionnaire adopted from PRIME theory	Persuasive courseware (PMA mode B- Redundancy Principle) Treatment #2	Post motivation test (Post-test) -using questionnaire adopted from PRIME theory

B. Participants

A total of 54 randomly selected participants were appointed to the experiment in which they were divided into two equal groups.

C. Instrument

- Adapting the PRIME Theory Questionnaire used in Smoking Cessation programme in the United Kingdom
- Persuasive Multimedia Application

D. Data Analysis and Results

The purposes of the analysis are to measure the effectiveness of Persuasive Multimedia Application on the teenager’s motivation towards smoking prevention and cessation, before and after the treatment. The scope for the analysis is based on the research hypotheses stated earlier in this study.

VII. DATA ANALYSIS

A. Combined effect of intervention and effects on modes of presentation

There is no significant difference between two multimedia principles on persuasive design principle (cause-and-effect) in two Persuasive Multimedia Applications in terms of increasing teenage motivation with regard to smoking prevention and cessation.

TABLE 2. TESTS OF BETWEEN-SUBJECTS EFFECTS. Dependent Variable: Combined smoking status post

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	30.036 ^a	48	.626	1.515	.345
Intercept	.734	1	.734	1.778	.240
Combined_smoking status_pra	1.230	1	1.230	2.978	.145
Combined_domain_post	21.507	47	.458	1.108	.513
Error	2.066	5	.413		
Total	586.609	54			
Corrected Total	32.102	53			

a. R Squared = .936 (Adjusted R Squared = .318)

Generally there was no significant effect of courseware on smoking status for both modes at F=1.108, p = 0.513 from the ANCOVA result after controlling for the effect of smoking status prior to the intervention. Hence H2 is rejected.

In terms of two different modes, group B in the redundancy mode showed a significant effect of courseware on smoking status at F=49.132, p = 0.004 from the ANOVA result.

TABLE 3. TESTS OF BETWEEN-SUBJECTS EFFECTS. Dependent Variable: B_Smoking Status Post

Source	Type III Sum of Squares	Df	Mean Square
Corrected Model	12.283 ^a	24	.512
Intercept	253.939	1	253.939
B_Domain_Post_B	12.283	24	.512
Error	.031	3	.010
Total	281.859	28	
Corrected Total	12.314	27	

a. R Squared = .997 (Adjusted R Squared = .977)

TABLE 4. TESTS OF BETWEEN-SUBJECTS EFFECTS. Dependent Variable: B_Smoking_Status_Post

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	12.283 ^a	24	.512	49.132	.004
Intercept	253.939	1	253.939	24378.128	.000
B_Domain_Post_B	12.283	24	.512	49.132	.004
Error	.031	3	.010		
Total	281.859	28			
Corrected Total	12.314	27			

a. R Squared = .997 (Adjusted R Squared = .977)

TABLE 5. TESTS OF BETWEEN-SUBJECTS EFFECTS. Dependent Variable: A_Smoking_Status_Post

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	16.463 ^a	23	.716	.526	.828
Intercept	280.585	1	280.585	206.144	.005
A_Domain_Post_A	16.463	23	.716	.526	.828
Error	2.722	2	1.361		
Total	304.750	26			
Corrected Total	19.185	25			

a. R Squared = .858 (Adjusted R Squared = -.774)

B. PRIME as a result of Persuasive Multimedia Application

Specifically, there is a significant difference at one domain (Evaluations) at F = 2.054, p = 0.038 as a result of PMA.

Domain Evaluations (Beliefs)

TABLE 6. TESTS OF BETWEEN-SUBJECTS EFFECTS. Dependent Variable: Combined_Smoking Status_Post

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	14.692 ^a	16	.918	1.951	.047
Intercept	2.726	1	2.726	5.793	.021
Combined_evaluation_pra	.948	1	.948	2.014	.164
Combined_evaluation_post	14.498	15	.967	2.054	.038
Error	17.410	37	.471		
Total	586.609	54			
Corrected Total	32.102	53			

VIII. DISCUSSION AND FINDINGS

This study adapted PRIME Theory by West [9], in order to simulate the three different domains under PRIME Theory in terms of smoking prevention and cessation. With the increase in the three preliminary domains of motivation, there will an increase in one’s motivation level which will promote smoking prevention and cessation.

Two types of Persuasive Multimedia Application (PMA) were developed as an intervention strategy to promote the three domains of motivation under PRIME Theory. The Persuasive Multimedia Application is developed based on Persuasive Technology Principle as learning strategy and Multimedia Learning Principles (Multimedia and

Redundancy) as a design strategy. The effectiveness of the Persuasive Multimedia Application (PMA) is tested using PRIME questionnaires developed by West [10].

A. Combined effect of intervention and effects according to modes of presentation

The overall analysis with regard to the second hypothesis also shows that, in general, there is no significant effect of courseware on smoking status for both modes at $F=1.108$, $p = 0.513$ from the ANCOVA result after controlling for the effect of smoking status prior to the intervention.

However, group B in the redundancy mode shows a significant effect in terms of courseware on smoking status at $F=49.132$, $p = 0.004$ from the ANOVA result, compared to group A in the Multimedia mode, where the result is $F=0.526$, $p = 0.828$. These results suggest that the redundancy mode related to group B had a more positive result in increasing teenage motivation with regard to smoking prevention and cessation, based on prior smoking status, compared to the multimedia mode.

Hence, despite the results of the overall analysis, the findings with regard to group B confirmed and were parallel with those of Toh, Waddah and Wan Ahmad Jaafar [11], where there are positive effects of redundancy principle on learning. One possible explanation is that the narration used in the redundancy mode in this study might have reduced the split-attention effect and learners' cognitive load, which then promoted their motivation.

B. PMA supports PRIME Theory

The overall results show that there is no significant effect of Persuasive Multimedia Application on three different domains of PRIME Theory in increasing teenage motivation towards smoking prevention and cessation at $F = 1.868$, $p = 0.252$ from the ANCOVA result in general. Specifically, however, there is a significant difference in terms of one domain (Evaluations) at $F = 2.054$, $p = 0.038$.

This finding supports the PRIME Theory that the internal environment and the stimulation of the human motivational system depend on the external environment. In this study, Persuasive Multimedia Application (PMA) acts as the external environment or stimuli to stimulate them. The results show that one domain of the human motivational system - the Evaluations domain - shows a significant difference after the treatment. This result is vital in strengthening teenage motivation towards smoking prevention and cessation. As West [10] stated, human motives in doing something (including smoking) depend on their beliefs or what he referred to as 'Evaluations' in PRIME Theory.

As the Evaluations domain is one part of the human motivational system, the results of the analysis with regard to the evaluations domain shows the effects of an interactive programme (Persuasive Multimedia Application) which in general is similar to the work of Fogg [3] in which an interactive programme can help someone to quit smoking when the urge (motivation) is strong.

The results of the analysis with regard to the evaluations domain also proved the belief of Parkinson et al. [8] that anti-smoking media may be an important means of targeting beliefs about smoking among youth. "Beliefs" is the same as the Evaluations domain in PRIME Theory. Therefore, findings with regard to this domain are vital for future research.

IX. IMPLICATIONS OF THE STUDY

The results of this study have confirmed that Persuasive Multimedia Application developed by using the principle of cause-and-effect as a persuasive design principle has stimulated human motivational system at macro level through stimulation.

On the other hand, the Redundancy principle as a multimedia learning principle, has shown the significant impact of stimulating the Evaluations domain in PRIME theory in terms of the human motivational system at micro-level.

Hence, in order to ensure that persuasive messages are successfully delivered through a multimedia application in terms of stimulating the human motivational domains, and thus strengthening human motivation levels in terms of the targeted behaviour, the following design guidelines may be considered:

- Persuasive Multimedia Application may be used as a medium for stimulating and strengthening human motivation, where the focus is on the cause-and-effect principle as the main learning strategy.
- The redundancy principle should be the main design strategy in delivering the persuasive message, especially when teenagers are the target group.

Based on the above design guidelines, a few suggestions have been made for future research.

X. SUGGESTIONS FOR FUTURE RESEARCH

Due to the study limitations, some areas were not covered in this study. The following are the areas that need further research based on the findings and the literature on which this study was based:

- A combination of persuasive principles with an integrative theory (CMOB: The Behaviour System and PRIME Theory of motivation) to provide a systematic basis for designing a Persuasive Multimedia Application and developing behaviour change techniques in order to elevate and strengthen the individual's motivation which will lead to smoking cessation.
- A combination of other persuasive principles in designing and developing a Persuasive Multimedia Application to maximize teenage learning.

- The effects of Persuasive Multimedia Application in elevating and strengthening the five domains of human motivational system according to PRIME Theory by using mobile persuasion strategy.

Findings, discussions, implication and suggestion for future research have led to the following conclusion.

XI. CONCLUSION

Smoking has been identified as one of the major problems in Malaysia. The literature review has revealed that motivation is closely connected with persuasion. Therefore, this research has added a new insight in terms of motivation with regard to the field of Persuasive Technology.

Persuasive Technology has been used in many fields of study including education and health, where one of the ultimate aims is to change people's attitudes or behaviour. Researchers have applied and tested different models and principles of design and used a variety of approaches in their studies, with various purposes and target audiences. Most of their attempts have produced significant results.

The Persuasive Multimedia Application (PMA) used in this study were designed and developed by integrating Persuasive Technology and PRIME Theory, as these are firmly believed to be able to elevate and strengthen teenagers' motivation with regard to smoking prevention and cessation.

Stimulating and strengthening human motivation levels is a fundamental and also a vital step in terms of the ultimate goal which is to change people's attitudes or behaviour. In this case, we are interested in smoking cessation. This Persuasive Multimedia Application thus is a preliminary intervention aimed at stimulating and strengthening motivation in terms of smoking cessation.

West [10] stated that recovery occurs when an individual is no longer experiences powerful motivations to engage in an addictive activity to an extent that is harmful. Therefore, developing an intervention with regard to reducing an individual's powerful motivation towards smoking is fundamental. This can be done by stimulating and strengthening the human motivational system.

Based on the findings from the study, specifically both Persuasive Multimedia Application (PMA) that uses the cause-and-effect Principle derived from Persuasive Technology [3] as a learning strategy are confirmed as having a significant impact on smoking status treatment.

The findings also confirm that a PMA that uses the Redundancy Principle from Cognitive Theory of Multimedia Learning [7] as a design strategy, will have a significant impact on the Evaluations domain. Therefore, a PMA that uses the Redundancy Principle is proven to be an effective tool in elevating and strengthening teenagers' motivation towards smoking prevention and cessation among the two multimedia principles. It is also a proof that Persuasive Technology may provide the right kind of encouragement to help a person quit smoking [3].

REFERENCES

- [1] Canadian Paediatric Society, *Journal List Paediatric Child Health*, 2003, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2794325/>, [retrieved: 9 February 2013].
- [2] R. C. Clark, and R. E. Mayer, *E-learning and the science of instruction: Proven Guidelines for consumers and designers of Multimedia Learning* (2nd ed.). San Francisco: Jossey-Bass, 2008.
- [3] B. J. Fogg, *Persuasive Technology: Using Computers to Change What We Think and Do*: Morgan Kauffmann Publishers, 2003.
- [4] A. M., Heikkinen, U. Broms, J. Pitkaniemi, M. Koskenvuo, and J. Meurman, *Key Factors in Smoking Cessation Intervention Among 15-16-Year-Old*, 2009. <http://www.tandfonline.com/doi/full/10.1080/08964280903232035>, [retrieved: 3 January 2013].
- [5] Institute of Medicine, *Growing up tobacco free: preventing nicotine addiction in children and youth*. Washington DC: National Academy Press, 1994.
- [6] W. M. P. Klein, and P. R. Harris, Self-Affirmation Enhances Attentional Bias Towards Threatening Components of Persuasive Message in *Research Report of Psychological Science*, vol. 20, no. 12, 2009.
- [7] C. L. Lee, *NHGP Smoking Cessation Program for Staff* (2003-2005), National Healthcare Group Polyclinics, Singapore, 2005.
- [8] R. E. Mayer, *Multimedia learning*. New York: Cambridge University Press, 2001.
- [9] C. M. Parkinson, D. Hammond, G. T. Fong, R. Borland, O. Maizurah, B. Sirirassamee, A. Rahmat, P. Driezen, and M. Thompson, *Smoking Beliefs and Behavior Among Youth in Malaysia and Thailand*, 2009. [http://davidhammond.ca/Old%20Website/Publication%20new/ITC%20SEA%20Beliefs%20Paper%20\(2009\).pdf](http://davidhammond.ca/Old%20Website/Publication%20new/ITC%20SEA%20Beliefs%20Paper%20(2009).pdf), [retrieved: 3 January 2013].
- [10] R. West, (2006a): *PRIME Theory of Motivation and its application to addiction* in SSA Annual Conference, 2006a, <http://www.primetheory.com>, [retrieved: 3 January 2013].
- [11] R. West, (2006b): *PRIME Theory of Motivation and its application to addiction*, <http://www.primetheory.com/downloadfile.php?filename=slides/Fact%20anmd%20theory%20in%20recovery%20from%20addiction.ppt>, [retrieved: 3 January 2013].
- [12] S. C. Toh, A. S. M. Waddah, & W. Y. Wan Ahmad Jaafar, (2010). Redundancy effect in multimedia learning: A closer look. In C.H. Steel, M.J. Keppell, P. Gerbic & S. Housego (Eds.), *Curriculum, Technology & Transformation For An Unknown Future*. Proceedings Ascilite Sydney 2010 (pp.988-998).
- [13] World Health Organization (WHO): *Orientation Programme on Adolescent Health for Health-care providers: Module B - Definitions Of The Term "Adolescence" And Of The Age Groups "Young People", "Adolescents" And "Youth"*, http://whqlibdoc.who.int/publications/2006/9241591269_Handout_eng.pdf, [retrieved: 26 December 2012].

An Objective Program for the Evaluation of Medical Equipment for Updates and Maintenance

Mona Aridi, Bassam Hussein, Mohamad Hajj-Hassan, Hassan M. Khachfe
Lebanese International University

Beirut, Lebanon

{mona.aridi@gmail.com}

{bassam.hussein, mohamad.hajjhassan, hassan.khachfe}@liu.edu.lb

Abstract — Medical equipment contribute to the quality of healthcare services on several levels. They play a key role in the diagnosis, the treatment, and the rehabilitation of the medical impairment and diseases. However, as any operating machine, medical equipment would have a definite lifespan that expires after a period of time. Theoretically, Taylor K. specified ten years as the lifespan of medical equipment. In fact, the status of the medical equipment defines its age. This status should be addressed according to a list of criteria that evaluate the efficiency and the performance of these equipment. The purpose of this study is to develop a well-designed plan for evaluating medical equipment. According to this evaluation, we can rank the equipment that should be replaced in the descending order of urgency taking into account many criteria and sub-criteria.

Keywords-*efficiency; healthcare; lifespan; medical equipment; performance.*

I. LITERATURE REVIEW

Assessment of medical equipment is increasingly becoming the concern of healthcare institutions. Many companies concentrated their studies on the evaluation of medical technology and the investigation of their accidents. In the early 1990s, the world raised the attention to the device-related activities and many regional offices were opened all over Europe, the Middle East, and Asia Pacific [1]. Moreover, the International Medical Device Regulators Forum (IMDRF) discussed the future directions in medical device regulatory harmonization [2]. Furthermore, the International Organization for Standards (ISO) defined ISO 13485 as a standard for assessing and maintaining the efficacy of medical equipment. It deals with the specifications of medical technology to meet healthcare requirements for healthier outcomes [3]. In addition, the US Food and Drug Administration (FDA) generated a Device Evaluation Intern Program (DEIP) to monitor the efficiency, safety, and degree of risk to public health of the medical equipment [4].

A. Kirisits and W. K. Redekop highlighted the economic evaluation as a critical key point that stands behind the decision making for an equipment-upgrading program [5]. The clinical investigation of medical devices in Europe

focuses on outlining the risks that may threaten both the patient and the staff [6]. However, among all the calls regarding the evaluation of medical equipment, a study done by Sharareh Taghipour in 2011 assigned six main criteria in which some of them are branched into sub-criteria [7]. Sharareh focused on the recalls and hazard alerts that may occur for medical equipment. Moreover, concerning the risks, a great deal of attention is given to the failure frequency, the possible redetect of the risk, and the failure consequences, where we investigated the safety and environment effect of the device.

On the other hand, Sharareh raised the attention to the operational and the non-operational consequences of a failure, to inspect the cost of repair. This inspection investigates the ‘manpower’ and the ‘spare parts’ costs to fix a defect. Besides, the Canadian study boosted the attention to the out of service periods and the number of patients waiting due to those failures, which is defined as the downtime of the device.

Here, a new evaluation technique, similar to the Canadian one, which will be highlighted later in the paper, is proposed but with less required data. In our model, we tried to make the investigation simple and direct so we focused on the function and the age of the medical equipment, as well as we focused on the mission criticality, the risks, and the maintenance requirements. Actually, collecting data for each criterion is very hard and requires a long questionnaire, so we designed a checklist questionnaire to gather the required data about each equipment. As a case study, we applied this model on a Lebanese public hospital and we came back with a list of equipment that should be replaced after a period of time as defined by the hospital.

In this paper, we are going to propose the methodology of the study in the “Proposed Methodology” paragraph. Then we are going to show the way to derive the weights and the intensities of the tested criteria in the “Parameters” Section. After that, we are going to present the missions to accomplish the assessment plan through the “Mission” section. In the “Evaluation and Discussion” section, we will be analyzing the obtained results and make a decision accordingly. This will be followed by “Case Study” to test

the validity of the presented technique. Finally, we will end up with a conclusion and our further expectations through the “Conclusion”.

II. PROPOSED METHODOLOGY

Medical devices play a significant role in providing healthcare as they affect the patient and the care providers directly. Besides, the design of the medical equipment gives a share in the safety of the environment [8]. The excessive use of the medical equipment is directly proportional to its performance with time, which will shorten its expected lifespan. The clinical evaluation of medical technology should be based on a comprehensive analysis that covers relevant criteria and parameters to appraise the efficiency of the equipment.

This paper proposes a model to evaluate the medical equipment according to measurable criteria and quantitative parameters that identify the time after which this equipment should be replaced. To start, we are going to identify some main criteria in which some of them are branched into sub-criteria. To make our work measurable, we assigned each criterion and sub-criterion to a specific weight that defines its criticality.

Many methods can be used to appraise and weight clinical data. In our study, we take into account five main criteria in which some of them are divided into sub-criteria. Each criterion has a certain weight that specifies its weight in the study. Moreover, each criterion is limited to a certain range of choices, where every choice is assigned to certain intensity.

After defining the grades and intensities for all criteria, the model will be ready for use to assess the devices. To compute the final score, we need to calculate the total score that is the summation of the product of intensities and weights for each criterion. After that, we should calculate the Normalized Score Value that indicates the relative importance of each device in comparison with other devices, from which we generated the Transformed Score Value. The transformed score value is the value that allows us to rank the medical device according to its importance.

III. PARAMETERS

For a measurable reliable ranking for the medical devices, we should introduce some grades known as intensities and weights for each criterion and sub-criterion. The grades may encounter several classes for one criterion. For example, the maintenance requirements of a device may be high, medium, or low. The definition of each class differs from one hospital to another depending on the decision makers at each hospital. Consequently, the term ‘low’ for maintenance requirements differs from hospital to another.

If the criterion of a device contributes with its maximum capacity to the upper-level of this criterion, then its intensity should record a value of 1.

According to Sharareh, the intensities and the weights are obtained from a pairwise comparison matrix of qualitative grades, which is built using expert opinion [7].

The weight of each grade is obtained using Equation 1:

$$v_i = \frac{(\prod_{j=1}^5 a_{ij})^{\frac{1}{5}}}{\sum_{i=1}^5 (\prod_{j=1}^5 a_{ij})^{\frac{1}{5}}} \quad i=1, \dots, 5, \quad j=1, \dots, 5 \quad (\text{Equation 1})$$

The intensity of each grade is obtained using Equation 2:

$$\text{Intensity} = \frac{v_i}{\max(v_i)} \quad i=1, \dots, 5, \quad (\text{Equation 2})$$

Table I. PAIRWISE COMPARISON MATRIX FOR THE GRADE OF CRITERION 'FUNCTION'.

	Life saving	Therapeutic	Diagnostic	Analytic	Misc.
Life saving	1.00	5.00	6.00	8.00	9.00
Therapeutic	0.20	1.00	1.60	1.40	1.80
Diagnostic	0.17	0.63	1.00	1.25	1.50
Analytic	0.13	0.71	0.80	1.00	1.29
Misc.	0.11	0.56	0.67	0.78	1.00

Table I shows the pairwise comparison matrix for the grades of criterion ‘Function’ as assigned by expert opinion. Using above table and formulas, we can calculate the intensities and the weight for the criterion ‘Function’. We listed the results in Table II, using the Equations 3 and 4:

$$\text{where } a = (\prod_{j=1}^5 a_{ij}) \quad (\text{Equation 3})$$

$$\text{and } b = (\prod_{j=1}^5 a_{ij})^{\frac{1}{5}} \quad (\text{Equation 4})$$

Table II. CALCULATING THE INTENSITIES OF THE CRITERION 'FUNCTION'.

	a	b	v _i	Intensity
Life saving	2160.00	4.64	0.62	1.00
Therapeutic	0.81	0.96	0.13	0.21
Diagnostic	0.20	0.72	0.10	0.16
Analytic	0.09	0.62	0.08	0.13
Miscellaneous	0.03	0.50	0.07	0.11
$\sum_{i=1}^5 b = 7.45$				

In our model, we discarded the sixth criterion, which I “Recalls and Hazards” from the study as it is not available in the hospital where the study was done. We distributed 0.16, the weight of recalls and hazards, on the other criteria by adding 0.032 on each of the five criteria. For example, the weight of the criterion “Function” is 0.45. After adding 0.032 it becomes 0.482.

IV. MISSIONS

Assessment of medical equipment requires five consecutive missions where each one deals with a criterion. The core of each mission is gathering data. Before going through any of the missions, we made up an identity card for each equipment by filling up its name, its serial number, its

brand, and its manufacturer. This information will not affect our study, but the aim is rather to identify each equipment to make sure that there is no overlapping in case the equipment is shared among the units and departments.

The intensities are obtained from a pairwise comparison of grades; experts construct these grades

First Mission: In the first mission, we classified the function of each medical equipment into five categories: lifesaving, therapeutic, diagnostic, analytic, and miscellaneous according to the classification developed by Fennigkoh, Smith, and Dhillion [9]. The weight of the function and the intensity of each category are shown in Table III.

Table III: THE INTENSITIES OF THE FUNCTION OF THE EQUIPMENT.

Function (0.482)				
Life saving	Therap	Diagnostic	Analytic	Miscellaneous
1.00	0.21	0.16	0.13	0.11

Second Mission: This mission accomplishes the second criterion; mission criticality of weight (0.132) is divided into two sub-criteria: the utilization and the availability of alternative devices, as shown in Figure 1.

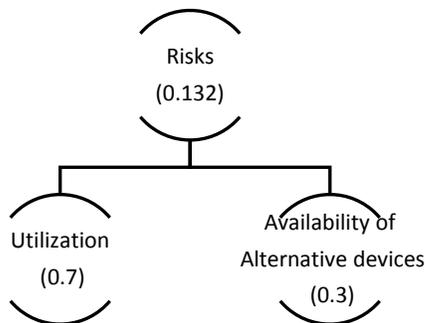


Figure 1. Hierarchy for mission criticality.

The usage of the device and its back-up devices identify the load of work on that device. Moreover, using the equipment excessively will increase the failure on the equipment [10]. In the first sub-criterion, utilization of a device is the total hours the device is used on average in a hospital (the unit can be defined as hours per day or days per week or weeks per year). In our proposed model, we considered the ‘average hours a device is used per week’ for the utilization criterion divided into three classes as shown in Table IV.

Table IV. THE WEIGHT AND INTENSITIES OF THE USAGE OF MEDICAL EQUIPMENT.

Usage hour/week (0.70)		
24≤	12≤x<24	<12
1.00	0.34	0.15

On the other hand, the availability of alternatives affects the mission criticality as it represents the number of similar or backup devices for one equipment. However, as the number of similar devices at hand becomes fewer because of lack of backup of the medical equipment the risks on that

equipment will increase. Furthermore, having several similar devices with low demand may also harm the device by affecting its performance from one side and by costing the hospital regular preventive maintenance from the other side. The weight and the intensities of the availability of alternatives are shown in Table V.

Table V. THE WEIGHT AND THE INTENSITIES OF THE ALTERNATIVES.

Alternatives (0.30)		
≤1	1 < x ≤4	>4
1.00	0.34	0.20

Third Mission: The third mission deals with the third criterion, which is the age of the equipment. The age of the medical device is based on the actual age of a device and its predictable life span. In general, 10 years is the average life span for a medical device. The equipment are divided into five categories according to the actual age of the equipment divided by the life span as shown in Table VI. As the ratio approaches 1, the equipment is considered as old otherwise, it is considered to be new as the ratio approaches zero. The age ratio is expressed in equation 5:

$$Age\ Ratio = \frac{Actual\ Age}{Life\ Span} \quad (Equation\ 5)$$

Table VI. THE WIGHT AND THE INTENSITIES OF THE AGE OF THE MEDICAL EQUIPMENT.

Age (0.092)				
>1	0.75 < x ≤1	0.5 < x ≤0.75	0.25 < x ≤0.5	0 ≤ x ≤0.25
1.00	0.67	0.43	0.17	0.12

Fourth Mission: The fourth mission addresses the fourth criterion, which is the risk of a device of weight (0.192). In a patient-centric environment, managing risk is the top priority that occupies a worthy space under the umbrella of the healthcare [11]. The risk of a device is the summation of all risks threatening patients. These risks can be estimated from the actual failures, which have occurred in that device, are shown in the figure below. Figure 2, shows the three sub-criteria of risks. The consequences associated to the risks of a device are assigned by the failure frequency, the detectability, and the failure consequences should be extracted or estimated from data history and device maintenance archive [12].

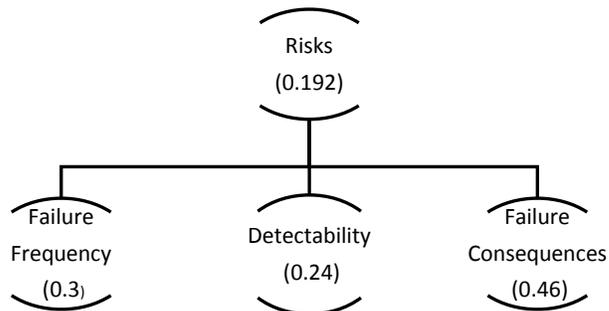


Figure 2. Hierarchy for risks on the medical equipment.

The frequency of failure tells whether the failure is occurring frequently or not. For that, we considered four levels for the frequency of failure shown in Table VII. If the failure is frequent, it means that the failure is likely to occur (several occurrences in 1 year). If the failure is occasional, it means that it probably will occur (several occurrences in 1 to 2 years). If it is uncommon, it means that it is possible to occur (one occurrence in 2 to 5 years). If it is remote, it means that it is unlikely to occur (one occurrence in 5 to 10 years).

Table VII. THE WEIGHT AND INTENSITIES OF THE FREQUENCY OF FAILURE.

Frequency of Failure (0.3)			
Frequent	Occasional	Uncommon	Remote
1.00	0.33	0.20	0.15

Failure detectability is the ability to detect a failure when it occurs. This is the most important criteria to assess harm [11]. We can detect the failure at many different levels. In our model, we used four levels of detectability. The failure maybe detected by error; that is when the equipment stops working, by inspection during the regular preventive maintenance rounds, it might be visible by naked eye or it can be detected by self-announcement, as summarized below in Table VIII:

Table VIII. THE WEIGHT AND INTENSITIES OF THE DETECTABILITY.

Detectability (0.24)			
Error	Inspection	Visible	Self-announcement
1.00	0.33	0.20	0.13

The failure consequences of weight (0.46) deal with the safety and the environment where we discuss the effect of the failure on the patient and the staff [13]. The failure of the medical equipment may harm the patient at different levels. It may cause death in extreme cases, injury in which it may disable the patient, inappropriate therapy, misdiagnosis, which makes the situation worse or the failure, which may cause a delay in the treatment. Finally, in some other situations, it may cause nothing. The intensities of those failures are summarized in Table IX.

Table IX. THE WEIGHT AND INTENSITIES OF THE FAILURE CONSEQUENCES.

Failure Consequences (0.46)				
Death	Injury	Inapp. Therapy or misdiagnosis	Delay in treatment or diagnosis	Non
1.00	0.34	0.21	0.14	0.09

The risk value can then be estimated as a function of frequency, consequence, and detectability for each failure mode. As a result, the risk of the device is the total risk of all its failure modes.

Fifth Mission: The last criterion, which is the fifth one where we studied the maintenance requirement for every medical equipment, is covered in the fifth mission. The availability of the medical equipment should be based on maintenance history and the maintenance requirements [14].

According to Fennigkoh and Smith [15], equipment that is predominantly mechanical, pneumatic, or fluidic often requires the most expensive maintenance. A device is considered to have an average maintenance requirement if it requires only performance verification and safety testing. Equipment that receives only visual inspection, a basic performance check, and safety testing is classified as having minimal maintenance requirements. We defined each of these classes as high, medium, and low with their corresponding intensities as shown in Table X.

Table X. THE WEIGHT AND INTENSITIES OF THE MAINTENANCE REQUIREMENTS.

Maintenance Requirements (0.102)		
High	Medium	Low
1.00	0.50	0.17

Identifying the main and the sub-criteria of each equipment allows us to determine their relative importance according to their goal or their upper level criterion using Saaty’s eigenvector technique—a mathematical technique that assigns a total score value for each medical device under study. This technique is used in multi-criteria decision-making missions [16]. This total score is generated from the weights and the intensities of those medical devices from the matrix of criteria and sub-criteria observed [17], [18]. Figure 3, show a schematic diagram of the main, and sub criteria of the evaluation test.

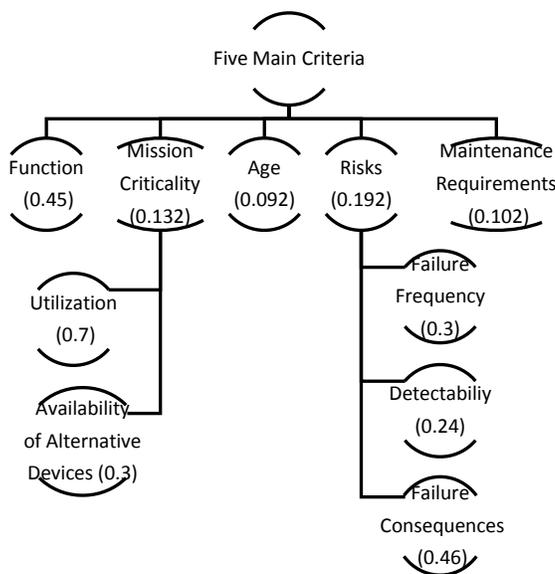


Figure 3. Hierarchy for the five main criteria.

V. EVALUATION AND DISCUSSION

After filling the above questionnaire for each equipment, we can compute the scores using the assigned weights and intensities. The total score of each equipment is the summation of the weight × intensity for the five criteria (Equation 6).

$$Total\ Score = \sum_{j=1}^5 W_j S_{ij} \quad (\text{Equation 6})$$

$$Total\ Score = w_{function} \times i_{function} + w_{age} \times i_{age} + w_{mission\ criticality} \times [w_{usage} \times i_{usage} + w_{back-up} \times i_{back-up}] + w_{risks} \times [w_{failure\ consequences} \times i_{failure\ consequences} + w_{detectability} \times i_{detectability} + w_{frequency} \times i_{frequency}] + w_{maintenance\ requirements} \times i_{maintenance\ requirements}$$

Where “w” is the weight of each criterion “j” = 1, 2 ... 5 and “i” is the intensity of each class.

At this stage, we listed the total score for the equipment in descending order from the highest score to the lowest score. This rank helps us in calculating the normalized score value that indicates the relative criticality of a device compared to other devices. Therefore, the Normalized Score Value of each equipment (Equation 7):

$$NSV = \frac{Total\ score\ of\ each\ device}{Maximum\ total\ score} \quad (\text{Equation 7})$$

The aim of this study is to prioritize the medical devices according to their criticality. To do so, we have to calculate the transformed score value from the above procedure, which can be used for prioritizing or ranking of devices. The Transformed Score Value depends on the Normalized Score Value of each device involved in the model and on the minimum and the maximum scores that could be achieved. The transformed score value plays an important role in assessing the medical equipment according to a percentage. In our proposed model, devices can have a total score between (0.1257592, 1.0) where score 1.0 is for a device, which gets the highest intensity when assessed against every single criterion and 0.1257592 is obtained when the device gets the lowest intensity from all criteria. The calculation is shown below using equation 6:

$$\begin{aligned} & \text{Minimum Total Score Value} \\ & = (0.482 \times 0.11) \\ & + 0.132[(0.7 \times 0.15) \\ & + (0.3 \times 0.2)] + (0.092 \times 0.12) \\ & + 0.192[(0.3 \times 0.15) \\ & + (0.24 \times 0.13) + (0.46 \times 0.09) \\ & + (0.102 \times 0.17) = 0.1257592 \end{aligned}$$

However, the total scores of devices can be used as absolute measurements for classification. The ranking of the medical devices can be done according to the normalized score value, however, for a better reading we can express the results in percentage, and so the normalized score value can then be mapped to (0, 100%) Transformed Score Value using the following equation:

$$TSV = \frac{Score\ value - Minimum}{Maximum - Minimum} \times 100 \quad (\text{Equation 8})$$

$$\begin{aligned} & = \frac{Score\ value - 0.1257592}{1.00 - 0.1257592} \times 100 \\ & = \frac{Score\ value - 0.1257592}{0.87311} \times 100 \end{aligned}$$

The whole process is summarized in Table XI:

Table XI. THE TRANSFORMED SCORE VALUE.

Eq up.	Total Score	NSV	TSV
↓	Descending order	$\frac{(Total\ score\ of\ each\ device)}{max.\ Total\ score}$	$\frac{Score\ value - minimum}{maximum - minimum} \times 100$
			$\frac{Score\ value - 0.1257592}{1.00 - 0.1257592} \times 100$
			$\frac{Score\ value - 0.1257592}{0.87311} \times 100$

The obtained list of medical equipment can be classified into many categories according to the prioritizing plan of the hospital, which is related to the budget assigned by the decision makers. In our study, the criticality of a device is classified into three categories in which a transformed score value should belong. The first category is for those, which should be replaced urgently. The second one for those, which should be replaced after a year and a half (their replacement can be limited to a deadline defined by the hospital according to their budget). The third one is for those, which are still functioning normally and can work for several years ahead. Using the transformed score value we can sort the medical equipment according to their urgency using Table XII.

Table XII. THE CRITICALITY OF A DEVICE FROM THE TRANSFORMED SCORE VALUE.

Criticality class	Transformed Score Value	Maintenance Strategy
High	65% < TSV ≤ 100%	To be changed urgently
Medium	50% < TSV ≤ 65%	To be changed after a year and a half
Low	0% ≤ TSV ≤ 50%	To be changed after three years

Using the above study, we can easily rank the equipment of a hospital in the order of their urgent need for replacement. If the equipment’s score is between 65% and 100%, it means that the equipment should be replaced immediately. If its score ranges between 50% and 65%, then the equipment should be replaced after a while. Finally, if its score is less than 50%, this means that the replacement of the equipment does not need to happen in the near future. Keep

in mind that we can consider other intervals to sort the tested devices according to the hospital's financial contribution.

VI. CASE STUDY

In this section, we are going to apply the assessment model on the medical equipment found in some units of a Lebanese hospital in order to evaluate them for an updating program.

To do this, we have chosen the Dialysis and the critical care units as a sample study. In these critical units, we have the Intensive Care Unit (ICU), which is dedicated to treat patients, who are seriously ill. Besides, we have the Coronary Care Unit (CCU), where patients with a pacemaker, intra-aortic balloon pump, or with cardiac telemetry are treated. Moreover, there is the Cardiac Surgical Unit (CSU), where patients having open-heart, lung, or vascular surgery are recovered. In addition, there is the Neonatal Intensive Care Unit (NICU) is the unit that monitors the neonates, who are facing newborn problems. Finally, the Pediatric Intensive Care Unit (PICU) is the intensive care specialized for the pediatrics.

In these units, we dealt only with the medical equipment that is in direct contact with the patient and that might affect the patients' safety. The equipment that are related to the ward medical equipment, housekeeping equipment, mortuary equipment, general furniture and accessories, are considered as not urgent at all so they are kept away from the study with "to be replaced after a determined period of time" as a general status. We gathered the required data for 324 equipment distributed over 35 different items and we came back with the results listed in Table XIII. As you can notice, from the obtained results, the same item may record different grades when used in different units. For example, the ECG in the ICU records a grade of 57.35 whereas the ECG in the NICU recorded a grade of 42.88. These two different grades for the same item reflect the different mode of use and different urgency of that equipment at its unit.

Table XIII. SCORES AND GRADES FOR EACH ITEM.

Nb	Name	Normalized Score	Transformed Score (%)
1	Defibrillator	1	100
2	Blood Gas system	0.84776143	82.563644
3	Pulse Oximeters	0.83167396	80.721096
4	Infusion pump (CCU)	0.80675075	77.866563
5	Monitor (ICU)	0.76745621	73.366037
6	Oximeters	0.76154527	72.689039
7	Syringe pump (ICU)	0.75121329	71.505686
8	Dialysis	0.74112659	70.350424
9	Monitor (CCU)	0.69471468	65.034724
10	Monitor	0.68912238	64.394221

	(Endoscopy)		
11	Syringe pump (PICU)	0.68817904	64.286177
12	Refrigerator (Pharmacy)	0.68541098	63.969142
13	Monitor (Dialysis)	0.68198543	63.576804
14	Incubator(PICU)	0.67304633	62.552981
15	Refrigerator (NICU)	0.66928522	62.122209
16	Refrigerator (PICU)	0.66928522	62.122209
17	Incubator (mobile)	0.66080627	61.151088
18	Syringe pump (floors)	0.65123852	60.055265
19	Incubator (Therapeutic)	0.64902559	59.801811
20	ECG (ICU)	0.62764624	57.353167
21	Fetal Monitor	0.62328606	56.853783
22	x-ray (ICU)	0.60806278	55.110213
23	Ultrasound Unit	0.59212049	53.284293
24	Reanimation & warming table	0.58451048	52.412695
25	ECG (CCU)	0.57761153	51.622536
26	ECG (Dialysis)	0.56972919	50.719747
27	Infusion Pump (NICU)	0.56173091	49.80368
28	Infusion Pump (floors)	0.54855002	48.294032
29	Lactina Electric pulse	0.52413795	45.498041
30	CPR	0.52413795	45.498041
31	ECG (NICU)	0.50133159	42.885958
32	Fetal Doppler	0.48090312	40.546222
33	Incubator (Delivery Unit)	0.43585151	35.386322
34	Otoscope	0.39837394	31.093899
35	Bair Hugger	0.24364574	13.372397

At this stage, we are able to make our decision. According to the hospital's budget, we can set three consecutive categories; each bounded within an interval of grades that matches the updating strategic plan of the hospital. In our case study, we assigned the three categories based on a strategic updating plan set by the hospital. The decision makers at that hospital were planning to spend a certain budget after the results of the study, and another amount after a year and a half and finally another amount after three years. Consequently, we set the coming three missions, as seen in Table XIV; the equipment with grades between 65% and 100% should be replaced directly. Those

with grades between 50% and 65% can be replaced after a year and a half, and finally, those with grades below than 50% can be replaced after three years from the first updating plan.

Table XIV. THE CRITICALITY OF A DEVICE FROM THE TRANSFORMED SCORE VALUE - CASE STUDY

Criticality class	Transformed Score Value	Maintenance Strategy
High	65% < TSV ≤ 100%	To be changed urgently
Medium	50% < TSV ≤ 65%	To be changed after a year and a half
Low	0% ≤ TSV ≤ 50%	To be changed after three years

Based on the above three ranges of grades, we can summarize the three groups of medical equipment as shown in Table XV:

Table XV. RESULTS FOR THE UPDATING PLAN.

To be changed urgently	To be changed after a year and a half	To be changed after three years
High 70% < TSV ≤ 100%	Medium 50% < TSV ≤ 70%	Low 0% ≤ TSV ≤ 50%
Defibrillator	Monitor (Endoscopy)	Infusion Pump (NICU)
Blood Gas System	Syringe pump (PICU)	Infusion Pump (floors)
Pulse Oximeter	Refrigerator (Pharmacy)	Lactina Electric pulse
Infusion pump	Monitor (Dialysis)	CPR
Monitor (ICU)	Incubator (PICU)	ECG (NICU)
Oximeters	Refrigerator (NICU)	Fetal Doppler
Syringe pump (ICU)	Refrigerator (PICU)	Incubator (Delivery Unit)
Dialysis	Incubator (mobile)	Otoscope
Monitor (CCU)	Syringe pump (floors)	Bair Hugger
	Incubator (Therapeutic)	
	ECG (ICU)	
	Fetal Monitor	
	x-ray (ICU)	
	Ultrasound Unit	
	Reanimation & warming table	
	ECG (CCU)	
	ECG (Dialysis)	

To make sure that the obtained results are correct and the devices to be changed meet the hospital’s requirements, we

designed a questionnaire that questions the physicians the technicians, and the doctors. In the questionnaire, we asked for the equipment that should be replaced directly and we came back with a list that matched the above list obtained by the scientific study.

One can do some modifications on the result, especially for the equipment on the boundaries. For example, the endoscopy monitor recorded 64.39% so it should belong to the second category. However, if the doctors and the physicians, who work on the endoscopy monitor, recommended an urgent replacement for this monitor, we can move it to the first category and add it to the equipment to be replaced directly. This will not be considered an error since the endoscopy monitor is on the boundary so it may belong to both categories.

Finally, once the hospital has the results, it should launch the procurement process for the first category list.

VII. CONCLUSION

Medical equipment is a critical interface between the patient and the diagnosis, the treatment, or the rehabilitation process. It provides an opportunity for a better medical service. Consequently, medical devices are expected to operate in the required way providing the ultimate results of accuracy, safety, and reliability for an efficient and healthy contribution. As such, this study provides a new model for assessing the life of medical equipment based on its actual usage and not only speculated based on its suppositional life span. This method would result in a more accurate scheme that would most probably extend the life and usage of the equipment thus resulting in substantial savings to the healthcare institution from one side and would serve as an assessment tool based on a multi criteria decision-making approach from the other side.

Using such a model of evaluation, we can drag the wheel of change in the assessment of medical equipment to overreach several sectors in the world of machinery. Moreover, adapting an automated management system to monitor the evaluation of the medical equipment will be revolutionary move towards safety and efficiency.

REFERENCES

[1] J. C. Lerner, "https://www.ecri.org/About/Pages/history.aspx," ECRI Institute, 2014. [Online]. [Accessed 2014].

[2] IMDRF Medical Device Single Audit Program Work Group, "http://www.imdrf.org/about/about.asp#man," International Medical Device Regulators Forum (IMDRF), 19 February 2014. [Online]. Available: http://www.imdrf.org/docs/imdrf/final/consultation

- s/imdrf-cons-assessment-outcomes-140402.pdf.
- [3] ISO 13485, Medical devices. Quality management systems. Requirements for regulatory purposes, second edition ed., Switzerland: ISO copyright office, 2003.
- [4] "http://www.fda.gov/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/DeviceEvaluationInternProgramCDRH/," 26 February 2013. [Online].
- [5] A. Kirists and W. K. Redekop, "The Economic Evaluation of Medical Devices," *Applied Health Economics and Health Policy*, vol. 11, no. 1, February 2013, pp. 15 - 26.
- [6] N. J. Stark, "Clinical Evaluation Report: The New Requirement," MD+DI, Chicago, 2010.
- [7] S. Taghipour, "Prioritization of Medical Devices," in *Reliability and Maintenance of Medical Devices*, Toronto, 2011, pp. 24 - 59.
- [8] I. P. Smirnov, "Organizing function of medical equipment in public health," *Biomedical Engineering*, vol. 6, no. 6, 1972 pp. 343 - 346.
- [9] B. S. Dhillon, "Medical Device Maintenance and Maintainability," in *Medical Device Reliability and Associated Areas*, Florida, CRC Press: Boca Raton, FL., 2000, pp. 179 - 195.
- [10] L. Pruitt and J. Furmanski, "Polymeric Biomaterials for Load-bearing Medical Devices," *Journal of Minerals, Metals, and Materials Society (JOM)*, vol. 61, no. 9, pp. 14 - 20.
- [11] M. Viswanathan et al., "Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions," in *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, AHRQ Publication No. 10(12)-EHC063-EF, April 2012, pp. 69 - 97.
- [12] J. Robson, P. Yeo, M. Riches, T. Carlisle, and N.I Kitto, "Risk Management and Biomedical Devices," in *Engineering in Medicine and Biology 27th Annual Conference*, Shanghai, China, 2006.
- [13] D. V. Agarkhed, "healthcare.financialexpress.com," Tuesday 13 November 2012. [Online]. Available: <http://healthcare.financialexpress.com/strategy/949-hazard-identification-and-risk-analysis>. [Accessed Wednesday 2 April 2014].
- [14] A.B. Khalaf, Y. Hamam, Y. Alayli, and K. Djouani, "The effect of maintenance on the survival of medical equipment," *Journal of Engineering, Design and Technology*, vol. 11, no. 2, 2013, p. 112.
- [15] L. F. a. B. Smith, *Clinical equipment management*, 1989.
- [16] T. L. Saaty, "Decision-making with the AHP: Why is the principal eigenvector necessary," *Europe Journal of Operational Research*, vol. 145, no. 1, February 16, 2003, pp. 85-91.
- [17] T. L. Saaty, "How to make a Decision: The Analytic Hierarchy Process," *European Journal of Operational Research*, 1990, pp. 9 - 26.
- [18] S. T. L., "The Analytic Hierarchy Process," in *Absolute and relative measurement with the AHP*, McGraw Hill: New York, NY., 1980, pp. 327 - 331.

Modelling and Simulation of Mechanical Behaviour of an Ultra-Long Porous Silicon Neural Microelectrode

Rayan Fayad, Soumaya Berro, Bakri AbdulHay, Houssein Hajj-Hassan, Hassan M. Khachfe, Mohamad Hajj-Hassan
Dept. of Biomedical Engineering
Lebanese International University
Beirut, Lebanon
{bakri.abdulhay, houssein.hajjhassan, hassan.khachfe, mohamad.hajjhassan}@liu.edu.lb

Abstract—Porous silicon has become the gold standard when it comes to improving biocompatibility and bioactivity. For this reason, it has become a primary candidate in neural electrodes research and development. Consequently, the purpose of this work was to investigate the mechanical strength of porous silicon neural electrodes. Thus, a finite element model representing the proposed electrode was generated. Mechanical simulation was done on porous and non-porous electrodes using COMSOL® Multiphysics. Results showed that porosity decreased the mechanical strength of the neural electrode without risking the mechanical requirements for neural applications.

Keywords-biocompatibility; finite element model; failure analysis; neural microelectrodes; porous silicon

I. INTRODUCTION

For centuries, people have fantasized about the possibility to communicate with the human brain to understand its structure and how it functions. In the recent decades, due to progresses in neuroscience and microtechnology, this fantasy became a reality with the introduction of neural electrodes. Neural electrodes are implantable micro-dimensional structures that enables a bidirectional communication between the brain and an outer electronic circuitry [1]. These electrodes are used in both recording action potentials from neurons and stimulating specific brain regions, which aid in the diagnosis and treatment of several brain diseases such as seizures, epilepsy, and migraine [2]. Such interfaces have applications in neuroscience research and brain-machine interfaces [3][4].

Several types of neural electrodes have been designed and developed to date. These electrodes can be classified under three main categories: metal wire based, silicon based, and polymer based neural electrodes. A metal-based electrode is composed of a metal wire entirely insulated except for its tip; it is left exposed acting as a recording site [5]. The drawback of this type is that only one recording site was available and any attempt to increase the number of recording sites would increase the overall size of the electrode which is not generally desired. This drawback was solved with the introduction of silicon based neural electrodes that emerged with the advances of microfabrication techniques. Silicon offers suitable biocompatibility and mechanical strength and allows the

incorporation of multiple recording sites without increasing the overall size of the electrode. Another type is the polymer-based neural electrode characterized by improved flexibility and biocompatibility. However, it suffers from lack of rigidity which leads to less accurate neural targeting [6].

This article covers the simulation of the mechanical behavior of porous silicon neural electrode. The next section presents the major limitation of neural electrodes and the advantages of using porous silicon. Section III introduces the design of the proposed electrode. Section IV discusses the simulation strategy followed. Section V details the results yielded.

II. ADVANTAGES OF POROUS SILICON FOR NEURAL ELECTRODES

The major limitation facing the previously mentioned types is the resultant tissue response, which is provoked by the neural injury upon the implantation of the electrode. This tissue response threatens the long-term functioning of the neural electrode. The implantation of any neural electrode is always a traumatic procedure. When a neural electrode is inserted into the brain, it breaches the vasculature and kills the neurons in its path. This provokes the activation of an acute immune response, which is characterized by the recruitment and activation of glial cells whose role is to digest the cellular debris with enzymes. This gives rise to a chronic response. This response results in the formation of an encapsulation layer termed the “glial scar” around the electrode. This scar isolates the electrode from nearby neurons and these neurons are in turn pushed away from the recording sites the thing that leads to signal deterioration [5].

It has been proven that tissue response is highly dependent on the surface topography. That is to say that rough surfaces such as porous ones are more biocompatible than smooth surfaces [7]. Particularly, porous silicon has shown enhanced biocompatibility and bioactivity [8]-[10]. For instance, in a study performed by Hajj-Hassan et al. [10], the biocompatibility and bioactivity of porous silicon wafers (Si) was assessed by examining the survival and replication of mesenchymal stromal cells (MSC) isolated from the bone marrow of

wild type mice. These results were compared with that of cells growing in 2D culture on tissue culture plastic (TCP) and on smooth titanium (SmTi), which is well known for its superiority (gold standard) for the manufacture of implants. In the first experiment performed, bone marrow derived MSC were seeded in porous silicon wafers etched to a depth of 20 μm (Si20) in 12 well plates and harvested after 3, 6, and 9 days of culture. Control cells plated at the same density on tissue culture plastic were harvested at 6 days and stained with toluidine blue to visualize the cells. Results showed that the Si20 substrate supported the MSC growth. Additionally, an Alamar Blue metabolic assay was used to analyze the metabolic activity of cells grown porous silicon substrates etched to a depth of 20 μm (Si20) or 30 μm (Si30) and compared with TCP or smooth titanium, which is a common implant material. Representative results of the Alamar Blue assay, shown in Figure 1(A), indicate a small increase in metabolic activity of the cells grown on Si20 and Si30 samples compared to smooth titanium and tissue culture plastic controls. The cell counts indicated a steady increase in numbers that appeared to be dependent on the substrate on which they were grown.

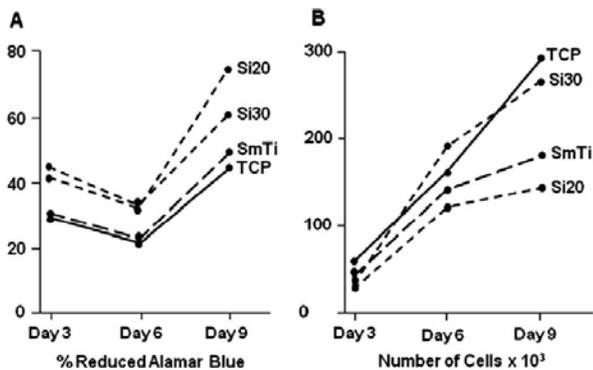


Figure 1. Quantitative analysis of MSC grown on porous silicon etched to a depth of 20 μm (Si20), 30 μm (Si30), commercial grade smooth titanium (SmTi) and tissue culture plastic (TCP) using the Alamar Blue assay to assess the metabolic activity [10].

So, it has been shown that the introduction of the pores improves the biocompatibility and bioactivity. However, a fundamental question imposes itself regarding whether their introduction influences the mechanical strength of the electrode. In other words, we are interested in knowing if the implanted porous electrode will still survive the forces exerted by the brain environment during and after implantation. The solution to this question is demonstrated in the sections that follow.

III. DESIGN

The following section covers the design of the proposed neural electrode. The developed neural electrode is constructed using a silicon substrate and is considered to be ultra-long with a length of 10.5 mm. Its overall structure is tapered, which facilitates the penetration. The geometry of the electrode is sectioned into three main

regions; a base region, a measuring region incorporating the metal recording sites, and a piercing region. The relative dimensions of these regions are indicated in Figure 2. The electrode was implemented using COMSOL[®] Multiphysics 4.3 as depicted in Figure 3.

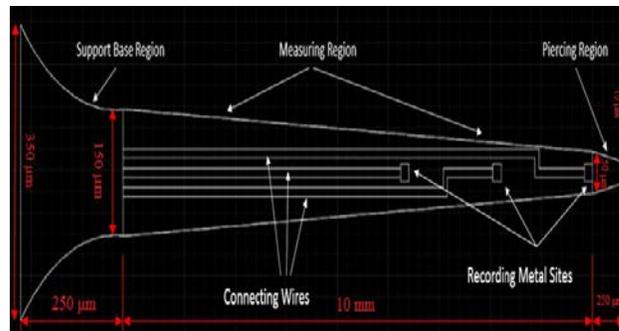


Figure 2. 2D drawing of the designed electrode with annotations.

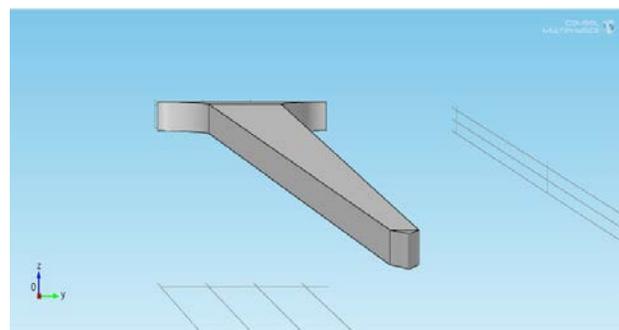


Figure 3. Complete 3D model of electrode.

As for the pores, they were characterized by a cylindrical geometry with a radius of 1.5 μm and a depth of 0.6 μm . This is illustrated in Figure 4.

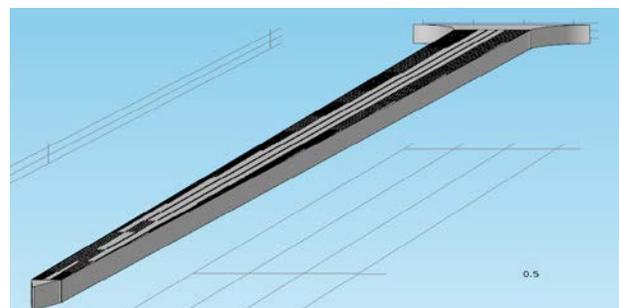


Figure 4. 3D model of porous electrode in COMSOL[®] Multiphysics.

Arrays of pores were distributed along the top surface of the electrode with a distance of 3 μm separating one pore and the other.

IV. SIMULATION STRATEGY

Regarding the adopted simulation strategy, increasing forces were gradually applied on both a porous and a non-porous electrodes until the failure stress of silicon, which is equivalent to 1GPa [11], is reached. During simulation,

two types of forces, which are naturally exerted by the brain environment, are applied on the electrodes [12]. The first force is vertical force that occurs as a result of the movement of the brain relative to the skull. This vertical force causes the bending of the electrode and is applied along the negative z-axis. The second force is an axial force that occurs during penetration and results in the buckling of the electrode. This force is applied along both the negative x and y axes. These forces were applied on the front face of the piercing tip while fixing the back face of the support base region as illustrated in Figure 5.

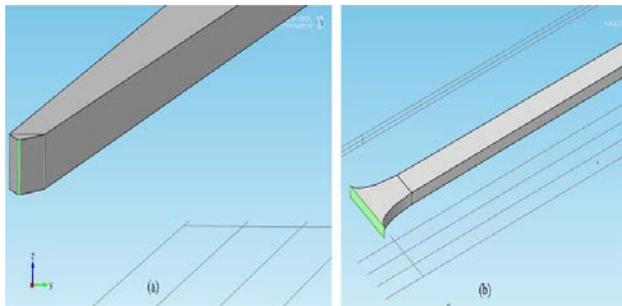


Figure 5. Marked in green is (a) Area on which the stress is applied, (b) area, which is a fixed constraint.

It is notable to mention that during the simulation of the porous electrode, pores were restricted to the weakest regions of the electrode as seen in Figure 6.

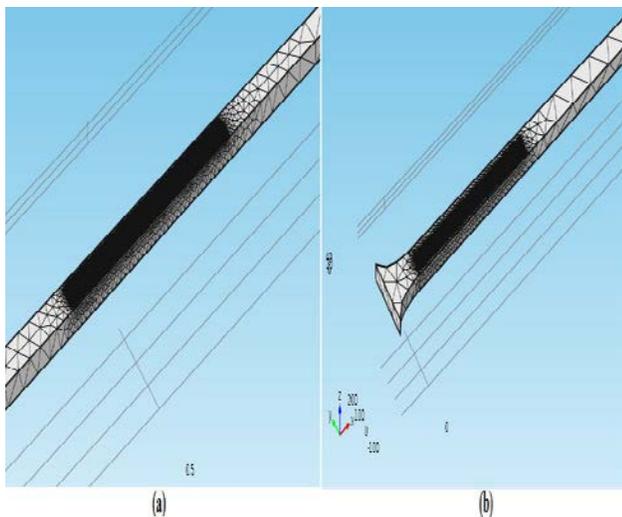


Figure 6. (a) Porous region on the middle of the probe, (b) porous region on the base.

This was done to reduce the computational complexity. These regions are the middle of the electrode (during axial loads), and the base region of the electrode (during vertical loads) [12].

V. RESULTS AND DISCUSSION

The following section elaborates on the results obtained from the simulation of both the porous and non-porous electrodes. For each simulation, a plot of the induced principal stress in MPa versus the length of the electrode in μm as a result of applying axial and vertical loads.

Regarding the application of an axial force along the negative x-axis on the non-porous electrode, a force of 527.5 mN induced a maximum critical stress of 1GPa at a length of around 10.5 mm as indicated in the graph in Figure 7. This location corresponds to the tip region of the electrode. As for the porous electrode, a force of 522.5 mN induced a similar response at a similar location as shown in Figure 8.

Most importantly, it is essential to mention that the maximum critical stress is determined using the “Maximum Distortion Energy Theory” also known as the “*R. von Mises Theory*”, which is demonstrated in equation 1 [13].

$$\sigma_e = (\sigma_1^2 + \sigma_1\sigma_2 + \sigma_2^2)^{1/2} \quad (1)$$

where σ_e is the effective stress or *von Mises* stress and σ_1, σ_2 are the principal stresses. The maximum distortion energy theory is one of the famous failure theories for ductile material. This theory states that failure is predicted to occur in the multiaxial state of stress when the distortion energy per unit volume becomes equal to or exceeds the distortion energy per unit volume at the time of failure in a simple uniaxial stress test using a specimen of the same material [14]. In other words, a given structural material is safe as long as the maximum value of the distortion energy per unit volume in that material remains smaller than the maximum distortion energy per unit volume required to cause yield in a tensile test specified of the same material. The simulated effective stress is then compared to the yielding stress of the material.

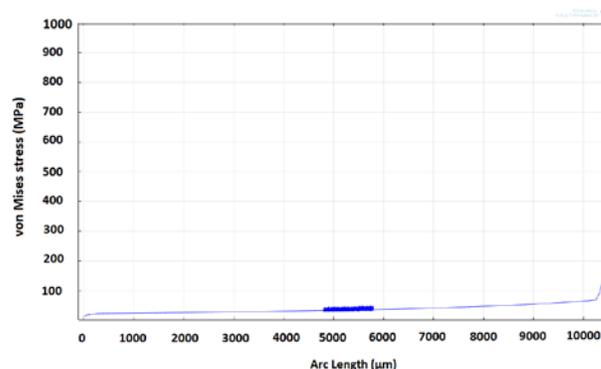


Figure 7. *Von Mises* stress induced upon applying an axial force along the negative x-axis versus the electrode length (non-porous).

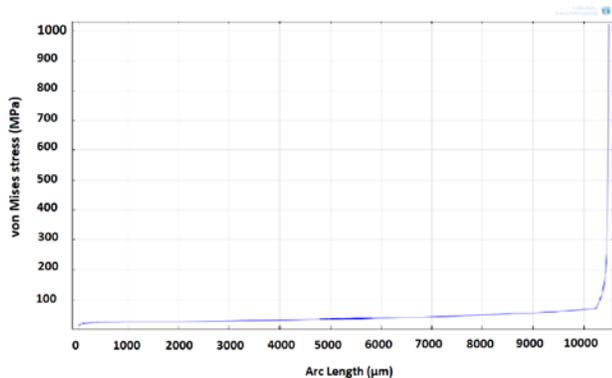


Figure 8. Von Mises stress induced upon applying an axial force along the negative x-axis versus the electrode length (porous).

As for the application of an axial force along the negative y-axis, for the non-porous electrode, a force of 47.5 mN, induced a maximum stress of 1GPa at a length of the electrode approximately equal to 5750 µm, which corresponds to the middle region of the electrode. Meanwhile, in the porous electrode, a force of 37.5 mN caused a fluctuation in the induced stress in the porous middle region. This region also incorporated the maximum stress of 1GPa. These results are indicated in the plots depicted in Figures 9 and 10, respectively.

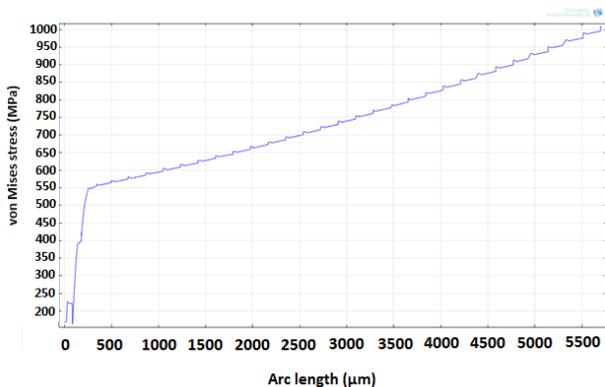


Figure 9: Von Mises stress induced upon applying an axial force along the negative y-axis versus the electrode length (non-porous).

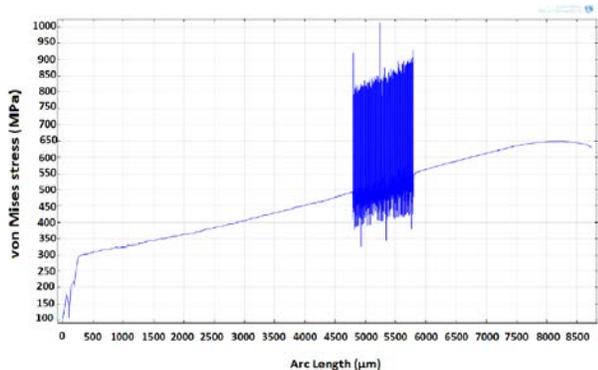


Figure 10. Von Mises stress induced upon applying an axial force along the negative y-axis versus the electrode length (porous).

Finally, regarding the application of a vertical force along the negative z-axis, for the non-porous electrode, a force of 18.25 mN, induced a maximum stress of 1GPa at a length of the electrode approximately equal to 400 µm which corresponds to the fixed base region of the electrode (Figure 11). On the other hand, in the porous electrode, a force of 11.5 mN caused a fluctuation in the induced stress in the porous base region. This region also contained the maximum stress of 1GPa (Figure 12). A summary of the results yielded is presented in Table 1.

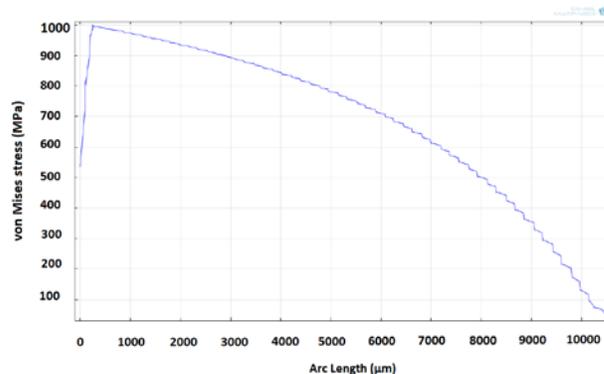


Figure 11. Von Mises stress induced upon applying a vertical force along the negative z-axis versus the electrode length (non-porous).

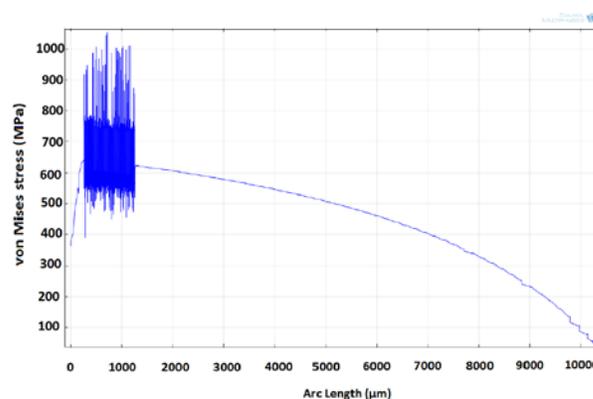


Figure 12: Von Mises stress induced upon applying a vertical force along the negative z-axis versus the electrode length (porous).

TABLE I. A COMPARISON OF FORCES THAT INDUCED 1GPa STRESS IN POROUS AND NON-POROUS ELECTRODES ALONG ALL THREE PRINCIPLE AXES.

Type of Force	Axis	Non-porous (mN)	Porous (mN)
Axial	Along – ve x	527.5	522.5
	Along – ve y	47.5	37.5
Vertical	Along ive z	18.25	11.5

Based on the mentioned results, since the forces needed to induce a maximum critical stress of 1GPa are less in the porous electrode than in the non-porous electrode, we can infer that the porous electrode is mechanically weaker than the non-porous electrode. This weakening is illustrated in Table 2.

TABLE II. RELATIVE WEAKENING OF POROUS ELECTRODE.

Weakening	Axial (-ve x)	Axial (-ve y)	Vertical (-ve z)
Percentage	0.1%	21%	37%

Additionally, it has been shown that the penetration force that an electrode must withstand is equal to 2.42 ± 0.77 [12]. Since the forces that brought the porous electrode near failure are much higher than the force that the electrode must withstand during penetrating the brain tissue, we can deduce that the porous electrode would definitely survive the axial penetration force.

VI. CONCLUSION

We have presented the novel idea of the mechanical simulation of a porous neural electrode. Even though the introduction of the pores relatively weakened the neural electrode, the electrode was found still capable of surviving the brain environment. Nevertheless, certain limitations were present especially related to the finite element model. The full arrays of pores could not be simulated due to computational complexity and they were restricted to the weakest areas. Moreover, different radii of pores and volume porosity percentages should be tested. The porous electrode is superior to the non-porous electrode due to the improved biocompatibility and bioactivity it offers. Furthermore, the presence of the pores gives an additional advantage where they can behave as scaffolds for entrapping neural growth factors that encourage the re-growth of neurons. This alteration to the electrode's design is able to advance the healthcare services provided to neural diseases' patients all around the world.

REFERENCES

[1] K. C. Cheung, "Implantable microscale neural interfaces," *Biomed Microdevices*, vol. 9, 2007, pp. 923–938.
 [2] R. Jung, *Biohybrid systems: nerves, interfaces and machines*: Wiley, 2012.
 [3] B. He, *Neural Engineering*: Springer London, Limited, 2013.
 [4] M. A. L. Nicolelis, "Brain-machine interfaces to restore motor function and probe neural circuits," *Nature Reviews Neuroscience*, vol. 4, 2003, pp. 417-422.
 [5] P. F. G. B. Kim, and M. R. Abidian, "Electrode-neural tissue interactions: immune responses, current technologies, and future directions," in *Biomaterials Surface Science*, J. F. M. A. Taubert, and J. C. Rodriguez-Cabello, Ed., ed: Wiley-VCH, 2013.

[6] V. C. M. Hajj-Hassan, and S. Musallam, "NeuroMEMS: neural probe microtechnologies," *Sensors*, vol. 6704-6726, 2008, pp. 6704-6726.
 [7] L. M. B. A. Rosengren, N. Danielsen, H. Persson, and M. Kober, "Tissue reactions to polyethylene implants with different surface topography," *Journal of Materials Science: Materials in Medicine*, vol. 10, 1999, pp. 75-82.
 [8] L. W. A. Rosengren, N. Danielsen, T. Laurell, and L. M. Bjursten, "Tissue reactions evoked by porous and plane surfaces made out of silicon and titanium," *IEEE Transactions on Biomedical Engineering*, vol. 49, 2002, pp. 392-399.
 [9] S. H. K. A. Moxon, A. Aslani, N. M. Kalkhoran, and P. I. Lelkes, "Bioactive properties of nanostructured porous silicon for enhancing electrode to neuron interfaces," *Journal of Biomaterials Science, Polymer Edition*, vol. 18, 2007, pp. 1263–1281.
 [10] M. K.-K. M. Hajj-Hassan, H. Wang, V. Chodavarapu, and J. E. Henderson, "Response of murine bone marrow-derived mesenchymal stromal cells to dry-etched porous silicon scaffolds," *Journal of Biomedical Materials Research Part A*, 2011, pp. 269-274.
 [11] S. C. L. K. A. Moxon, G. A. Gerhardt, K. A. Barbee, and J. K. Chapin, "Ceramic-based multisite electrode arrays for chronic single-neuron recording," *IEEE Trans Biomed Eng.*, vol. 51, 2004, pp. 647-656.
 [12] V. C. M. Hajj-Hassan, and S. Musallam, "Reinforced silicon neural microelectrode array fabricated using a commercial MEMS process," *Journal of Micro/Nanolithography, MEMS, and MOEMS*, vol. 8, 2009, pp. 033011-033018.
 [13] A. Blake, *Handbook of Mechanics, Materials, and Structures*: Wiley, 1985.
 [14] J. A. Collins, H. R. Busby, and G. H. Staab, *Mechanical Design of Machine Elements and Machines*: Wiley, 2010.

Standards for Medical Information Interchange Design of Modern Mobile Devices and Solutions

Dimitar Tcharaktchiev
University Hospital of Endocrinology
Sofia, Bulgaria
e-mail: dimitardt@orange.fr

Vesselin E. Gueorguiev, Ivan Evg. Ivanov
Technical University Sofia
Sofia, Bulgaria
e-mails: {veg, iei}@tu-sofia.bg

Abstract—In the area of medical information collection, transportation, presentation, and analysis there are a lot of standards. Many of them contradict each other. Mobile devices are a new domain of medical equipment. To enable their communication with different hospital information systems, standards have to be implemented. Standards selection and implementation is a hard process. The aim of this paper is to present the available standards concerning medical data exchange and how to transfer these standards and their applicability to the current mobile devices and remote applications oriented to medical and health care. A solution oriented to archetype data representation is presented, as a way to solve some information presentation problems.

Keywords—telemedicine; medical standards; conformance; electronic health record.

I. INTRODUCTION

The increasing use of mobile and individual healthcare devices is one of the major tendencies in out-of-hospital care. Many vendors provide extensive sets of those devices. Unfortunately, most of them cannot work outside their servers and service software. Transition of health data between hospitals, healthcare providers and health insurance companies is still very limited. Some of these limitations are defined by law restrictions, but many result from data format differences and general incompatibilities. The only way to solve these incompatibilities is to follow available standards and to maintain all new devices to be compatible with those standards. Common use and exchange of information between different actors in the healthcare process, in particular in clinical diagnostics process, is only possible if all partners adopt a common format, content, structure and meaning of exchanged messages.

This article targets some ideas and standards for their implementation in the area of health informatics and the correspondence between them and new generations of personal mobile healthcare devices.

This present paper is structured as follows: Section II presents the health care data exchange process and appropriate to it communication standards; Section III presents the archetypes as conceptual structures and their place in the medical data presentation process; Section IV briefly presents the design steps for mobile device software outlined in the archetype concept; Section V concludes the paper.

II. HEALTH DATA EXCHANGE AND COMMUNICATION STANDARDS

Exchange and interaction between the different actors can be discussed in terms of infrastructure or the application side.

A. Infrastructure level

This level corresponds to the interchange formats related to communication and transport protocols used from layer 1 (physical) to layer 6 (representative) of the OSI (Open System Interconnection) model [20] of the ISO (International Standard Organization). At this level, there are defined channels of communication (network connections, satellite communications, telephone systems, etc.).

B. Application level

This level corresponds to the content of the message, and it is divided into the layers of the syntax, semantics and pragmatic. According to the OSI model, that corresponds to the layer 7 (application layer).

Syntax layer describes the rules presenting how various phrases, signs and other may be combined into corresponding messages containing data or control information. These rules define the shape, consistency and physical representation of the messages.

Semantic layer (content layer) describes the content of the message and it requires an agreement on how to interpret the data unambiguously. An external system of terms representing medical concepts can explain the meaning. Many health organizations describe the data using their own conventions. As a result, in the process of data exchange, the receiving system cannot understand these codes if it does not have appropriate classification catalogue. Data exchange between many organizations is practically impossible. That is why standardized clinical nomenclatures are widely applied (clinical vocabularies, controlled medical terminology, etc.). A standardised clinical vocabulary provides a means of accurately, clearly, and reliably communicating medical information.

Context (pragmatic) layer describes the information and knowledge about the environment (context) where the message is generated. Together with semantic, the pragmatic level describes some of the content of the message.

At higher levels, it is much more difficult to achieve a common understanding of the content of the message elements.

Hereafter, we present the major existing and evolving standards in the field of medical informatics. The presentation is made from the lowest to higher levels of application level, i.e., the level of syntax to pragmatic level. By “standard”, we understand collection of specifications adopted by a standards organization or group. In the last two decades, many organizations have proposed standards for data exchange, but unfortunately most of them are defined at the level of syntax only.

A. Syntax layer standards

These are generic standards, such as ASN.1 (Abstract Syntax Notation One) [21], EDIFACT (Electronic Data Interchange for Administration Commerce and Transport) [22], XML (Extensible Mark-up language) that are independent of the field of application. Specific to the field of health are standards of the HL7 organization (Health Level 7) [23], the DICOM (Digital Image and Communications in Medicine) [9] of the American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA), representing a standard for the formatting, processing and storage of digital images and its associated data and the standard IEEE 1073 - MIB (Medical Information Bus). MIB is applicable to the exchange of data between devices located in intensive care, critical care and operating rooms (such as monitors, infusion pumps, ventilation devices). However, the DICOM was published back in 1993; so the standard precedes the development of the web technologies like XML and web services and uses binary en-coding for the graphical information. To overcome this problem, two additional supplementary standards were developed - Web Access to DICOM Persistent Objects (WADO) [10] and DICOM Structured Reporting (SR) [24].

Work on the specialization of the generic standards, such as XML, to answer service specific requirements of health applications, has started in the past few years.

B. Semantic layer standards

The following standards can be assigned to this level: LOINC (Logical Observation Identifiers, Names and Codes) [25], GALEN (Generalized Architecture for Languages, Encyclopaedias and Nomenclatures in medicine) [26], GRAIL Language (GALEN Representation And Integration Language) [26] and the multi-axial Systematized Nomenclature of Medicine-Clinical Terms SNOMED – CT [27]. The KIF (Knowledge Interchange Format) [28] is language for knowledge exchange and is characterized by declarative semantics, i.e., the meaning is straightforward and well defined.

C. Pragmatic layer standards

The list of these standards is presented by the model of the European Committee for Standardization (CEN, French: Comité Européen de Normalisation) - European Healthcare Record Architecture (EH CRA). In 2004, the ISO Technical Committee 215 published the specification TS 18308 – Requirements for an Electronic Health Record Architecture. It is extended with ISO/TR 20514 published 2005. This

report introduces the generic definition of the Electronic Health Record (EHR) – a repository of information regarding the health status of a subject of care, in computer processable form. Most of the novel developments like CEN EN 13606 and OpenEHR are based on this technical specification.

III. ARCHETYPES AS CONCEPTUAL STRUCTURES

When attempting to “plug-and-play” a new device from some vendor in an existing health network, the most important is the pragmatic layer.

The GEHR (Good European Health Record) initiative started at the beginning of the 90-s as European Union project. Currently, this initiative is maintained by an international online, non-profit organization, called the OpenEHR Foundation [29].

The most noteworthy concept of this initiative is a knowledge-based model, also known as the archetype modelling technique. It facilitates, on one hand, the specification of a generic clinical record structure, and on the other hand the specific semantic definitions of clinical contents. This model utilizes a dual-level methodology to define the EHR structure. More specifically, the first level is used to define a small, but constant in time, Reference Object Model (ROM) for an EHR, which typically contains only a few generic, concepts/classes (e.g., role, act, entity, participation, observation, etc.). In addition, at this level (the level of the ROM), additional methods on how to organize and group clinical information, capture contextual information, query and update the health record, and use of versioning to safely manage clinical information from a medico-legal point of view, are specified [4]. The second level is used to define constraining rules and mechanisms called archetypes. The archetypes role is to specify the common data structures, which have been created in the first level.

The OpenEHR initiative defines a formal language called ADL (Archetype Definition Language). The main purpose of this language is to describe the three main parts of each archetype: descriptive data, constraints and ontological definitions [7]. The descriptive data usually contains a unique identifier for the archetype; machine readable code, which describes the clinical concepts modelled by this archetype; different metadata, like version, author etc. The constraining rules describe the core of the archetype, define the possible constraints of a valid structure and also describe the contents of the component models for EHR. The ontological part defines controlled vocabulary, which can be used in specific parts in the archetype instance. Archetypes are chunks of declarative medical knowledge that are designed to capture maximally expressive and internationally reusable clinical information units. They encode knowledge about clinical observations, evaluations, actions and instructions regardless the context, in a coherent and holistic manner. Archetypes are based on conceptual structures of medical knowledge. Medical ontologies conceptualise domain objects, actions and relationships among them; the archetypes, representing the blueprints of defined medical domains, are focused on capturing clinical information about the patient.

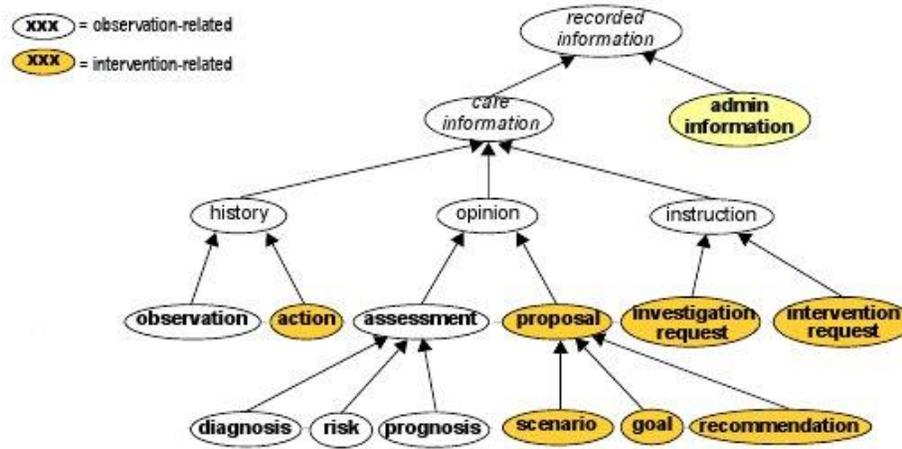


Figure 1. The Clinical Investigator Record Ontology [12]

Analysing the important types of information in the health care process, we select the Clinical Investigator Record Ontology, where the observations (evidences) and opinions (inferences) are different categories (see Figure 1). This taxonomy provides the categories in the Entry classes of the openEHR reference model [31].

In 2008, the archetype approach to structuring patient-related records became ISO standard 13606-2:2008, as a specification of the information architecture required for interoperable communications between systems and services dealing with EHR data [14]. This way, ISO 13606-2:2008 defines how to organise hierarchically the EHR content, how to define the individual data items and their aggregations, what types of values or measurement units are appropriate, and so on. Archetypes are viewed as a serialized representation, an exchange format for communicating individual archetypes between archetype libraries.

All this work makes archetypes as a platform for integration in future mobile device connectable to extended hospital or other health care networks.

IV. DESIGN STEPS OF SOFTWARE FOR MOBILE APPLICATIONS CONFORMING TO ARCHETYPE CONCEPT

To design a new mobile device which can be “plug-and-play”-ed the following steps are recommended (technical design is excluded):

- Definition of minimum clinical data set - the main goal of this step is to prepare appropriate data set for clinical data measurements. This involves the definition of the measurements to be performed. A specialized data set of clinical markers for patient’s status description has to be provided.
- Data standardization - the goal of this step is to prepare presentation of all registered markers and measurement results as clinical archetypes according CEN EN ISO 13606 standard. The possibility to integrate the obtained measurement and analysis results to available EHR has to be proposed.
- Design of infrastructure level communication depending on the exact communication environment.

This number of steps looks simple, but they offer several possibilities to design devices with standardised

interconnection interface. As an example, the archetype for blood pressure introduced in [19] will be discussed.

Minimal data set consists of the following elements:

- Blood pressure (BP)
 - systolic BP*
 - diastolic BP*
 - mean arterial BP*
 - pulse BP*
- State/ Position
 - Standing*
 - Sitting*
 - Reclining*
 - Lying*
 - Lying with the tilt on the left*
- Other - *cuff size, location of measurement, method, mean arterial pressure formula, diastolic endpoint, etc.*

Based on this data, we can obtain an extended archetype as presented in Figure 2.

The presented in Figure 2 archetype gives a basis for software development and extended presentation of obtained patient’s data and environment of its obtaining for electronic health records and its transfer to hospital information system.

We did a preliminary software design, based on the proposed archetype. Simple implementation on a single-board-computer based on ARM processor is done, as well. The implementation is only for design validation. The design and testing environment includes a program generator for embedded devices and semi-natural simulator [30][31], which were used to build the software and to simulated operating environment. No real sensors, actuators and similar were installed. The module operated in a simulated space, connected to an external computer. This computer ran a simplified model of the blood-pressure measurement device physical hardware and communicated via physical signals to the embedded computer. Some of simulations were very simplified and only imitated some behaviour. This did not degraded the validation process because its target was the archetype software representation not the real device control and precise measurements. According to some previous work [32] and prototype of a Hospital Information System (HIS), implemented under Bulgarian National Science Fund Do02-113, some data transfer has been realized. All

activities were only test and validate the idea to use archetypes as software design paradigm for unified medical data transfer from mobile medical device to HIS.

It does not have any medical validity and only proves the possibility to implement the presented formal technology on a physical device.

Some lessons from this implementation are that software design has to be very precise and to follow the archetype design without variants and “adaptations”. The communication increases because more data are transferred. Data composition in the mobile device and its parsing in the HIS are simple. Here is one of the most useful elements of this design. Data can be recognized without some specific extra information because the archetype model is implemented both in the HIS and the mobile device. Every mobile device conforming this this archetype can exchange data to the HIS. Of course, the protocol can be unified also, but we discussed this in the previous sections.

V. CONCLUSION

In this paper, we presented a general overview about the available standards for medical information interchange and their usability for system-to-system and device-to-system connection. We discussed about availability of standard elements in clinical descriptions. It is evident that the conceptual structures, designed to capture patient-related clinical information in order to ensure its systematic representation, need a long period of development, standardisation and wide adoption in order to provide interoperability. First step in this direction is the presented way to generate a formal archetype and after that – to transfer it on a specific hardware, implementing all needed data acquisition and communication actions. Technically, this is not a problem. Today the problem is to achieve a common understanding of the exchanged content between systems and not a used data transfer technique. The proposed new type of thinking in terms of archetypes and conceptual structures solves many problems in this area and reduces standards contradictions.

REFERENCES

- [1] I. Nikolova, G. Angelova, D. Tcharaktchiev, and S. Boytcheva, Medical Archetypes and Information Extraction Templates in Automatic Processing of Clinical Narratives, In Proceedings of ICCS 2013, 10-12 January, Mumbai, India, Conceptual Structures for STEM Research and Education, Springer, Lecture Notes in Computer Science, vol. 7735, 2013, pp. 106-120.
- [2] I. E. Ivanov, V. Gueorguiev, V. Bodurski, and E. Markov, Electronic Health Record: The State of The Art, Computer Science'2009, 05 - 06 November 2009, Sofia, Bulgaria.
- [3] I. E. Ivanov, V. Gueorguiev, N. Balgzhiev, and B. Kehayov, Software Architecture For Medical Information Systems, Computer Science'2009, 05 - 06 November 2009, Sofia, Bulgaria
- [4] R. Smith, What clinical information do doctors need? British Medical Journal, 1996, Oct. 313, pp. 1062-1068.
- [5] P. C. Tang, and C.J. McDonald Electronic health record systems. In Cimino, J. J. And Shortliffe, E. H. (eds.) Biomedical Informatics: Computer Applications in Health Care and Biomedicine (Health Informatics), Springer-Verlag, New York, Inc. 2006.
- [6] B. Blobel, Evaluation and harmonization of electronic healthcare record architecture approaches. Business Briefing: Global Healthcare, pp. 1-5. 2002.
- [7] T. Beale, The OpenEHR Integration Information Model. OpenEHR Reference Model. The OpenEHR foundation. 2005.
- [8] HL7 CDA Release 2.0 The HL7 version 3 standard: Clinical data architecture, re-lease 2.0. ANSI Standard, 2005.
- [9] The DICOM standard. Joint DICOM standards committee. <ftp://medical.nema.org/medical/dicom/2008/> [last accessed: 21.04.2014].
- [10] DICOM Supplement 85. Web Access to DICOM Persistent Objects (WADO). Joint DI-COM standards committee / ISO TC215 Ad Hoc WG on WADO, final text. ftp://medical.nema.org/medical/dicom/Final/sup85_ft.pdf. [last accessed: 21.04.2014]
- [11] DICOM Supplement 86. Digital Signatures in Structured Reports. Joint DICOM standards committee. ftp://medical.nema.org/medical/dicom/Final/sup86_ft2.pdf. [last accessed: 21.04.2014]
- [12] T. Beale and S. Heard. An Ontology-based Model of Clinical Information. In K. Kuhn et al. (Eds.), Proceedings MedInfo 2007, IOS Publishing 2007, pp. 760–764.
- [13] T. Beale and S. Heard (Eds.), Archetype Definitions and Principles. openEHR Report, March 2007.
- [14] ISO 13606-2:2008 Health informatics - Electronic health record communication - Part 2: Archetype interchange specification, http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=50119 [last accessed: 21.04.2014]
- [15] B. Onyshkevych, Template Design for Information Extraction. In Proc. of the TIPSTER Text Program: Phase I, September 1993, Virginia, USA, pp. 141–145, <http://www.aclweb.org/anthology/X93-1015>, [last accessed: 25.06.2014]
- [16] J. Sowa, Conceptual Information Processing in Mind and Machines. Reading, MA, 1984.
- [17] N. Chambers and D. Jurafsky, Template-Based Information Extraction without the Templates. Proc. of the 49th ACL Ann. Meeting, Oregon, June 2011, pp. 976–986.
- [18] http://standards.cen.eu/dyn/www/?p=204:32:0:::FSP_ORG_ID.FSP_LANG_ID:6232,25&cs=1FFF281A84075B985DD039F95A2CAB820, [last accessed: 21.04.2014]
- [19] D. Tcharaktchiev et al. Data Base for patients with pituitary and adrenal tumors. Soc. Med. 2010, 2-3:73-79.
- [20] http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=20269 [last accessed: 09.07.2014]
- [21] <http://www.itu.int/en/ITU-T/asn1/Pages/introduction.aspx> [last accessed: 09.07.2014]
- [22] <http://www.unece.org/trade/untidd/welcome.html> [last accessed: 09.07.2014]
- [23] www.hl7.org [last accessed: 09.07.2014]
- [24] www.dclunie.com/pixelmed/DICOMSR.book.pdf [last accessed: 09.07.2014]
- [25] loinc.org [last accessed: 09.07.2014]
- [26] www.openclinical.org/prj_galen.html [last accessed: 09.07.2014]
- [27] <http://www.ihtsdo.org/snomed-ct/> [last accessed: 09.07.2014]
- [28] <http://www.ksl.stanford.edu/knowledge-sharing/kif/> [last accessed: 09.07.2014]
- [29] <http://www.openehr.org/> [last accessed: 04.08.2014]

[30] Nikolay Baldzhiev, Velizar Bodurski, Vesselin Gueorguiev, Ivan Evg. Ivanov, Implementation of Objects Simulators and Validators using Program Generation Approach, DESE 2011, Dubai, UAE, December 2011

[31] E. Markov, V. Gueorguiev, I. E. Ivanov, Program Generation Approach for Semi-Natural Simulators Design and

Implementation, SIMUL 2014, Nice, France [accepted for publishing - July.2014]

[32] O. Nakov, V. Gueorguiev, I. E. Ivanov, V. Trifonov, Metadata organization for Electronic Health Record [in Bulgarian]. Computer Engineering, vol. 2, 2009

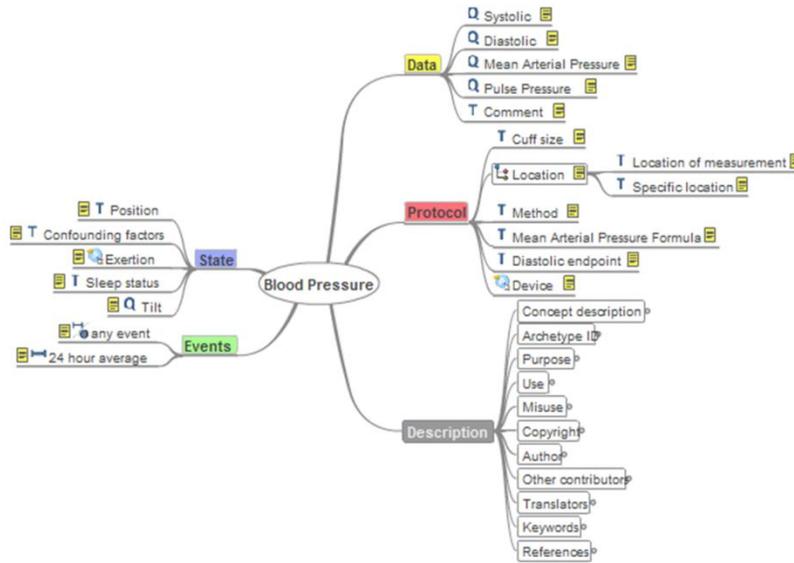


Figure 2. Map View of the 'Blood Pressure measurement' archetype [1]

An Optimized Research Process for Real-time Drug Response Analysis

Matthieu-P. Schapranow*, Konrad Klinghammer[§], Cindy Fähnrich*, and Hasso Plattner*

*Hasso Plattner Institute
Enterprise Platform and Integration Concepts
August-Bebel-Str. 88
14482 Potsdam, Germany
{schapranow|cindy.faehnrich|plattner}@hpi.de

[§]Charité – Universitätsmedizin Berlin
Comprehensive Cancer Center
Charitéplatz 1
10117 Berlin, Germany
konrad.klinghammer@charite.de

Abstract—Latest medical diagnostics, such as genome sequencing, generate increasing amounts of "big medical data". Healthcare providers and medical experts are facing challenges outside of their original field of expertise, such as data processing, data analysis, or data interpretation. Specific software tools optimized for the use by the target audience, as well as systematic processes for data processing and analysis in clinical and research environments are still missing. Our work focuses on the integration of data acquired from latest next-generation sequencing technology, its systematic processing, and instant analysis for researchers and clinicians in the course of precision medicine. We share our research results on developing specific software tools for drug response analysis built on top of our distributed in-memory computing platform for genome data processing. For that, we present our technical foundations, as well as process aspects of integrating and combining heterogeneous data sources, such as genome, patient, and experiment data in the clinical routine.

Keywords—Drug Response Analysis; Genome Data Analysis; Process Integration; In-Memory Database Technology; Precision Medicine; Next-Generation Sequencing.

I. INTRODUCTION

The Human Genome (HG) project that was officially launched in 1990 involved thousands of research institutes worldwide and required more than a decade to sequence and decode the full HG [1]. Nowadays, Next-Generation Sequencing (NGS) devices enable processing of whole genome data within hours at reduced costs [2]. NGS is used to support precision medicine, which aims at treating patients specifically based on individual dispositions, e.g., genetic or environmental factors [3].

The In-Memory Database (IMDB) technology has proven to have major advances for analyzing big en-

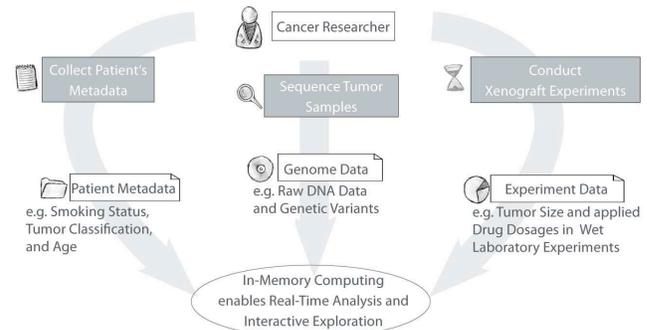


Figure 1. The optimized drug response analysis process involves data in heterogeneous formats from different data sources.

terprise and medical data, e.g., to support researchers and clinicians in evaluating best therapies for cancer patients [4, 5, 6].

In this work, we present our findings of applying IMDB technology to enable integration of experiment results, real-time analysis, and prediction of drug response in silico in course of precision medicine. We introduce an integrated research process for oncologists built upon our High-performance In-memory Genome (HIG) cloud platform to reduce media breaks and to improve the efficiency of drug response testing [7]. The HIG platform provides services for processing of huge amounts of high-throughput genome data in real-time. In interdisciplinary teams we developed jointly with cancer researchers a special purpose application to evaluate results of conducted Xenograft experiments without significant delay [5, 8]. Figure 1 depicts the optimized research process and the involved data sources.

The rest of the paper is structured as follows: In Section II, our work is set in context of related work

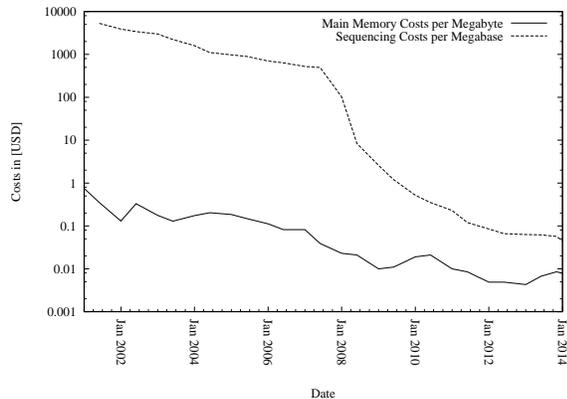


Figure 2. Costs for next-generation sequencing and main memory from 2001 to 2014 adapted from [9, 10].

and in Section III, we introduce our applied research methodology. We present the current drug response process in Section IV and introduce optimized research process in Section V. In Section VI, we discuss our contribution and our work concludes with an outlook in Section VII.

II. RELATED WORK

Figure 2 provides a comparison of costs for sequencing and main memory modules. Both costs follow a steadily declining trend, which facilitates the increasing use of NGS for whole genome sequencing and IMDB technology for its data analysis. Related work in the field of genome data processing has increased in recent years. However, work focusing on implementing end-to-end processes is still rare. Thus, we focus on implementing innovative processes, e.g., by tight integration of genome data processing and statistical data analysis in course of drug response analysis.

Sun investigated gene regulations in prostate cancer samples combining latest sequencing technology and bioinformatics approaches. We agree that an integrated data processing and analysis approach is also essential for other application fields. Thus, we integrate various heterogeneous data sources to enable multi-modal modeling of diseases. Furthermore, we enable researchers for the first time to perform data analysis a) in real-time without any delay and b) without the need to involve dedicated IT experts, e.g., to prepare analysis reports.

Rossello et al. propose the use of Xenograft models as data sources for preclinical models when primary tumor samples are rare, e.g., for small cell lung cancer. They share very detailed insights into their methodology using state-of-the-art alignment and variant calling tools, such as BWA, GATK, and snpEff [13, 14, 15]. However, they still miss a tight integration of their genome sequencing pipeline and their data analysis pipeline, which consumed a major part of the their experimental time.

Our contribution enables tight integration of various experimental data, such as NGS tumor data, and their real-time data analysis as described in Section IV.

III. METHODOLOGY

In the course of this project, we followed the design science methodology to improve the existing research process with the help of software artifacts [16].

For that, we applied the Design Thinking (DT) methodology, which proposes to work in interdisciplinary teams [17]. The idea behind this proposal is that team members from different disciplines, e.g., a software developer and a medical researcher, will have different viewpoints on the same problem domain. Thus, if a team is comprised of members from different disciplines relevant to the problem at hand, chances that an important aspect is forgotten are minimized. Additionally, an interdisciplinary team will not suffer from rivalry between experts of the same field, instead all expertise necessary to implement the solution is already available in the team. Besides suggesting interdisciplinary team compositions, DT provides a process framework as depicted in Figure 3. It asks for constant communication between the developing team and the stakeholders and targeted end users.

Following DT, we conducted user interviews with cancer researchers and physicians to document the existing research process as described in Section IV. Furthermore, we developed an optimized process by integrating heterogeneous data sources and manual process steps within a software prototype. Based on the obtained insights, we iteratively extended software prototypes in short development sprints, evaluated the functionality either in workshops at the users' sites or conducted telephone interviews, while giving end users the chance to use the software artifacts via screen sharing. Based on the input from the workshops and interviews, the next iteration was planned according to the scrum software development methodology [18].

IV. CURRENT DRUG RESPONSE ANALYSIS PROCESS

Nowadays, drug response analysis consists of a) conducting drug experiments, e.g., in Xenograft models, and b) the analysis of the obtained experiment results [19]. The following selected data sources are used for drug response analysis as depicted in Figure 1:

- **Patient Metadata** is retrieved from Clinical Information Systems (CISs) and contains specific patient details, such as age, gender, and anamnesis. Its data volume typically ranges from one to 100 MB excluding any diagnostic data, such as imaging data,
- **Genome Data** is obtained by sequencing resected tumor material, e.g., with NGS devices. Its data

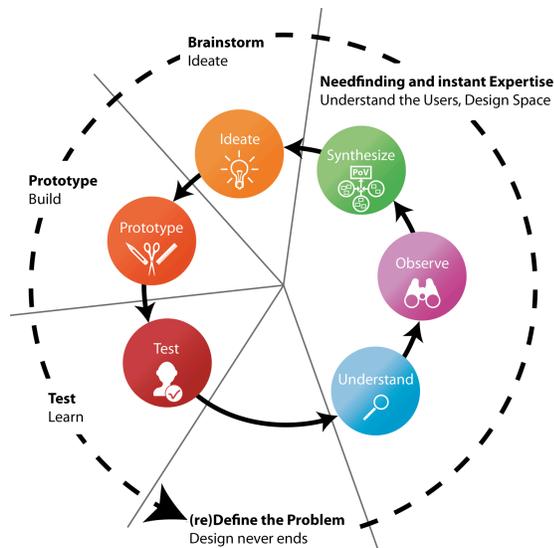


Figure 3. Design thinking process as defined by the HPI School of Design Thinking in Potsdam and Stanford adopted from [17].

volume is in the range of some 100 MB for panel sequencing and up to 500 GB for NGS.

- **Experiment Data** is obtained by wet laboratory assistants, e.g., documenting the individual drug tests in Xenograft experiments. Its data volume is in the range from 10 MB to 1 GB.

The time consumed in wet laboratories can range from days to weeks depending on the conducted experiments. Although the data analysis phase is assisted by use of software, it still takes days up to weeks to perform complex data analysis. The reasons are many-fold, e.g., the absence of specific tools for flexible data analysis, tools limited to a small set of data sources, and transformation of relevant data.

Manual or semi-manual time-consuming process steps, such as the use of Microsoft Excel for complex data analysis, characterize all phases of the existing process. From a software engineering perspective, we focus on all process steps where digital data processing and analysis is conducted. Thus, our work focuses on the data analysis phase of the existing process to optimize the overall research process.

V. ENABLING REAL-TIME DATA ANALYSIS

Figure 4 depicts a screenshot of our developed drug response cloud application. It shows details of genetic changes of a specific mama carcinoma tumor sample. Our optimized research process is divided in the following process steps:

- **Computational biology** performs data processing, e.g., raw DNA,
- **Clustering of tumor data** enables real-time classification of results, and

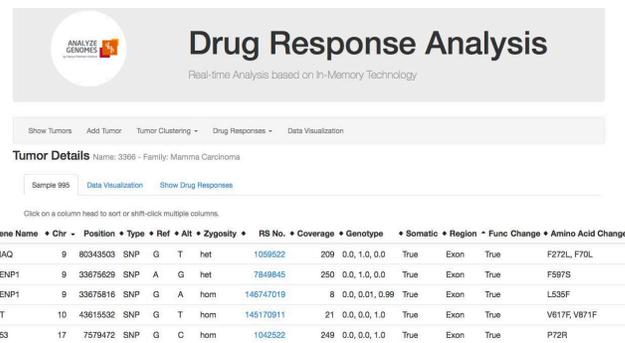


Figure 4. Screenshot of the drug response analysis cloud application of the HIG project.

- **Visual data exploration** supports the interactive testing and verification of research hypotheses.

A. Computational Biology

In the following, we share insights of our process extensions focusing on processing of raw DNA data.

1) *Open Reading Frame Detection in the In-Memory Database:* The detection of Open Reading Frames (ORFs) builds the foundation of finding potential gene locations within the genetic code [20].

The detection of ORFs is two-fold as follows. In the first phase, we search for start and end codons in all possible reading frames, i.e., three reading frames per strand of the double helix. In the second phase, pairs of corresponding start and end codons within the same reading frame are analyzed to identify ORFs with a minimum length.

Within the first phase, we process the forward and the backward strand in parallel. For example, when searching for the start codon "ATG" on the forward strand, we also search for the reserve-inverted triplet "CAT" to detect the start codon on the backward strand. The reading frame is determined by the position of the first base of the codon modulo three on the forward strand and by adding three for the position on the backward strand. In addition to the reading frame, we store the type and the position of the found codons.

In the second phase, we group the results from the first phase by reading frame and search for a start followed by its corresponding stop codon.

We implemented the ORF detection algorithms directly within IMDB. For that, we used the programming languages SQLScript and L [21, 22]. As a result, our implementation can directly incorporate advances of in-memory computing by performing all data processing directly on top of the genome data stored within our HIG platform without the need for data transformations.

2) *Evaluation of Genetic Variants to Detect Functional Changes in In-Memory Database:* The detection of functional changes is an essential step of genome

NAME	ABBREV	POS BASE	VARIANT
Alanine	A	1 G	1
Alanine	A	2 C	1
Alanine	A	3 A	1
Alanine	A	3 T	1
Alanine	A	3 C	1
Alanine	A	3 G	1
Arginine	R	1 A	2
Arginine	R	1 C	1
Arginine	R	2 G	1
Arginine	R	2 C	2
Arginine	R	3 A	1
Arginine	R	3 A	2
Arginine	R	3 T	1
Arginine	R	3 C	1
Arginine	R	3 G	1
Arginine	R	3 G	2

Figure 5. The columnar database implementation of the amino acid coding sun [23].

data analysis. Each genetic variant needs to be analyzed according to its potential impact on the Amino Acid (AA) built from the genetic code. As a result, a potential change in the product built from the AA is an indicator for a genetic variant that describes a harmful mutation within the DNA [23].

Our algorithm for processing of the genetic variants is described in the following. Firstly, we check if a concrete variant is located within the range of a known gene. For that, we join the variant's location consisting of chromosome and position with a database table containing a list of known genes [24]. If the current location is outside of a known gene range, we consider its impact as minor, since the current medical knowledge about variants outside the range of genes is very limited. However, once a new gene is added to the list of known genes, it is automatically analyzed.

If the variant is located on a gene, all splicing variants of the gene are analyzed in parallel to derive the individual impact per splicing variant.

Each splicing variant consists of introns and exons [25]. Thus, the reading frame of the splicing variant is determined by the codon of the genetic variant. This allows us to identify the position of the changed nucleotide within the affected codon. The codon of the variant and corresponding codon of the reference genome are translated into AAs using our database table implementing the AA coding sun as depicted in Figure 5 [23].

An AA change is documented by the expected and the detected AA followed including the position of the affected triplet, e.g., S12Y donating an AA change of Serine to Tyrosine at triplet location 12.

If the resulting AAs of the reference genome and the variant differ, we refer to it as functional genetic change.

The reading frame around the variant remains the same for all splicing variants of the gene. Thus, the reading frame for a variant is only calculated once independent of the number of splicing variants of the concrete gene.

Our algorithm can be applied to the forward and the backward strand of the DNA. If a gene is located on the backward strand of the DNA the list of exons needs to be considered in the reverse order as well. However, all other steps of the algorithm can be reused.

In our case, a specific version of the stored procedure within the IMDB is executed to translate codons on the corresponding strand.

B. Real-time Clustering of Tumor Data

In the following, we share our process extension for automatic classification of processed research data.

1) *Tumor Data Association Rules*: Association Rules Mining (ARM) requires a set S of item sets S_i as its data basis: $S = \{S_1, \dots, S_m\}$. Every item set S_i consists of several items i_i from the list I of distinct items: $I = \{i_1, \dots, i_n\}$. These item sets are processed to detect reliable rules of type: $A \Rightarrow B$ where $A \subseteq I \wedge B \subseteq I$. A is called prior whereas B is called posterior.

In our use case, items are all distinct variants found in the library of available tumors. Item sets correspond to the set of variants found for one tumor together with respective drug response classes determined by Xenograft experiments. In the context of our current work, we only focus on functional changes. The goal in our use case are rules of type $A \Rightarrow B$, where A is a set of functional changes and B is a specific drug response class. We investigate the impact of single functional changes on drug responses to limit the problem space, i.e., we restrict $|A| = 1$.

Two important measures for association rules are support and confidence. Support $supp(A)$ represents the relative frequency of $A \subseteq I$ in all items sets S as defined by Equation 1.

$$supp(A) = \frac{|\{S_i | S_i \in S \wedge A \subseteq S_i\}|}{|S|} \quad (1)$$

$$conf(A \Rightarrow B) = \frac{supp(A \cup B)}{supp(A)} \quad (2)$$

Confidence $conf(A \Rightarrow B)$ is the relation of the number of item sets where A and B occur to the number of items sets where only A can be found defined by Equation 2.

Support defines how important a found rule is, with respect to all data, while confidence shows how reliable it is. We applied the Apriori algorithm for ARM by using the PAL integrated in the IMDB and by using the implementation provided by the R package `arules` [26, 27, 28].

For tumor classification, either the Tumor/Control (T/C) value or the RECIST value can be used. Therefore, cancer researchers can decide individually per analysis run. In the remainder of this paper, we investigate both measures.

In order to use Apriori ARM for classification, we need to add drug response classes to each item set. Possible classes are Partial Response (PR), Stable Disease (SD), and Partial Disease (PD). The thresholds, by which a drug response is classified in one of the classes, can be adapted individually.

C. Visual Data Exploration

We developed specific visualizations to enable researchers to work a) interactively with the data instead of having statically generated charts and b) with commonly used graphical representations.

In the following, we share details about our extensions for interactive exploration of tumor data.

1) *Real-time Classification of Tumor Experiment Data with Support Vector Machines*: Classifying tumor data can be used to identify similarity measures in an unsorted set of data. Thus, an automatic classification of tumor data can be used to generate hypotheses, e.g., to identify new tumors subtypes.

Our implementation builds on Support Vector Machine (SVM) as machine learning algorithm. SVM is available in many popular statistical frameworks, such as R [26]. To leverage the complete performance advance of in-memory computing, we built on the implementation directly integrated within our IMDB as part of the Predictive Analysis Library (PAL). Since the algorithm can directly access experiment data without the need to export/import data. It improves the existing process by eliminating media breaks. Furthermore, the SVM implementation within the IMDB incorporates technology advances and performs faster than the aforementioned implementations, e.g., due to reduced disk I/O.

Our tumor classification algorithm incorporates the steps configuration, preparation, and execution.

Configuration Stage: During configuration stage, the researcher is guided through a web page to configure relevant SVM parameters, e.g., drugs to predict and experiment data to be used as training data.

The result of a SVM prediction depends on the criteria selected during the configuration phase, e.g., a concrete Tumor/Control (T/C) or a RECIST value for a specific pharmaceutical based on the selected tumor attributes. SVM uses a regression mode also known as Support Vector Regression (SVR) to estimate correlation between attributes of the train data and applies these correlations to the data points to predict [29].

In addition to prediction of concrete values, we focus on classification of data in response classes as introduced in Section V-B1. For our concrete use-case, we classified values from 0.0 to 0.7 as PR, representing a reduction in tumor growth by administering the drug, 0.7 to 1.2 is as SD, which represents no significant change, and values

greater than 1.2 as PD, representing a negative response and thus growth of the tumor.

SVM in classification mode calculates class membership probabilities instead of drug efficiency values [30].

Preparation Stage: Input and output tables are created, training data is selected, and the database procedure is prepared to process SVM model during preparation stage.

The input database table for SVM is constructed according to the chosen tumor attributes, with each column representing a specific tumor attribute. A table record in the input table represents all relevant data for a single tumor entity based on the configured attributes.

Execution Stage: The train formula in the R procedure is “**drug .**”, telling R that the drug column of the data frame is the depending variable, whereas the rest are deciding variables, indicated by a dot. SVM decides whether to perform classification or prediction by investigating the dependable variable in the SVM training formula, i.e., if a numeric value is encountered, SVM will run in regression mode otherwise in classification mode.

The execution of SVM for multiple drugs is done by running preparation and execution stages individually per drug isolated from each run ensuring that no side effects influence the SVM algorithm.

2) *Clustered Heat Map using Hierarchical Clustering*: Hierarchical clustering is a clustering method that builds a hierarchy of clusters from the given data by iteratively merging the closest data points to one cluster (agglomerative hierarchical clustering). In order to identify the clusters that should be combined, the clustering algorithm needs a measure of dissimilarity between sets of observations. Figure 6 shows a clustered heat map based on a hierarchical clustering algorithm. For hierarchical clustering, the measure is formed by combining an appropriate metric for distance calculation between data points and a linkage criterion for calculating the distance between merged data points [31].

We used row- and column-wise vectors, the Euclidean distance function as distance metric, and single link clustering to create the heat map.

The result of any hierarchical clustering is a dendrogram, i.e., a binary tree with data points as leaves. It represents the clustered data points and the nested clusters at certain similarity levels as depicted in Figure 7. The dendrogram is used to rearrange / reorder the heat map and identify positions for adding cluster gaps to the heat map. For example, rearranging rows in the heat map according to the clustering result can be done by traversing the dendrogram tree and leveraging the order of the leaves, which are by our definition the row vectors. Thus, similar rows will be side by side or at least close to each other.

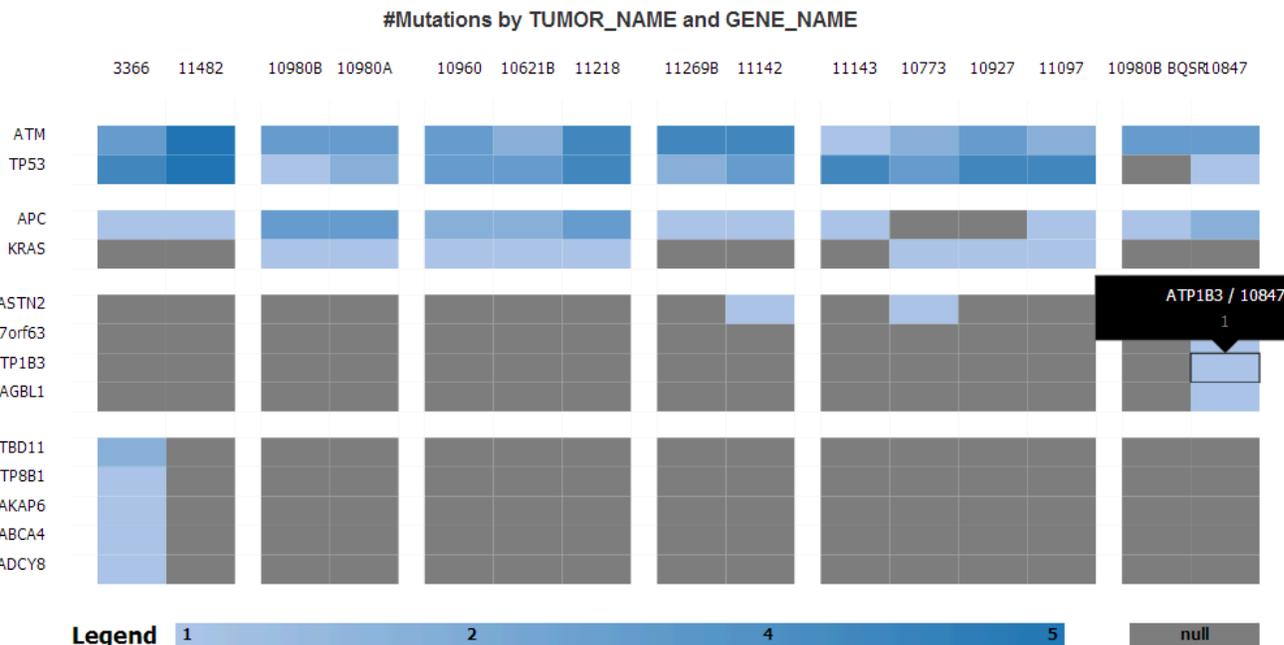


Figure 6. Clustered heat map using hierarchical clustering comparing mutation count, a subset of genes, and tumor samples.

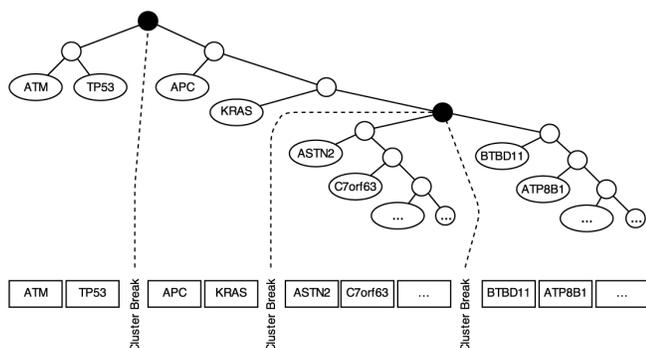


Figure 7. Dendrogram tree as the result of applying hierarchical clustering. Cluster borders are the turning points in the tree that split up in two clusters denoted as black nodes.

VI. EVALUATION AND DISCUSSION

With the help of oncologists, we have been able to verify that our introduced research process improves their daily work. We focused primarily on improving aspects of data processing and analysis to create an integrated and reproducible research process. The incorporated IMDB technology provides a data integration platform, which minimizes the need for additional third-party tools. As a result, we were able to reduce media breaks, provide flexible and individual real-time analysis of acquired data, and establish a single source of truth, which holds all acquired data and enables a consistent and iterative research process.

In the following, the advantages and enhancement of our proposed research process are summarized:

- Integration of heterogeneous data sources,
- Elimination of media breaks and improved processing time,
- Automated data processing by integration of algorithms for computational biology,
- Flexible data analysis built on latest in-memory technology, and
- Interactive graphical data exploration enabling direct verification of research hypotheses.

VII. CONCLUSION AND OUTLOOK

In our contribution, we shared details about our proposed research process for drug response analysis. We incorporated latest in-memory technology as the key enabler for real-time analysis and exploration of experiment data and the integration of various data sources. We outlined the applicability of our HIG platform for processing of genome data and the specific drug response analysis application to optimize existing research processes in this specific field of cancer therapy. Furthermore, we shared detailed insights in our applied research methodology, which involved experts from interdisciplinary teams.

Our future work will focus on applying the research process to additional fields of cancer research in course of precision medicine. Furthermore, we will investigate how a huge library of tumor samples can be used as training data to create more stable prediction models to discover new medical insights.

REFERENCES

- [1] F. S. Collins *et al.*, “New Goals for the U.S. Human Genome Project,” *Science*, vol. 282, no. 5389, pp. 682–689, 1998.
- [2] W. J. Ansorge, “Next-generation DNA Sequencing Techniques,” *New Biotechn*, vol. 25, no. 4, pp. 195–203, 2009.
- [3] K. Jain, *Textbook of Pers Med.* Springer, 2009.
- [4] M.-P. Schapranow, H. Plattner, C. Tosun, and C. Regenbrecht, “Mobile Real-time Analysis of Patient Data for Advanced Decision Support in Personalized Medicine,” in *Proceedings of the 5th Int’l Conf on eHealth, Telemedicine, and Social Medicine*, 2013, pp. 129–136.
- [5] M.-P. Schapranow, F. Häger, and H. Plattner, “High-Performance In-Memory Genome Project: A Platform for Integrated Real-Time Genome Data Analysis,” in *Proceedings of the 2nd International Conference on Global Health Challenges*. IARIA, Nov 2013, pp. 5–10.
- [6] M.-P. Schapranow, *Real-time Security Extensions for EPCglobal Networks: Case Study for the Pharmaceutical Industry*. Springer, 2013.
- [7] —, “Analyze Genomes Project Page,” <http://we.analyzegenomes.com/> [retrieved: Jun, 2014], 2014.
- [8] R. S. Kerbel, “Human Tumor Xenografts as Predictive Preclinical Models for Anticancer Drug Activity in Humans: Better than Commonly Perceived But They Can Be Improved,” *Cancer Biology & Therapy*, vol. 2, no. 4, pp. 134–139, 2003.
- [9] National Human Genome Research Inst, “DNA Sequencing Costs,” <http://www.genome.gov/sequencingcosts/> [retrieved: Jun, 2014], Apr 2013.
- [10] J. C. McCallum, “Memory Prices (1957-2014),” <http://www.jcmit.com/memoryprice.htm> [retrieved: Jun, 2014], Apr 2014.
- [11] Y. Sun, “Identification of REST Regulated Genes in Prostate Cancer via High-throughput Technologies,” Master’s thesis, Instituto Superior Técnico, Universidade Técnica, Lisboa, Portugal, Dec 2012.
- [12] F. J. Rossello *et al.*, “Next-Generation Sequence Analysis of Cancer Xenograft Models,” *PLoS ONE*, vol. 8, no. 9, p. e74432, Sep 2013.
- [13] H. Li and R. Durbin, “Fast and Accurate Short Read Alignment with Burrows-Wheeler Transformation,” *Bioinform*, vol. 25, pp. 1754–1760, 2009.
- [14] A. McKenna *et al.*, “The Genome Analysis Toolkit: A MapReduce Framework for Analyzing Next-Generation DNA Sequencing Data,” *Genome Research*, vol. 20, no. 9, pp. 1297–1303, 2010.
- [15] P. Cingolani *et al.*, “A Program for Annotating and Predicting the Effects of Single Nucleotide Polymorphisms,” *Fly*, vol. 6, no. 2, pp. 80–92, 2012.
- [16] A. R. Hevner, S. T. March, J. Park, and S. Ram, “Design Science in Information Systems Research,” *MIS Quarterly*, vol. 28, no. 1, pp. 75–105, 2004.
- [17] H. Plattner, C. Meinel, and L. Leifer, Eds., *Design Thinking Research*, ser. Understanding Innovation. Springer, 2012.
- [18] R. Pichler, *Agile Product Management With Scrum: Creating Products that Customers Love*, ser. Agile Software Development. Addison-Wesley, 2010.
- [19] S. Oesterreich, A. M. Brufsky, and N. E. Davidson, “Using Mice to Treat (Wo)men: Mining Genetic Changes in Patient Xenografts to Attack Breast Cancer,” *Cell Rep*, vol. 4, pp. 1061–1062, Sep 2013.
- [20] N. Rani, R. Singh, and G. Arora, “Detection of ORF Frames Using Data Mining,” *International Journal of Computer Science and Telecommunications*, vol. 2, no. 3, pp. 90–94, Sep 2011.
- [21] SAP AG, “SAP HANA SQLScript Reference,” help.sap.com/hana/hana_dev_sqlscript_en.pdf [retrieved: Jun, 2014], 2012.
- [22] A. Hannan, “The L Programming Language & System,” <http://home.cc.gatech.edu/tony/uploads/61/Lpaper.htm> [retrieved: Jun, 2014], Jan 2005.
- [23] C. Bresch and R. Hausmann, *Klassische und molekulare Genetik*, 3rd, Ed. Springer-Verlag, 1972.
- [24] F. Hsu *et al.*, “The UCSC Known Genes,” *Bioinformatics*, vol. 22, pp. 1036–1046, 2006.
- [25] B. Alberts *et al.*, *Molecular Biology of the Cell*, 5th, Ed. Garland Science, 2007.
- [26] SAP AG, “SAP HANA Database R Integration Guide Version 1.1,” https://help.sap.com/hana/SAP_HANA_R_Integration_Guide_en.pdf [retrieved: Jun, 2014], Mar. 2014.
- [27] —, “SAP HANA Database Predictive Analytics Library (PAL) Reference Version 1.1,” https://help.sap.com/hana/SAP_HANA_Predictive_Analysis_Library_PAL_en.pdf [retrieved: Jun, 2014], Mar. 2014.
- [28] M. Hahsler, B. Grün, and K. Hornik, “Introduction to arules: Mining Association Rules and Frequent Item Sets,” in *Special Interest Group on Knowledge Discovery and Data Mining*, 2007, pp. 1–28.
- [29] A. J. Smola and B. Schölkopf, “A tutorial on Support Vector Regression,” *Statistics and Computing*, vol. 14, no. 3, pp. 199–222, 2004.
- [30] C. Cortes and V. Vapnik, “Support-Vector Networks,” *Machine Learning*, vol. 20, no. 3, pp. 273–297, 1995.
- [31] A. K. Jain, M. N. Murty, and P. J. Flynn, “Data Clustering: A Review,” *ACM Computing Surveys*, vol. 31, no. 3, pp. 264–323, 1999.

Probing the Inflammatory Pathways Associated With Increased Levels of Oxidized LDL Through the Structural Analysis of B17

Soumaya Berro, Bassam Hussein, Mohamad Hajj-Hassan, Bassam Hamam, Wiam Ramadan, Hassan M. Khachfe
 Lebanese International University
 Beirut, Lebanon
 {10830001, bassam.hussein, mohamad.hajjhassan, bassam.hamam, wiam.ramadan, hassan.khachfe}@liu.edu.lb

Abstract—The structure of the 17% N-terminal domain of apolipoprotein B-100, apo B-17 (or simply B17), was homology-modeled after the structure of the N-terminus of lipovitellin (LV), a protein that shares not only a sequence homology with B17, but also a functional aspect of lipid binding and transport. The model structure was first forced to accommodate the six disulfide bonds found in that region, and then dynamically relaxed to minimize the free energy of the molecule. The content of secondary structural elements in this model structure correlates excellently with the reported data from other biophysical probes. The C-terminus of B17 shows a considerable homology with a conserved region in the constant domain of the T-cell receptor containing several residues that are essential in the interfacial connectivity with the variable domain. This structural insight may be the first potential link between atherogenic LDL and inflammation.

Keywords—Apolipoprotein; atherosclerosis; homology modeling; LDL; inflammation.

I. INTRODUCTION

Atherosclerosis is a complex disease that has been linked to many risk factors, including hyperlipidemia, dyslipidemia, high blood pressure, and endothelial dysfunction [1]. Oxidative modification to the small Low-density Lipoprotein (LDL) has been dubbed the central event that initiates and propagates coronary artery diseases [2][3], and therefore, LDL is considered a major risk factor for atherosclerosis [4]. It has been also shown that systemic inflammatory mechanisms may underlie the pathogenesis of atherosclerosis [5][6][7]. This is probably why atherosclerosis is called an inflammatory disease [8]. The atherosclerotic process begins when cholesterol-rich LDL particles accumulate in the intima, and then activate the endothelium [8]. Leukocyte adhesion molecules and chemokines help in the recruitment of monocytes and T cells, and thus the inflammatory pathways [8]. However, the specific structural interactions implicated in these mechanisms have not yet been elucidated.

This report introduces a work-in-progress about the relation between inflammation and atherosclerosis, by probing the structural aspects of the apo-B. The next section gives some background information about the topic. It is followed by the experimental design. Subsequently, the

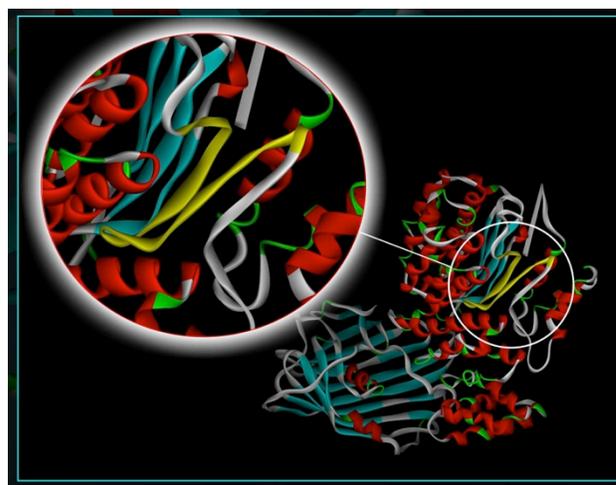


Figure 1. The structure of B17 modeled after lipovitallin, with the TCR homology region (yellow stretch) shown magnified [11].

results are discussed. Finally, some conclusions are summarized at the end.

II. BACKGROUND

Apolipoprotein B-100 (apo B) is the sole protein component of LDL [9], but its large size (4536 a.a.) and the limitation of current experimental techniques require that it be studied in pieces corresponding to its structurally organized domains [10]-13]. Biochemical [13][14], calorimetric [15][16], computational [11][17]-[20], and spectroscopic [21][22] approaches were used to probe the domain arrangement and characterization of the protein, but no molecular structure has ever been assigned to any of the different domains. These techniques, however, helped in the understanding of the overall arrangement of apo B on the LDL particle and the interactions that the various secondary structures have with both the lipid and aqueous phases, and in the ability to genetically engineer protein truncations that correspond to these various domains [14][23]-[25].

In this project, we will use the model structure of the 17% N-terminus of apo B [10] – the first 782 a.a. of apo B (17% of the full-length sequence), a region that is rich in disulfide bonds [26][27], essential for the secretion of the protein from hepatic cells [23] and behaves like an independent globular protein [21] – to further understand

the C-terminus of the protein. This part of B17 shows a considerable homology with a conserved region (25 aa) in the constant domain of the T-cell receptor (TCR) – a protein that is necessarily present during inflammation (Figure 1). It also contains several residues that are essential in the interfacial connectivity with the variable domain, which binds to the different antigens specific to each inflammatory pathway. We will try to establish a potential link between LDL and the inflammatory state correlated with atherosclerosis.

III. EXPERIMENTAL DESIGN

The structure of B17 was modeled using Insight II (Accelrys Inc., Insight Modeling Environment, Release 2000.1, San Diego: Accelrys Inc., 2002), based on the crystal structure of lipovitellin (LV) [11]. The secondary structure of the unstructured region was predicted using the Chou-Fasman Algorithm [28], the PROF methods [29][30] and the Deep View modality [31] (Figure 2). The calculation will be performed using the CHARMM molecular dynamics application [32].

The project will continue to have the following outputs and activities:

- Output 1: Explore the structural characteristics of the potential TCR homology region;
 - Activity 101: Further assessment of the model in various solvated states;
 - Activity 102: In-silico exploration of the ability of the TCR homology region to interact with ligands, by probing the propensities of the different exposed residues;
- Output 2: Study the ability of the region to adopt several conformations based on the lipidation state of the protein or the environmental conditions in the plasma;
 - Activity 201: Simulation of the various conditions to explore the corresponding conformations, by working out the energy minimization of the proposed structure;
 - Activity 202: further refinement of the model based on the environmental interactions and conditions, by introducing parameters pertaining to these conditions into the energy function;
- Output 3: Probe the interactions that might exist between this particular region and inflammation markers, i.e., interleukins and interferon.
 - Activity 301: Possibility of in-vitro interaction between a synthesized peptide corresponding to the TCR homology region with inflammation markers;

IV. RESULTS AND DISCUSSION

Inflammatory mechanisms have been reported to underlie the pathogenesis of atherosclerosis [5][6][7]. The C-



Figure 2. The unstructured region of B17 (aa 706-782). The H's below the sequence denote regions predicted to have helical secondary structure.

terminus of B17 shows a considerable homology to a conserved region in the constant domain of the T-cell receptor – a protein that is necessarily present during inflammation. It also contains several residues that are essential in the interfacial connectivity with the variable domain, which binds the different antigens specific to each inflammatory pathway. The current model clearly shows that this region is fairly exposed and flexible, which – along with the normal protrusion of B17 from the small dLDL particle – may suggest that some kind of interactions may take place between apo B and other cell surface proteins, thus mimicking or competing with the T-cells during atherogeneity. This model, therefore, establishes a potential structural link between LDL and the inflammatory state correlated with atherosclerosis.

V. CONCLUSIONS

In this report, a solid link between atherosclerosis and inflammation is established. During atherogenesis, Monocytes recruited upon the activation of the endothelium differentiate into macrophages and upregulate pattern recognition receptors, including scavenger receptors and toll-like receptors. Scavenger receptors are responsible for lipoprotein internalization, and hence, foam-cell formation, one of the major steps in the plaque formation, characteristic of atherosclerosis. On the other hand, toll-like receptors transmit effector signals that lead to the release of cytokines, proteases, and vasoactive molecules. The T cells in these lesions recognize local antigens, and therefore, mount T helper-1 responses characterized by the secretion of pro-inflammatory cytokines, which contribute to local inflammation and the growth of the plaque [8].

While the cascade of events in the above inflammatory response is well organized, the structural link between the various players, in general, and between the oxidized LDL and the inflammation markers, namely the T-cells, has not been observed, let alone elucidated. In the current project / report, an exposed amino acid stretch in the C-terminus of

the first 17% amino-terminal end of apo B-100 was found to adopt the structure of that of the T-cell receptor binding domain. This constitutes the first evidence of a structural link between atherosclerosis-causing LDL and inflammation.

After establishing such a link "*in silico*," we anticipate that *in vitro* experimentations take place, probing the cytokines – and possibly interleukins – involved, then followed by *in vivo* tests to determine the real physiological effects correlated with such a link vis-à-vis the roles of the different involved factors.

REFERENCES

- [1] S. Perez, "Thinking intelligently about therapy of atherosclerosis.," American Journal of Therapeutics, vol. 10, 2003, pp. 429-437.
- [2] S. Yla-Herttuala, W. Palinski, M. Rosenfeld, S. Parthasarathy, T. Carew, S. Butler, J. Witztum, and D. Steinberg, "Evidence for the presence of oxidatively modified low density lipoprotein in atherosclerotic lesions of rabbit and man," Journal of Clinical Investigation, vol. 84, no. 4, 1989, pp. 1086-1095.
- [3] S. Yla-Herttuala, W. Palinski, M. Rosenfeld, D. Steinberg, and J. Witztum, "European heart journal," Lipoproteins in normal and atherosclerotic aorta, vol. (Suppl E), no. 4, 1990, pp. 88-99.
- [4] R. A. Archbold and A. Timmis, "Modification of coronary artery disease progression by cholesterol-lowering therapy: the angiographic studies," Current Opinion in Lipidology, vol. 10, 1999, pp. 527-534.
- [5] K. Bach-Ngohou, H. Nazih, F. Nazih-Sanderson, Y. Zair, D. L. Carrer, M. Krempf, and J. Bard, "Negative and independent influence of apolipoprotein E on C-reactive protein (CRP) concentration in obese adults. Potential anti-inflammatory role of apoE *in vivo*," International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, vol. 25, 2001, pp. 1752-1758.
- [6] J. Hulthe and B. Fagerberg, "Circulating oxidized LDL is associated with increased levels of cell-adhesion molecules in clinically healthy 58-year old men (AIR study).," Medical Science Monitor, vol. 8, 2002, pp. CRI 48-52.
- [7] V. Titov, "The functional role of arterial intima. Endogenous and exogenous pathogens and specificity of atheromatosis as an inflammation," Klinicheskaia Laboratonaia Diagnostika, 2003, pp. 23-24.
- [8] G.K. Hansson, A.K. Robertson, and C. Söderberg-Nauclér, "Inflammation and atherosclerosis," Annual Review of Pathology, vol. 1, 2006, pp. 297-329.
- [9] R. Mahley and B. Angelin, "Type III hyperlipoproteinemia: recent insights into the genetic defect of familial dysbetalipoproteinemia," Advances in Internal Medicine, vol. 29, 1984, pp. 385-411.
- [10] M. A. Mitsche, L. Wang, Z. G. Jiang, C. J. McKnight, and D. M. Small, "Interfacial Properties of a Complex Multi-Domain 490 Amino Acid Peptide Derived from Apolipoprotein B," Langmuir, 2009, pp. 2322-2330.
- [11] H. Al-Ali and H. Khachfe, "The N-Terminal Domain of Apolipoprotein B-100: Structural Characterization by Homology Modeling," BMC Biochemistry, 22 July 2007.
- [12] C. Claradas, R. Nolte, D. Atkinson, V. Zannis, and C. M. Hadzopoulou-Claradas, "The Complete sequence and structural analysis of human apolipoprotein B-100: relationship between apoB-100 and apoB-48 forms," EMBO Journal, vol. 5, 1986, pp. 3495-3507.
- [13] C. Y. Yang, Z. Gu, S. A. Weng, T. W. Kim, S. H. Chen, H. J. Pownall, P. Sharp, S. W. Liu, W. H. Li, and A. M. Gotto Jr, "Structure of apolipoprotein B-100 of human low density lipoproteins," Arteriosclerosis, vol. 9, 1989, pp. 96-108.
- [14] H. M. Khachfe and D. Atkinson, "Expression, purification, and quantification of the 17% N-terminal domain of apolipoprotein b-100," Journal of Cell and Molecular Biology 9(2), 2011, pp. 37-42.
- [15] H. M. Khachfe and D. Atkinson, "Confirmation and stability properties of B17-I: analytical investigations using circular dichroism," Eur Biophys J, 25 July 2012.
- [16] M. T. Walsh and D. Atkinson, "Calorimetric and spectroscopic investigation of the unfolding of human apolipoprotein B," Journal of lipid research, vol. 31, 1990, pp. 1051-1062.
- [17] R. T. Nolte, "Structural Analysis of the human apolipoproteins: an integrated approach utilizing physical and computational methods," In PhD Dissertation, Boston University, Department of Biophysics, 1994.
- [18] J. Segrest, D. W. Garber, C. Brouillette, S. Harvey, and G. Anantharamaiah, "The amphipathic alpha helix: a multifunctional structural motif in plasma apolipoproteins," Advances in protein Chemistry, vol. 45, 1994, pp. 303-369.
- [19] J. P. Segrest, M. K. Jones, V. K. Mishra, V. Pierotti, S. Young, J. Boren, T. Innerarity, and N. Dashti, "Apolipoprotein B-100: conservation of lipid-associating amphipathic secondary structural motifs in nine species of vertebrates," Journal of lipid research, vol. 39, 1998, pp. 85-102.
- [20] J. Segrest, M. Jones, H. De Loof, and N. Dashti, "Structure of apolipoprotein B-100 in low density lipoproteins," Journal of lipid research, vol. 42, 2001, pp. 1346-1367.
- [21] H. khachfe and D. Atkinson, "Confirmation and stability properties of B17-II: analytical investigations using differential scanning calorimetry," Eur Biophys J, vol 42, 2013, pp. 309-314.
- [22] M. Walsh and D. Atkinson, "Physical properties of apoprotein B in mixed micelles with sodium deoxycholate and in a vesicle with dimyristoyl phosphatidylcholine," Journal of lipid research, vol. 27, 1986, pp. 316-325.
- [23] C. Cladaras, M. Hadzopoulou-Cladaras, H. Herscovitz, M. T. Walsh, V. Zannis, and D. Small, "Expression, secretion and lipid-binding characterization of the N-terminal 17% of apolipoprotein B," Proceedings of the National Academy of sciences of the United States of America, vol. 88, 15 October 1991, pp. 7313-7317.
- [24] H. Herscovitz, A. kritis, I. Talianidis, E. Zanni, V. Zannis, and D. Small, "Murine mammary-derived cells secrete the N-

terminal 41% of human apolipoprotein B on high density lipoprotein-sized lipoproteins containing a triacylglycerol-rich core," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 92, 1995, pp. 659-663.

- [25] H. M. Khachfe, "Spectroscopic and Calorimetric Studies of the 17% N-terminal domain of apolipoprotein B-100," In PhD Dissertation, Boston University, Department of Biophysics, 2002.
- [26] G. S. Shelness and J. T. Thornburg, "Role of Intramolecular disulfide bond formation in the assembly and secretion of apolipoprotein B-100-containing lipoproteins," *Journal of lipid research*, vol. 37, 1996, pp. 408-419.
- [27] C. Y. Yang, T. Kim, S. A. Weng, B. R. Lee, M. Yang, and A. M. Gotto, "Isolation and Characterization of sulfhydryl and disulfide peptides of human apolipoprotein B-100," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 87, 1990, pp. 5523-5527.
- [28] P. Y. Chou and G.D. Fasman, "Prediction of protein conformation," *Biochemistry*, 13(2), 1974, pp. 222-245.
- [29] B. Rost and C. Sander, "PROF," *J Mol Biol*, 232, 1993, pp. 584-599.
- [30] B. Rost, P. Fariselli, and R. Casadio, "PROFhtm," *Prot Science*, 7, 1996, pp. 1704-1718.
- [31] Swiss-PDB viewer [<http://www.expasy.org/spdbv>]
- [32] B.R. Brooks et al., "CHARMm: A program for macromolecular energy, minimization, and Dynamics Calculations," *J Comp Chem*, 4, 1983, pp. 187-217

A Health VC for Chronic Disease Management in a Global Context

Christo El Morr, PhD
School of Health Policy
and Management, York
University Toronto,
ON Canada
elmorr@yorku.ca

Shadi Saleh, PhD
Department of Health
Management and
Policy, American
University of Beirut
Beirut, Lebanon
ss117@aub.edu.lb

Walid Ammar, MD
Ministry of Public
Health
Beirut, Lebanon
mphealth@cyberia.net.l
b

Nabil Natafgi
Department of Health
Management and
Policy, American
University of Beirut,
Beirut, Lebanon
nmn13@aub.edu.lb

Karen Kazandjian
Department of Health
Management and
Policy, American
University of Beirut,
Beirut, Lebanon
kk03@aub.edu.lb

Abstract— This paper presents an implementation of hybrid Health Virtual Community (Health VC) using a predefined model to design Health VC in a developing country. It provides an analysis of the components needed in an environment where high technology is not as available as in a developing country. We argue that virtual community researches should take into consideration a more flexible approach to model VCs and we suggest changes to the model.

Keywords-Health Virtual Communities; Virtual Communities; Online Communities; Chronic Disease Management; Chronic Disease; Modeling; Global Health; Developing Countries; LMIC.

I. INTRODUCTION

Worldwide, chronic diseases (e.g., diabetes, hypertension, cardiovascular diseases, and chronic respiratory diseases) are hitting an increased number of the population. Globally, Chronic diseases related caused 35 million death out of 58 million in 2005; moreover, the fatalities caused by cardiovascular diseases is almost twice the number of fatalities caused all infectious diseases combined (e.g., tuberculosis, malaria, AIDS) [1]. Besides the lower life expectancies, populations in developing countries suffer from chronic diseases [2]; in fact, the number of deaths from Cardio-Vascular Diseases (CVD) in developing countries is twice the same number in developed countries, and more than three-quarters of deaths related to diabetes are occurring in developing countries [1].

An intervention that uses eHealth System has the ability to allow chronic disease management. Health Virtual Communities has been identified as one eHealth tool that allow such intervention. Virtual Communities (VCs) were subject to investigation from many sides to explore their advantages and challenges. Researchers in healthcare investigated ways to use VCs for healthcare delivery and support [3][4]. In an attempt to understand and sketch the VC, models were proposed for static and mobile virtual communities [5][6].

In this paper, we will describe the development a health VC in a developing country for chronic disease management. The health VC was designed based on previously suggested model [7]. We will explain the Health VC components and

discuss the ability of this model to satisfy the requirements of virtual community definition, taking into account the technological challenges of developing countries in a global health context.

We will start with a description of the health VC for chronic disease management Virtual Community in section II. We will, then, explain the design of our Health VC in section III. We provide a discussion of our Health VC in section IV and conclude the paper in section V.

II. BACKGROUND: HEALTH VIRTUAL COMMUNITIES

A Health Virtual Community cover a wide range of clinical specialties, technologies and stakeholders [8]. Members of a Health VC can be health care providers, educators, patients, health professionals. We can classify Health VCs into two categories: professional-centered or patient-centered. A professional centered VC is focused on exchange of knowledge among professionals and forms a community of practice. Members in such communities are health professionals that interact and work in virtual teams in order to exchange knowledge and create new knowledge if possible.

Members of patient-centered VCs include health professional, patients and possibly their family members. Patient centered VCs permit professionals-to-patient and patient-to-patient communication. Health care professionals can tele-monitor and support patients and their families in their day-to-day management of their health condition. Moreover, individuals diagnosed with the same condition (e.g., chronic disease) can exchange and share health information and personal experiences. Hence, patient centered VC ensures continuity of care.

The communication between patients and their doctors improves patient care [9]. Hence, the creation of patient-centered Health VCs constitute a mean to strengthen patient-doctor interaction and flow of information, providing improved care while overcoming geographical boundaries.

Managed care is considered to take place when the right care is provided by qualified health team members to a person “at the right frequency and duration that will best support that person” [10]. Tools to remotely monitor and/or educate patients and people at risk, play an important role in managed care. This allows the patients and people at risk to

be involved in the management of their own conditions. That is the idea behind self-managed care [11].

In a Low-Middle Income Country (LMIC), in a global health context, a project involving the implementation of health VC is underway. The internet penetration in LMICs allows implementation of health VCs with potential benefits to healthcare health care providers and their patients. We will explain in the following the design of a patient-centered health VC for chronic disease management in a LMIC.

III. A VIRTUAL COMMUNITY FOR CHRONIC DISEASE MANAGEMENT

Healthcare VCs emerged in the online environment as an attempt to benefit from the advantages VCs offer for patients [4] such as those with chronic diseases [3] or diabetes and hypertension [5]. Mobile VCs present also many possibilities, and many models have been proposed to use them, with in a general context [6] or in the health sector [12] (e.g., for cancer patients [13][14]). Our project consists of building a collaborative health virtual community in Lebanon to enhance equity in access to primary care in rural areas and Palestinian refugee camps. The research team includes researchers from the American University of Beirut, Lebanese Ministry of Public Health (MoPH), the United Nations Relief and Works Agency (UNRWA), York University, and University of Toronto.

In Lebanon, a LMIC, 84% of all deaths are due to chronic diseases [15]. Age-standardized death rates from CVDs diabetes reach 404.4 and 262.7 per 100,000 individual, respectively [16]. This problem is intensified in disadvantaged populations in the rural areas and the Palestinian refugee camps. Non-Governmental Organization (NGO) that run primary health care centers available in the underserved rural areas often suffer from limited resources [17].

This project takes a proactive integrated approach that couples community-based and health care initiatives. A health VC is being developed in order to support both patients and healthcare providers in 10 primary health care (PHC) centers located in rural areas and enrolled in the Lebanese Ministry of Public Health (MoPH) PHC National Network (Network) and 6 UNRWA PHC centers will comprise the study population. Agency (UNRWA) centers will comprise the study population. These centers are randomly assigned into the intervention and control groups. The intervention has two components:

- **A Provider Oriented Component:** it targets the physicians (supply)

- **A patient Oriented Component:** it targets patients having appointments at the primary care centers and suffering from diabetes and hypertension (demand). Another aspect of the patient oriented component includes screening potential patients in the community.

We designed a health virtual community to provide the necessary tools. The hardware and software infrastructure was already provided by the network connection between the healthcare community centers and the MoPH. The tools needed for doctors and patients can be summarized in 3 sub-

systems: patient-oriented, provider-oriented and a service-oriented one.

A. *Provider-oriented Sub-System*

The healthcare providers need to have access to information related to the clinical guidelines, the physician-patient communication strategies, and online forums and Frequently Asked Questions (FAQ). An online portal was designed to enable healthcare providers from the PHC centers to meet and discuss online. Moreover, a FAQ section was designed to contain health information relevant to diabetes and hypertension. A coordinator of the Forum was designated to receive questions from the healthcare providers in the PHC centers, formulate answers, and ultimately create new FAQs. The clinical system and the online portal would be independent, and any information to be posted on the portal was to be de-identified to protect patients' and health providers' privacy.

B. *Patient-oriented Sub-System*

The patient oriented component was composed of targeted consumer Short Message Service (SMS) containing either health information related to disease self-management or reminders to appointments at the community PHC centers. We have used the Application Programming Interface (API) of a commercially available SMS service available in the local market to integrate our SMS-based patient oriented component into the existing system at the community centers.

Regarding the patient e-education material; even though Lebanon has a high penetration of internet (52%) and cell phone use (3,350,000 mobile-cellular telephone subscriptions, equivalent to 78.65 subscriptions per 100 inhabitants) [18], smart phones were not judged to be a good tool in the rural communities. The eHealth research team decided to deliver the educational material targeting screened patients, using a more accessible medium, namely a.

C. *Service-oriented Sub-System*

The provider-patient relationship had to be managed through two components: a health indicators collection component and an appointment-scheduling system component.

The health indicators component was needed to enter clinical data related to the collection of the baseline and the evaluation of the intervention. The MoPH provides the clinical system in the community centers; however, we needed to update it in order to collect the additional clinical indicators (e.g., rate of controlled glycosylated hemoglobin or HbA1c, controlled hypertension, and annual eye exam). The related additional modules were designed using a minimalist approach; the design was straightforward and did not add complexity to the already existing system.

The appointment-scheduling system component was designed through an existing commercial service. We have decided to use the commercial Application Programming Interface (API) to embed the SMS messaging strategy into

the clinical application that is present in the community centers.

The design of the Health VC is presented in Figure 2.

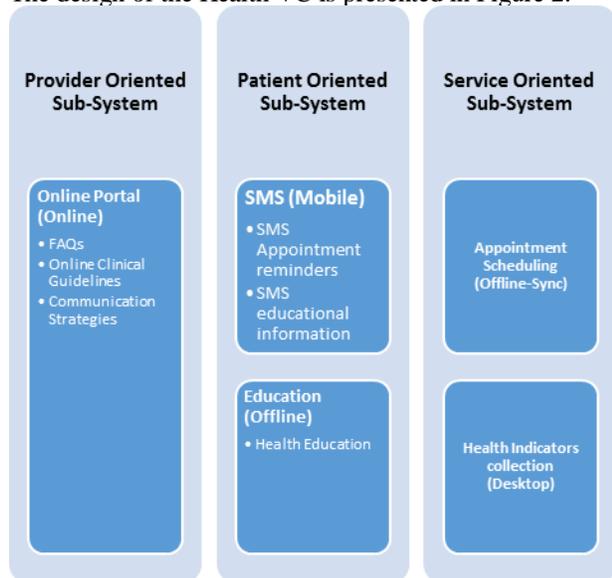


Figure 1. The Health VC Design

IV. A HYBRID VC MODEL

Based on our analysis and design of the Health VC, we find that the models proposed in the literature [5, 6, 19-24] are more focused on developed countries and exclude the situation in developing countries. We suggest a more inclusive design of a hybrid virtual community model that takes into consideration that the VCs can be developed using a myriad of technologies. Some of these technologies can be traditional (e.g., DVDs), others can be desktop based, while others can be off-line and then synchronized once they are connected to the whole system.

We suggest a three dimensional hybrid model for virtual communities that takes into account the diversity of technologies that can be available to implement a virtual community. The model, shown in Figure 3, is composed of

- *Hybrid Communication Mechanisms* that allows for Synchronous (e.g., online) and/or asynchronous (e.g., offline/synchronization) communication between members
- A *Hybrid Infrastructure* that can be web-based, desktop-based, and/or offline (e.g., DVD)
- *Hybrid Delivery Channels* that allow multichannel communication with the community members, including mobile, non-mobile (Desktop), and offline (e.g., DVD)

This model is inclusive of experiences in developing countries that have different levels of access to ICT.

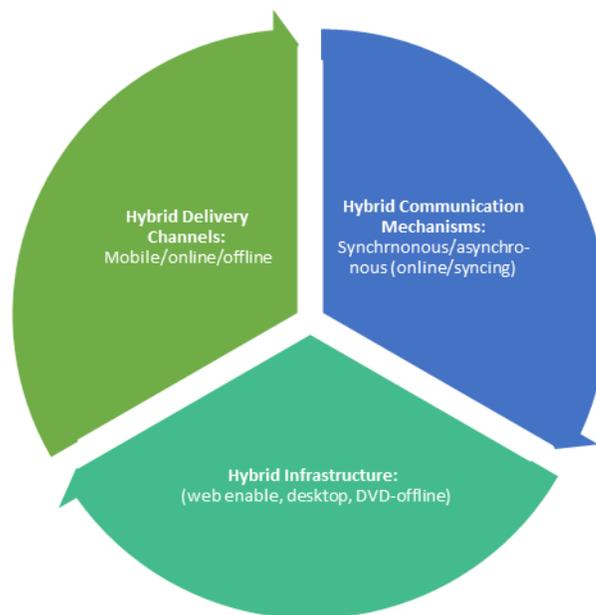


Figure 2. A Hybrid Virtual Community Model

V. DISCUSSION

The actual analysis and design of the Health VC faced many challenges. Our model may look surprising as it contains off-line material and information that need to be synchronized at a certain point in time. Nevertheless, our model complies with the definition of a virtual community.

Preece [25] suggests a working definition for online community that is broad enough to cover a wide range of communities but precise enough to fit into social science definitions. According to Preece (2000), an online community consists of:

- Socially interacting people performing special roles or satisfying their needs
- A purpose, which is the reason behind the community
- Policies to govern people's interaction
- Computer systems that support social interaction

Weissman [26] identifies two types of systems that form when humans get together: the organization type designed for a specific aim and the association type formed out of the individuals' dedication for shared objectives or beliefs. Had systems been of the former or latter type, they all share all or some of the characteristics that are outlined by Weissman. These are causal reciprocity, purpose, design, roles, circumstances, officers, passion, needs, loyalty, and access.

Our system complies with both Preece's definition of online communities or VCs, as well as Weissman's ten characteristics of communities.

Our Health VC:

- Is composed of socially *interacting people* constituting the *users* of the Health VC. There are four types of users of the Health VC: patients, health providers, fieldworkers, and the forum coordinator. Users perform special *roles*; the fieldworkers aim to screen the population and schedule appointments, the healthcare providers provide the diagnosis and patient follow-up, they interact with the portal (forum) coordinator for FAQs and access the online modules. Finally, the portal coordinator manages the online forum and answers questions related to new situations sent by healthcare providers remotely. The patients get access to educational materials (DVDs) and to SMS health messages and appointments reminders. Patients have mainly the role of information consumers while both fieldworkers and healthcare providers are information producers and consumers (e.g., access to information on the online portal). The coordinator is mainly a producer of information.
- Has a *purpose* to provide equity in access to healthcare for populations with chronic diseases in rural areas and /or deprived areas, using eHealth tools.
- Is endowed with strict *policies* to govern the way users (e.g., healthcare providers, fieldworkers, coordinator, and patients) interact with the system. Patients receive SMS messages, they cannot generate information; the fieldworkers feed the system with appointments. Healthcare providers enter clinical information into the community centers information system; and send questions and receive answers on the portal. The coordinator receives questions, organizes them and feeds answers into the forum.
- Comprises a computer system that supports the users' roles described. It is true that the computer system is not integrated in some aspects, for instance, the portal, community centers clinical system, and the field appointment scheduling; however, this does not diminish the fact that a computer system is in place and facilitates the users' tasks in order to achieve the community purpose.

If we look at Weissman's ten characteristics of a community, we find that our model satisfies them:

- *Causal reciprocity*: this aspect is about the usual "give and take" that drives people to stick together and it applies to our Health VC model where patient users are interested in consuming the information and clinicians and fieldworkers are interested in providing care.
- *Passion, needs, loyalty, and circumstances*: are all embedded in our system. Our Health VC facilitates

users' task to live their passion to achieve an aim (equitable healthy living), and fulfill their needs (be healthy, provide care). The loyalty to the Health VC is driven by the benefit each user gets out of it. The circumstances that created the community are related to enhancing public healthcare delivery in rural areas.

- *Purpose* and *roles*: are both described in our above discussion to Preece's characteristics.
- *Design*: the design of our Health VC facilitates the fulfillment of the purpose by coordinating the roles of the members.
- *Access*: is given to all users to fulfill their roles, e.g., internet connection, laptops and information system.
- *Officer*: is the system administrator that oversees the Health VC to make sure that all components are working well and that all users are abiding by the policies in place.

We conclude that having parts of a model offline, or not in sync, or not web-based does not affect the fact that the model describes well a Virtual Community.

VI. CONCLUSION

This paper presents a Hybrid Health Virtual Community model and analyzes its components based on a research project in a developing country. Some of the model components present asynchronous and off-line aspects; however, the model aligns with the definition of a virtual community and the characteristics of communities in general. VC models suggest usually a continuous online presence and access to advanced ICT devices; we provided a more comprehensive and an *inclusive* model that encompasses the circumstances of the developed countries while taking into account the ICT situation in developing ones.

REFERENCES

- [1] World Health Organization, "Preventing Chronic Disease: A Vital Investment," World Health Organization (WHO), Geneva, Switzerland 2005.
- [2] World Health Organization, "The World Health Report 2003—Shaping the Future," World Health Organization (WHO), Geneva, Switzerland 2003.
- [3] C. El Morr, "Mobile Virtual Communities in Healthcare The Chronic Disease Management Case," in Ubiquitous Health and Medical Informatics: The Ubiquity 2.0 Trend and Beyond, ed: IGI Global, 2010, pp. 258-274.
- [4] C. El Morr, "Health Care Virtual Communities: Challenges and Opportunities," in Handbook of Research on Developments in E-Health and Telemedicine: Technological and Social Perspectives, ed: IGI Global, 2010, pp. 278-298.
- [5] C. El Morr, "A Model for Global Health Virtual Communities," in The Second International Conference on Global Health Challenges, GLOBAL HEALTH 2013, Lisbon, Portugal, 2013.
- [6] C. El Morr and J. Kawash, "Mobile Virtual Communities Research: A Synthesis of Current Trends and a Look at Future Perspectives,"

- International Journal for Web Based Communities, vol. 3, pp. 386-403, 2007.
- [7] C. El Morr, S. Saleh, W. Ammar, N. Natafqi, and K. Kazandjian, "A Health Virtual Community Model: A Bottom Up Approach," in *eTELEMED 2014, The Sixth International Conference on eHealth, Telemedicine, and Social Medicine*, 2014, pp. 99-104.
- [8] G. Demiris, "Virtual Communities in Health Care," in *Intelligent Paradigms for Healthcare Enterprises*. vol. 184, B. Silverman, A. Jain, I. A., and L. Jain, Eds., ed: Springer, 2005, pp. 121-137.
- [9] M. R. Cornelia, W. Thomas, S. Marguerite, F. Gilbert, and M. K. Samir, "Effects of a computerized system to support shared decision making in symptom management of cancer patients: Preliminary results," *Journal of the American Medical Informatics Association*, vol. 10, p. 573, 2003.
- [10] HealthCanada, *Handbook 3A-Service Delivery Plan for the Home and Community Care Program*, 2000.
- [11] B. H. Stamm, "Creating Virtual Community: Telemedicine and Self Care," in *Secondary Traumatic Stress: Self-Care Issues for Clinicians, Researchers and Educators*, B. H. Stamm, Ed., ed: Sidran Press, 1999, pp. 179-207.
- [12] C. El Morr, "Mobile Virtual Communities in Healthcare: Managed Self Care on the move," in *International Association of Science and Technology for Development (IASTED) - Telehealth (2007)*, Montreal, Canada, 2007.
- [13] J. M. Leimeister, M. Daum, and H. Krcmar, "Mobile Communication and Computing in Healthcare: Designing and Implementing Mobile Virtual Communities for Cancer Patients," presented at the Tokyo Mobile Business Roundtable, Tokyo, 2002.
- [14] J. M. Leimeister, M. Daum, and H. Krcmar, "Towards m-communities: the case of COSMOS healthcare," in *The 36th Annual Hawaii International Conference on System Sciences(2003)*, 2003.
- [15] W. H. Organization, "Facing the Facts: The Impact of Chronic Diseases in Lebanon," WHO2012.
- [16] W. H. Organization, "NCD Country Profiles," WHO2011.
- [17] C. B. and C. M., "Informal politics and inequity of access to health care in Lebanon," *International Journal for Equity in Health*, vol. 11, 2012.
- [18] I. T. Union. (2012, Oct. 19). *ICT Data and Statistics*.
- [19] Y. Arnold, J. M. Leimeister, and H. Krcmar, "CoPEP: A Development Process Model for Community Platforms for Cancer Patients," presented at the The XIth European Conference on Information Systems (ECIS), 2003.
- [20] M. B. Chhetri, R. Price, S. Krishnaswamy, and W. L. Seng, "Ontology-Based Agent Mobility Modelling," in *39th Annual Hawaii International Conference on System Sciences (HICSS '06)*, 2006, p. 45a.
- [21] S. Glissmann, S. Smolnik, R. Schierholz, L. Kolbe, and W. Brenner, "Proposition of an m-business procedure model for the development of mobile user interfaces," 2005, pp. 308-314.
- [22] J. Kawash, C. El Morr, and M. Itani, "A Novel Collaboration Model for Mobile Virtual Communities," *International Journal for Web Based Communities*, vol. 3, 2007.
- [23] J. Page, A. Zaslavsky, and M. Indrawan, "A buddy model of security for mobile agent communities operating in pervasive scenarios," in *second workshop on Australasian information security, Data Mining and Web Intelligence, and Software Internationalisation - Vol. 32*, Dunedin, New Zealand, 2004, pp. 17-25.
- [24] P. Schubert and J. F. Hampe, "Business Models for Mobile Communities," in *38th Annual Hawaii International Conference on System Sciences(HICSS '05)*, 2005, pp. 172-183.
- [25] J. Preece, *Online Communities: Designing Usability supporting Sociability*. USA: John Wiley & Sons Ltd., 2000.
- [26] D. Weissman, *A social ontology*: Yale University Press, 2000.

The Development of Action Model that Integrate Tuberculosis Case Detection and Completeness of Treatment through Women Empowerment at District Level in Indonesia

Indang Trihandini, Popy Yuniar, R. Sutiawan
Dept. of Biostatistics and Population
Faculty of Public Health, University of Indonesia
dini05@ui.ac.id

Abstract—*Mycobacterium tuberculosis* (Mtb) is the causative agent of human tuberculosis (TB) with an estimated 8.8 million new TB cases and 1.4 million deaths annually. According to MDG (Millennium Development Goals), Indonesia should be able to reduce half the number of patients with infectious diseases including tuberculosis by 2015. Based on Health Survey data in Indonesia, 2010, Lebak is a district in Banten Province with the highest TB prevalence rate of 1,282 per 100,000 population. In 2013, Lebak District Health Office stated that one of the main problems in treating tuberculosis patient was the patient's reluctance to go to a hospital or health center. Therefore, encouragement for the patients is very important to reduce this reluctance. On the other hand, women in Lebak are socially active, including in their religious group. This active social group in Lebak can be a good medium to encourage patients with tuberculosis to go to the hospital. Therefore, we develop an integrated system model for finding out new cases and completeness of TB treatment through women empowerment in the family and community.

Keywords- Action model; Tuberculosis; Case detection; Completeness of treatment; Women empowerment

I. INTRODUCTION

Mycobacterium tuberculosis (Mtb) is the causative agent of human tuberculosis (TB) [1] with an estimated 8.8 million new TB cases and 1.4 million deaths per annum [1]. According to MDG, by 2015, Indonesia will have to decrease by half the number of the patients with contagious diseases, including TB. Unfortunately, sustainable and accurate information on TBC epidemic does not exist [2]. This situation leads to the deployment of costly surveys and discontinuous information. TB case detection deserves to be better treated. According to WHO reports in 2012 [1], the increase of prevalence numbers obviously showed that TB in Indonesia has become a global health problem. This was measured from several indicators such as morbidity, prevalence, and incidence. Prevalence in Indonesia was 281 per 100,000 people, which was higher than China, India and Thailand (104, 249 and 161). On the other hand, the number of incidences in Indonesia was 187, which was also higher than China, India and Thailand (75, 181 and 124) [1].

Indonesia has implemented the DOTS strategy since 1995, but unfortunately the tuberculosis treatment problem cannot be handled only by concentrating on the medical treatment aspect, but also through discovering new patients. Therefore, estimated CDR (Case Detection Rate) of TB incidence is still low, and the proportion of TB which has not been handled is still fairly large [2][3].

Lebak is one of districts in Indonesia with a large population of poor people with TB. The percentage of TB patients in Lebak who took treatment for less than 6 months was 19.3 % and TB patients who did not take any medication was 4.5%. In 2013, The Lebak District Health Office (DHO) stated that one of the main obstacles in treating patients with tuberculosis was the patient's reluctance to go to a hospital or health center. Therefore, encouragement for patients is important to reduce this feeling of reluctance. On the other hand, the Lebak women are socially active, and social groups can be a good medium to encourage patients with tuberculosis to go to the hospital. One active group in particular is the women's religious group Fatayat NU. Therefore, there is a necessity to develop an integrated system model to identify new cases and maintain the completeness of TB treatment through women empowerment. This study offers a program to treat communicable diseases, especially TB in Lebak district. Through the implementation of this program, every component involved in the application of TB prevention program will benefit directly and indirectly [4].

This paper is structured as follows. In Section II, we present the research method. In Section III, the results are presented. Section IV presents a solution for increasing the community knowledge regarding the TB disease and developed system. In Section V, we discuss our findings. Section VI concludes the paper.

II. RESEARCH METHOD

This study has been ongoing for 17 months (began March 2013) and will conclude on October 2014. A variety of

methods were employed to develop the model in this study [5][6][7]:

1. Literature study of baseline data on case detection and number of drop-outs, and selected priority area had been conducted.
2. Knowledge and behavior of women in the communities to detect and treat TB cases have been assessed through quantitative and qualitative approaches.
3. Training on how to detect and treat TB cases in religious meetings for two months have been conducted.
4. Communication media to increase their knowledge of TB symptoms have been designed.
5. A short message application based on System Development Life Cycle (SDLC) and web design. Those methods were deployed to develop the information systems had been developed.
6. The integrated patients' database between the Health Center and community have been developed
7. A standard operating procedure (SOP) and knowledge suitable for other districts/counties to enable replication had been developed.

Three Primary Health Centers (PHC) were involved in this study, namely PHC Mandala, PHC Karanganyar and PHC Cibadak.

III. RESULTS

A. Problem Identification on Communities

150 women from 3 villages (50 women from each PHC) were interviewed, and results indicate that only 20% knew about the symptoms of TB, 50% had heard of TB, and only 1% knew about TB treatment. The result from problem identification indicated that the community tends to have poor knowledge and tends to be very passive toward TB treatment. Therefore, we developed an implementation strategy training to increase community awareness in detecting TB cases with an understanding of symptoms of TB diseases, such as:

1. Coughing for 2 weeks or longer
2. Sputum is mixed with blood
3. Cold sweats at night (while not conducting any activities)
4. Chest pains and shortness of breath
5. Decreased appetite and body weight
6. Fever in the evening for a month or longer

Each training took 3 days per season within two months. We held four trainings for the Lebak women. We also suggested the women who have received training to teach about TB symptoms to their social groups, such as their Quran recitar (*pengajian*) group and local women empowerment (PKK) (Fig. 1).



Figure 1. Training of women to detect and understand the symptoms of TB diseases

B. Media Communications Development

A communication media by creating leaflet and pocket book had been designed. This aims to provide information of TB, its signs and symptoms, and preventive measures. In this leaflet, there was also information of a Short Message System (SMS) gateway number that can be reached by the target group if TB symptoms are found in the family or surrounding community. On the other hand, the pocket book provides information on how to use the SMS application information system for health officers in PHC and mothers. Figure 2 illustrates the design process of leaflets, booklets about TB symptoms should be known and understood by mothers through several meetings.



Figure 2. Finished leaflet and process of designing leaflets

C. Problem Identification on System

Several problems were also identified in the assessment system conducted. Problems were divided into three components: input, process and output. From the input component, problems that occurred were [8][9]:

1. Recording and reporting process were still conducted manually and was potential to human error;
2. The software that can improve community-based

reporting and monitoring of TB patients' treatment completeness was not ready yet. The problem which occurred during the process is that the transformation process from data to information was still manually performed and, in turn, was not effective for creating routine reports. Because the manual process took some time, this in turn impacted on performing the output, such as the need for extra time for feedback to respond to cases and the difficulties for community to understand the sign and symptom of TB.

The constraint of the information systems development was that the system was not developed in an integrated manner. It should be developed by seeing the behavior of the unit of observation, ability of the operators, infrastructure constraints, standard operating procedures and decision makers' needs. Good information systems should be tiered, from the smallest unit to the decision-making units. The integrated information model unit that can perform well was the availability of trigger unit, which could enforce the observation unit to be very effective [10]. The TB patients, as the smallest observation unit, and women can be the trigger units which needs to be observed periodically. Therefore, in this proposal, empowerment of women in the family was chosen as the trigger unit in the integrated information system development.

Considering the aims of this study, we made problem solving *breakthroughs*, such as the use of SMS or text messaging to register suspected TB Patients into certain Primary Health Center [11]. Preliminary findings indicated by SMS had many advantages, such as: lower unit cost (no telephone calls or visits to PHC for reporting), no staff needed to administer (we designed the system to connect directly through SMS and PHC's system), and cost effective and efficient. In Lebak, most women have GSM mobile phones. Unfortunately, there are still fees for sending SMS or text messages.

IV. SOLUTIONS

There are a number of alternate solutions to overcome these problems [12][13]:

1. Share information on signs and symptoms of TB with the community;
2. Conduct trainings to increase health officers' capabilities so they can function as facilitators to increase community awareness;
3. Develop an information system to effectively assist communities to report cases to health officers.
4. Improve the integrated system process. A development that can reduce the delay in reporting process is required. Besides, this can improve access to the information, and information can be monitored and evaluated.

The expected output from this solution is the real time information which will improve case detection and reduce drop-outs [8][10]. Prior to these alternate solutions,

empowering community, especially women, to be able to perform active surveillance was a key element in the implementation of the information system. In order to reduce the difficulties experienced by that target user in using information system, in the early stages of implementation, health officers and community organizations will provide continuous assistance (Fig. 3) [14]. SMS or text messages are used to register suspect TB patients which are sent by trained women. If problems persist, health officers are to provide manual records to grant data transmission. These two activities will be conducted by considering the community's ability to adapt to the information system (technology acceptance).



Figure 3. Schematic of the SMS system report

A. The SMS for Life system

The system consists of two components [15][16]: an SMS management tool and a web-based reporting tool. The SMS management tool (Fig. 4) is an application stores with single registered mobile telephone number for each health care worker.

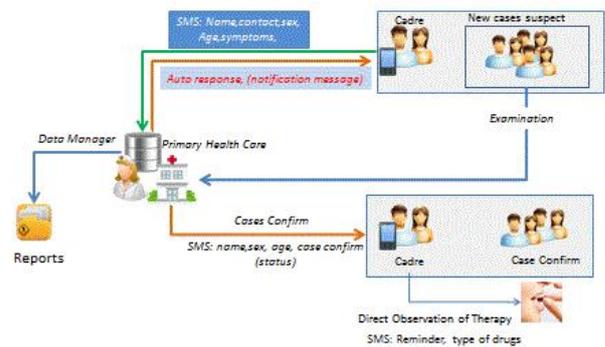


Figure 4. Scheme of the SMS system in the SMS for Life Pilot

B. Training and Socialization

Training and socialization participants include representatives of the Lebak District health office, data

management and information centers of Primary Health Centers, and 25 Fatayat NU cadres. These activities were held at the Fatayat NU Center over two days. The procedure of sending messages and patients data with symptoms as well as on leaflets and posters through sms is an important stage, given that this information system is built based on the patient data. Leaflets and posters were distributed over two weeks ago during a meeting with study groups in the organization Fatayat NU.

Participants were equipped with the knowledge to use the SMS tools, as well as the procedures for sending SMS module and assistance for patients to take medication. These activities were performed in conjunction with training in community health centers to receive cadre reports, as well as to send an automatic reply delivery cases and information on TB patients who had been positive TB diagnosed (Fig. 5). Health providers of Primary Health Centers has a number of responsibilities for the systems developed, such as monitoring TB patients to complete their treatments along with a Fatayat NU cadre, and compiling entire reports for Primary Health Center and Health District Office every three months.

The simulation to find cases done in these training was aimed to train participants to understand field situations and discuss potential scenarios. The training included question and answer session and an agreement to send SMS to primary health center if there is anyone suspected of having TB disease based on the symptoms explained in this training.



Figure 5. Training and socialization for Fatayat NU cadres and Primary Health Care providers

The trial specific procedures to recruit, enroll and follow-up participants were integrated within existing health care services pathways which were also discussed as well.

TABLE I. PATIENTS WITH SUSPECTED TB, POSITIVE TB DIAGNOSIS AND FOLLOWING TREATMENT

PHC Sub-districts	Years	Suspect			Diagnosed			Treatment			DO
		TW 2	TW 3	TW 4	TW 2	TW 3	TW 4	TW 2	TW 3	TW 4	
Kalangany	2013	5	24	25	3	10	5	3	7	5	3*
Mandala	2013	37	20	30	2	8	8	2	6	8	2*
Cibadak	2013	34	31	24	6	9	3	6	9	1	2*

Note: TW = quarter

Table I shows a tendency of TB suspect patients on the increase. This indicates that Fatayat NU cadres have actively approached and monitored the community in their area. Moreover, TB positive patients also increased in line with increased TB suspected patients. The numbers are quite similar to those of the Lebak District health office’s estimates on TB positive patients.

However, there are still patients who dropped out (DO) of their TB treatments. The main reasons of this are that the patients are unable to pay the cost of treatment and they felt healthier and, in turn, ended their treatments.

V. DISCUSSION

According to our findings, the women willing to enroll in this study such as cadres, were worried of contagious diseases and thought that the diseases will infect their families and friends. Ideally, women should be able to choose when and how frequently they would receive text messages, since a majority of women use their own mobile phones.

On the other hand, poor internet access via mobile phones and computer was one of the biggest obstacles for communicating with this community. However the strengths of this study included the representative sample of the general population. The unique personal identifiers made it possible to extract information through multiple record linkages on demographic and socioeconomic factors as well as previous hospitalization for all of the selected individuals.

The major weakness was the uncertain generalizability of our findings. However, there was still the benefit that can be obtained from the data that were linked with the registered based population, for instance the possibility to access the socio-demographic data. Coordination with partners (Department of Health and Fatayat NU) were carried out in order to perform a more precise analysis of the TB SMS trials system. In addition, this system showed that the majority of users were educated and younger individuals. The model was designed through media design communication and effective information system applications. The implementation of a system involving commitment between partners (Fatayat NU and Department of Health) as well as volunteers who were able to play an active role in carrying out these activities was necessary. Applications were developed by considering the efficiency and user friendliness which helped the system to be used optimally.

The benefit of an integrated information system is to increase the ability of community to recognize the signs and symptoms of TB disease. The increase of public awareness towards TB also affected the number of reports health workers received on presence of TB symptoms among communities [17]. The health workers will then proceed the reports by reminding the patients' families of the medical schedule that have been prescribed through Fatayat NU cadres.

As for the science development, this integrated information can be used as the reference for the further in-depth research on community empowerment through appropriate information technology. Moreover, this research can also be used to increase case detection and decrease drop-out rate from the TB medical treatment. Furthermore, this research can also be useful as reference in developing more user friendly information system for health workers and communities.

There are weaknesses in this system, such as dependency on computers, electricity, internet networks, and communication networks associated with mobile phone signals, as well as fees for sending SMS.

VI. CONCLUSION

This study shows that mobile phones are an acceptable approach for detecting new cases of TB and TB treatment completion and as a desirable and acceptable means of communication. However, we still need an effective communication media such as a leaflet that can be provided information of TB, its signs and symptoms, and preventive measures. Defining program success is not only determined by statistical significance, but also determined by the perception of users. In addition, monitoring and evaluation phase of designing a system is crucial to its success and needs to be enforced on a regular basis to maintain the true potential and continue to adapt with the needs of the patients.

ACKNOWLEDGMENT

The author would like to thank to the University of Indonesia that gave us financial support to conduct the research with number 2765/H2.R12/HKP.05.00/2013

REFERENCES

- [1] WHO, Global Tuberculosis Report, 2012.
- [2] Ministry of Health Republic of Indonesia, Regulation Health Minister Of The Republic Of Indonesia Number 565 / Menkes / PER / III / 2011 on National Tuberculosis Control Strategy Year 2011-2014, 2011.
- [3] National Development Planning Agency (BAPPENAS), Report of the Millenium Goals in Indonesia, 2011.
- [4] Ministry of Health Republic of Indonesia, Regulation Health Minister Of The Republic Of Indonesia Number 192/ Menkes/ SK/ VI/ 2012 about Roadmap Plan for strengthening of Health Information Systems, 2012.
- [5] D. Gundersten Storla, S.Yimer, and G. Aksel Bjune, "A systematic review of delay in the diagnosis and treatment of tuberculosis", *BMC Public Health*, vol 8, 2008, doi:10.1186/1471-2458-8-15.
- [6] Kushniruk, Andre. Human, Social and Organizational Aspect of Health Information System. Medical Informatic Series. Hershey New York, 2008.
- [7] M. Lynne Markus, C. Tanis, "The enterprise system experience-From adoption to success", In R.W. Zmud, Ed., *Framing the Domains of IT Research: Glimpsing the future through the past*, Cincinnati. 2007.
- [8] WHO, *Electronic Health Record: Manual for Developing Country*. Western Pacific Region, 2006.
- [9] V. Venkatesh, M.G. Morris, G.B. Davis, and F.D. Davis, "User acceptance of information technology: Toward a unified view", *MIS Quarterly* 27 no 3, 425-478, September 2003.
- [10] J. Tan, *E-Health Care Information Systems: An Introduction for Students and Professionals*. Jossey-Bass, a Wiley Imprint, 2005.
- [11] Ministry of Health Republic of Indonesia, Regulation Health Minister Of The Republic Of Indonesia Number 004/ Menkes/ SK/ I/ 2003 Decentralization Policies and Strategies on Health, 2003.
- [12] M. Rahmat, Ibrahim, Samik, *Penelitian Bidang Sistem Informasi Manajemen di Indonesia (SIMDI), "Quo Vadis? Sistem Informasi"*, 2005, MTI-UI, Vol 1(2).
- [13] S. Gondodiputro, "Medical Records and Health Information Systems in Primary Health Care (PHC)". Section of Public Health, FK-Universitas Padjadjaran, Bandung, 2007.
- [14] H. Eko, B.P. Agung, N.S. Fuad, "Hospital Information System Applications in the Web-Based Framework Using Sub-system Pharmacy Prado", Universitas Diponegoro, Semarang, 2008, Vol. 7 No. 1 Januari - Juni.
- [15] S. Albino, K.M. Tabb, D. Requena, M.Egoavil, M.F. Pineros-Leano, F.R. Zunt and P.J. Garcia mail, "Perceptions and Acceptability of Short Message Services Technology to Improve Treatment Adherence among Tuberculosis Patients in Peru: A Focus Group Study", *PLOS ONE*. Volume 9, Issue 5, May 2014, doi: 10.1371/journal.pone.0095770.
- [16] D.Lloyd Johnson, *Re-architecting Internet Access and Wireless Networks for Rural Developing Regions*. A Dissertation for the degree of Doctor of Philosophy. University Of California. Santa Barbara, March 2013.
- [17] A. Beith, R. Eichler, D. Weil, *Worldwide: Incentives for Tuberculosis Diagnosis and Treatment*, In *Performance Incentives for Global Health: Potential and Pitfalls*, 2009.

Constituting a Model for Obesity Control:

Possible Experience From the WHO Framework Convention on Tobacco Control

Xiangcheng Wang

Zhou Enlai School of Government, Nankai University
Tianjin, China
wangxiangcheng@mail.nankai.edu.cn

Tao Sun

Zhou Enlai School of Government, Nankai University
Tianjin, China
suntao@nankai.edu.cn

Abstract—The World Health Organization Framework Convention on Tobacco Control (WHO FCTC) has effectively controlled tobacco use worldwide, and its successful experience could be drawn to control obesity, which poses increasing dangers to people's health globally. Although the policies and regulations included in the WHO FCTC could not be adapted for controlling obesity wholesale, the WHO FCTC can indeed constitute a model to constrain the market availability of unhealthful foods and beverages for obesity control. The key measures suggested by the WHO FCTC, which are economic approach, educational strategies, labeling measure, restrictions on marketing as well as clinical intervention, can be applied to restrain the market availability of unhealthful foods in order to control obesity. However, the issue of obesity control is more complicated than tobacco control, since not all the foods are lethal, and the food companies are much more powerful than tobacco companies. Governments and organizations should cooperate globally and closely, and apply those measures comprehensively to create synergy in order to better control obesity. Though the potential model for obesity control may face some challenges such as the difficulty of implementation and obstruction of food industry, it has already made some achievements at current stage, for example, the WHO Global Strategy on Diet, Physical Activity and Health has been endorsed, which indicates that the future of the model for obesity control will possibly be bright.

Keywords—*global health policy; public health policy; obesity control; tobacco control*

I. INTRODUCTION

The World Health Organization Framework Convention on Tobacco Control (WHO FCTC) has enjoyed tremendous success in restraining the market availability of tobacco product, which is a lethal commodity and is responsible for millions of deaths every year. It is suggested that the model, seminal ideas and key measures of WHO FCTC can be used to inform the policy-making to restrain the market availability of unhealthful foods and beverage in order to effectively control obesity, which poses increasing dangers to people's health globally. To explore whether the model of the WHO FCTC can be applied in obesity control, this paper firstly

examines the achievements of the WHO FCTC in controlling tobacco use; secondly, it discusses the differences and similarities between tobacco and obesity control; thirdly, it introduces the key measures which are included in WHO FCTC and could be used in obesity control; fourthly, it discusses the challenges and achievements of the potential model for obesity control; and finally it will come to a conclusion that although there are differences between tobacco and obesity control, and the policies could not be adapted in the movement of obesity control wholesale, the WHO FCTC could indeed constitute a model to constrain the market availability of unhealthful foods and beverages for obesity control.

II. THE ACHIEVEMENT OF THE WHO FCTC

The WHO FCTC is believed to have successfully restrained the market availability of tobacco products. As the global health interdependence accelerates, the governments and international organizations recognize the necessity for cooperation to solve essential public health problems, such as the non-communicable diseases, among which tobacco is one of the most serious culprits. Numerous scientific evidences have shown that tobacco products are responsible for nearly six million people's deaths every year, which accounting for about 10% of all deaths worldwide (1). Both the WHO and its member states have political will to fight against the harm caused by tobacco products, and the WHO FCTC is the achievement of their long-period negotiation. The WHO FCTC, which entered into force in 2005, "has enjoyed tremendous global success, with more than 170 Parties, and is often called the most powerful tool in the fight against tobacco related morbidity and mortality" (1, p.847).

The WHO FCTC raises the states' and international organizations' awareness of the benefits of using legal instruments to achieve public health goals (1). The achievements of the WHO FCTC have led to calls to translate its successes to other global public health issues, particularly to the non-communicable diseases factors, such as the issue of obesity, which poses increasing dangers to people's health globally (1).

III. DIFFERENCES AND SIMILARITIES BETWEEN TOBACCO AND OBESITY CONTROL

Although the history of the epidemic of obesity and obesity-related diseases is comparatively short, obesity can exert negative impact on people's health to a large degree. It is one of the most blatantly global public health problems at the current stage. Obesity is not only a medical disorder, but also a harbinger of other diseases, such as cardiovascular disease, type 2 diabetes, obstructive sleep apnea, osteoarthritis, and several types of cancer (2). It is one of the most important risk factors contributing to the overall burden of disease and one of the most serious public health problems of the 21st century (3). More than one-third of American children born in 2000 are expected to suffer from diabetes sometimes in their lives, largely due to expected overweight or obesity (4). Besides, the mortality and health care costs of obesity-related diseases in the United States may possibly surpass those of tobacco-related diseases in recent years (4). Therefore, a series of measures and policies should be implemented to fight against obesity. Figure 1 makes a sketch of "globesity"—the escalating global epidemic of obesity problems.

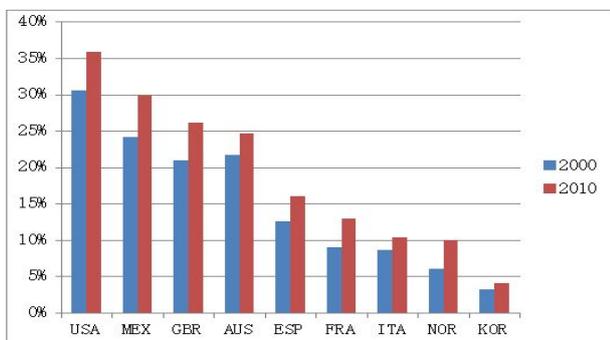


Figure 1. The obesity rate of the chosen countries in 2000 and 2010.

Adapted from the OECD Fact Book 2013 (5).

It is argued that the approaches for obesity control must be different from tobacco control. Tobacco product is not

necessaries for most people, and is a lethal commodity for a much higher proportion of its users (6). While the obesity issue, which is related to food and physical activity, is much more complicated than tobacco issue. Specifically and in direct contrast with tobacco, both appropriate food and physical activity are essential to life and must available to all people, and only the improperly intake of food and the physical activity levels that do not match energy intake could result in obesity, if regardless of the genetic factor (1). Therefore, due to the inherent challenges, it is suggested that the WHO FCTC cannot constitutes a model in controlling obesity.

However, the obesity issue has numerous similarities with tobacco issue. Firstly, some overweight or obese individuals struggle with similar compulsive tendencies as smokers by eating food for gratification beyond their nutritional requirement; besides, and overweight individuals as well as smokers are affected by social influences and advertising pressures to consume much more (8). Moreover, the profit-pursuing multinational companies in both tobacco and food area play an important role, which is obstructive and negative in most times, in the tobacco control as well as obesity control (4). Those similarities suggest that there may possibly be overlap between the points involved in the control of obesity as well as tobacco, and the successful experience of the WHO FCTC can be drawn for obesity control.

Therefore, both differences and similarities exist between the issue of tobacco and obesity. The WHO FCTC can be used for reference in constituting the model to control obesity. At the same time, when drawing lessons from the success of the WHO FCTC for the efforts to control obesity, governments and international organizations should consider more about the nuanced difference.

IV. A MODEL FOR OBESITY CONTROL

The key issues to control obesity are to regulate the policy in the food area as well as to encourage people to do more physical activities, in which the former issue is comparatively more important and complicated. “The template of the WHO FCTC can be used to consider the components potentially useful to the development of national diet and nutrition policies” (6, p.276). This part generally introduces the key measures and provisions included in the WHO FCTC and discuss their potential

application to obesity control, in particular to the area of food. The keys measures include: price and tax measures; educational strategies; labelling requirements; restrictions on advertising, sponsorship and promotion; clinical interventions.

A. Price and tax measures

The FCTC uses the price and tax measure, which is a key approach, to reduce tobacco consumption. Economic theory suggests that the demand for a product will decline as its price increases, and adolescents as well as individuals in low-and-middle-income countries are particularly sensitive to the increasing prices (7). That theory can be applied in the tobacco control. The Article 6 of the WHO FCTC (8, p.7) points out that the “price and tax measures are an effective and important means of reducing tobacco consumption by various segments of the population, in particular young persons”. In other words, raising the tax of tobacco product is a very effective way to decrease the affordability of cigarettes and to reduce people’s demand and the behaviour to purchase cigarettes, especially for those youngsters and adolescents that are comparatively sensible to the price change (7). It is estimated that a 10% increase in the price of tobacco products will lead to a 3-5% and 6-10% decline in overall consumption in high-income countries and low-and-middle-income countries respectively (9).

The price and tax measures can be used in the food area for obesity control. The governments could raise the taxes on the processed food, snack and beverage while do not raise taxes on or even subsidize fruit and vegetable, so that the fruit and vegetable are more affordable (10). Besides, it has been suggested that taxes on low-nutrient foods could be used to reduce the consumption of them as well as fund health promotion programmes (11). Therefore, economic forces can clearly affect food choices and consumption patterns, and deserved to be used by the governments in the food area for obesity control.

Numerous studies have already supported the positive effect of the price and tax measures on obesity control with solid data or evidence to a considerable degree. For instance, to exercise or increase 10% tax for all of the cheese and butter products, sugar and fat products, as well as ready-made meals could decrease the body weight

by 1.3kg per year in France (12); to exercise or increase 20% tax on the solely salty snack food could decrease the body weight by up to 0.17kg per year in the United States (13); to exercise or increased 10% tax on solely sugared soft drink could result in a drop in body weight by up to 1.4 kg per year in the United States (14); to increase the price of meat, butter and fact by 5% and the tax on fat, saturated fat and sugar by 15% could result in 8% decrease of saturated fat consumption fat and 16% decrease of sugar consumption in Denmark (15); to increase the price of the fats and oils by 24% could decrease 17.5% of energy consumption as well as 20% of the fat consumption in Scotland (16).

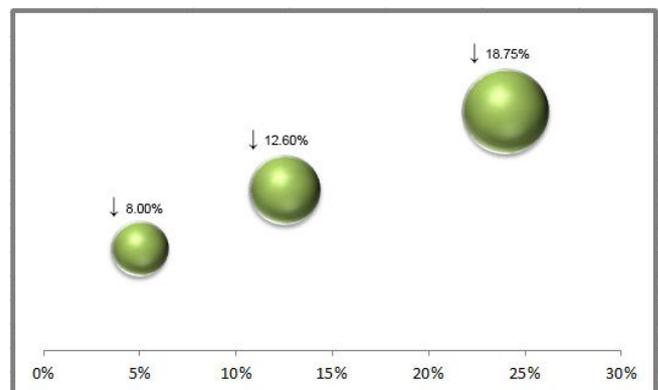


Figure 2a

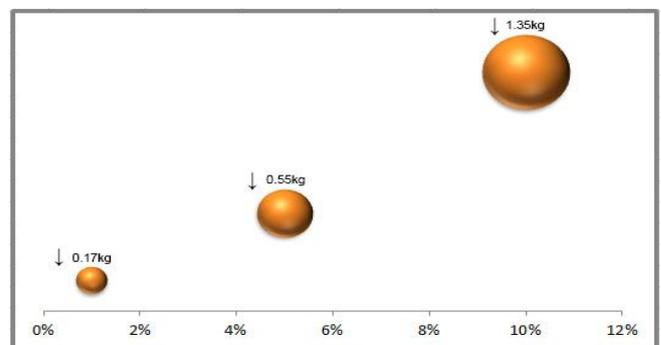


Figure 2b

Figure 2. The general trend in the relationship between the the increase in price or tax on food and drinks causing obesity per year (the bottom lines) and the decrease in the consumption (2a) as well as the decrease in body weight per year (2b). Adapted from the studies of Cash et al (12), Kuchler (13,14), Smed et al (15), Santarossa and Mainland (16).

However, the issues of price and taxation need to be considered much more cautiously in the food area, which is essential to life. Firstly, the price elasticity of processed foods which is of low nutrient value is not clear (10). Secondly, the low income groups are possible to be

greatly impacted by the taxes on processed foods. Those groups of people are likely to buy the food of comparatively low price, which includes the so called “junk food” or the food of low nutrient value, so if the price of such kinds of food increases, then those people’s life could possibly be impacted. Thirdly, it is argued that the taxation of certain foods may not sufficiently viable to tackle the problems of diet and nutrition, and it needs more research to assess the impact of the price and tax policies. Therefore, the price and tax policies for the obesity control are rather complex and should be considered prudently by the governments or the World Health Organization.

B. Educational strategies

The FCTC uses education campaigns to raise people’s awareness of health risks and to reduce the consumption of tobacco products. The Article 12 of the WHO FCTC stresses the importance of health education, communication, training and public awareness. It suggested that health education campaigns which contain a range of public-determined messages can promote the public awareness of health risks of tobacco use, and of the benefit of tobacco-free lifestyle (10). Once people receive the correct knowledge and alter their minds, they would possibly change their behaviors too. Therefore, a large number of people have been influenced by the health education campaigns to different degrees, and some of them decide to quit or not to start smoking.

Education campaigns can also be used in obesity control and would probably exert great influence. Education campaigns can be spread in schools, workplaces and public sites, and then most students and adults could understand the correct knowledge and information about healthy food and physical activity in avoid being obese (7). For the people who have already been obese, education campaigns could inform them of how to eat healthily and do physical exercise effectively to lose weight. The education campaign can be taken in various forms, such as posters, lectures, media programs and public service advertisements.

However, education campaigns may not achieved desired effect in the absence of external support. According to the study of King (17), education campaigns have relatively limited impact on the general public when being carried

out without other interventions. For example, if the price of fruit and vegetable are comparatively higher than that of the food of low nutrient value, people may still prefer to purchase the latter one, even if they know the former one is much healthier. Therefore, the government, food industries along with the NGOs should cooperate jointly to ensure that not only the health knowledge and information are properly and effectively delivered to the general public, but also the healthy choices become easy choices (10).

C. Labeling requirements

The regulations on packaging and labeling of tobacco products are also a method of the WHO FCTC to reduce the consumption of cigarettes. Many tobacco companies use deceptive descriptions such as “mild”, “light”, and “low tar” on their products’ labels and packages to mislead people, and use some lovely and charming pictures which may create erroneous impression on the cigarette cases to attract people to purchase. To deal with the problem, the Article 11 of the WHO FCTC (8, p.9) states that the packaging and labeling of tobacco product should not “promote a tobacco product by any means that are false, misleading, deceptive or likely to create an erroneous impression about its characteristics, health effects, hazards or emissions”. This measure is believed to be rather effective and to achieve desired effect in some countries.

The labels and packages of food can also be misleading by using the confusing health claims, and need to be strictly regulated and reformed. It is argued that the nutrition labeling can always be difficult for the public to understand, and it lacks unified nutrition labeling and health claims both internationally or regionally (10). To tackle with this problem, Codex Alimentarius, the Food and Agriculture Organization and World Health Organization international food code, has been developing guidelines on health claims to supplement the General Guidelines on Claims and Guidelines for Use of Nutrition Claims; in which the former one establishes general principles to ensure that no food and drink is presented in a approach which is misleading and deceptive, and the latter one defines the health, nutrient content and nutrient comparative claims (18). People would eat food comparatively rationally and properly if

the packaging and labeling of foods comply with those guidelines and the science-supported criteria for health claims. In other words, the consumer purchase behaviors would be affected significantly by nutrient labeling (7).

However, the labeling measures may exert little influence on consumer's choices of foods and drinks in some conditions. Foods are not like tobacco products and have different tastes; sometimes people like to eat some foods for just for their taste rather than nutrients. Therefore, it is argued that if substitution effect is large, the consumption of less healthful foods may not be changed by nutrient labeling (7).

D. Restriction on advertising, sponsorship and promotion

To enforce restriction on various forms of promotion is another strong measure of the WHO FCTC. The Article 13 of the WHO FCTC (8, p.11) requires all the Parties "undertake a comprehensive ban of all tobacco advertising, promotion and sponsorship" to reduce the consumption of tobacco products. Before the WHO FCTC came into being, to raise the awareness and visibility of products in order to gain as much profit as possible, many tobacco companies invest a lot into advertising and promotion, and sponsor some public games and events (19). The FCTC's restriction, preferably a complete ban, on all forms of advertising and promotion have been supported by governments in many member states of the WHO, and have reduced the tobacco companies' influence on the general public to a certain degree (20).

Similarly, the advertising, sponsorship and promotion of some kinds of food should also be restricted in order to control obesity. Some food advertising, which includes the snacks, soft drink and fast food advertisements, can directly exert impact on the general public, especially the children and young students. Some food companies place the soft drink and snack vending machines within school campuses; some food advertisements always interrupt children's television or radio programmes; children and young students are comparatively vulnerable to those advertisements and promotions, and buy the energy-dense, nutrient-poor foods, snacks and beverages which could lead to weight gain and obesity (21). Therefore, the restrictions of some foods are needed. In fact, some countries, including Canada, European and Asian

countries, have already imposed restrictions on the food marketing towards children in different degrees and achieved success to a certain extent (7).

E. Clinical interventions

The FCTC also requires governments to use clinical interventions to reduce the demand of cigarettes. The Article 14 of the WHO FCTC (8, p.13) states that each member state should take effective measures based on the scientific guidance "to promote cessation of tobacco use and adequate treatment for tobacco dependence". To achieve the goal, each Party should: design and implement effective clinical programmes in schools, workplaces and health care facilities; include diagnosis and treatment in national health and education programmes; and facilitate the accessibility and affordability for treatment of tobacco dependence (8). The clinical interventions can effectively increase the level of cessation of tobacco use, and may rapidly decline the morbidity and mortality from tobacco (7).

The clinical interventions addressed in the WHO FCTC can also be applied for obesity control. The governments could follow the methods introduced in the FCTC and make another series of policies to provide more clinical interventions and resources, such as physician counselling and pharmacotherapy, to help people to control their weight by eating healthily and doing more physical activities (7). However, at current stage, the nutritional and physical activity counselling for obesity control comparatively remains underused and imperfectly designed. Successful clinical interventions for dietary change require collaborative goal-setting, individually-tailored programmes, personalized feedback and personalized follow-up (9). Therefore, when using clinical interventions to control obesity, governments should consider more comprehensively.

The above discussion suggests that the measures involved in the WHO FCTC can be applied for obesity control, while it still needs close cooperation between governments, international organizations and civil societies to create synergy. The obesity control still cannot be dealt with by one country alone, many small countries may not have enough authority and power to implement the regulations and policies in the food industries, for example, require the multinational food

and beverage companies to include the specific health warnings on their products' labels, as those companies may simply refuse the governments requirements relying on their high popularity and market share (4). "Only an enforced international standard would change the balance of power"(4, p.293). Relying on the international resolution and the support from the international organizations as well as civil societies, governments of most countries can have more confidence and power to restrain the market availability of unhealthful food and beverage in order to successfully control obesity. Therefore, an effective international model which is similar to the WHO FCTC is highly necessary, especially for those small or developing countries.

V. DISCUSSION: CHALLENGES AND ACHIEVEMENTS OF THE POTENTIAL MODEL FOR OBESITY CONTROL

The WHO FCTC and the potential model for obesity control may have shared the challenges. This part will firstly introduce the challenges of the WHO FCTC, and then discuss the challenges of the potential model for obesity control, and finally introduce the potential model's achievements at current stage.

Similar to all the other ambitious political movements, the WHO FCTC also has some challenges. Besides the negotiating process is relatively slow and difficult, the main challenges include the difficulty to enforce bans on advertisements, and the obstruction of tobacco industry.

The first challenge is that the anti-tobacco campaigns are difficult to be enforced. The Article 13 of the WHO FCTC, which requires all the Parties enact comprehensive bans on the advertising, sponsorship and promotion of tobacco industry, is proved to be rather difficult to implement. Firstly, the anti-tobacco advertising campaigns cannot be effective unless they are run over long periods (1). It is suggested that such strategies should run for at least half a year to affect the public awareness, and one to two years to have obvious impact on people's attitudes and behaviors (22). However, such measures are expensive, and the tobacco control programs may lack the sufficient resource, especially the financial support, to run extensive and sustained campaigns (23). Moreover, the tobacco industry always tries to act against the tobacco control programs. Many

tobacco companies claim that those programs' information on tobacco use are inaccurate and misleading, and try every method to dodge and prevent the anti-tobacco advertising programs (23). The outcome is that at the current stage, there are only 19 countries enforce comprehensive bans on all forms of advertising, sponsorship and promotions of tobacco products (23).

The other challenge to the WHO FCTC implementation is the tobacco industry. To fight for its existence and to maximize their profit, the tobacco companies continuously adapt tactics and create loopholes to circumvent the new policies and regulations controlling their activities (1). A recent study found that when opposing the anti-tobacco legislation and programs, the tobacco industry always argue that those policies lack of jurisdiction and accuracy, and impose technical barriers to trade (24). Besides, tobacco companies have been researching how to make new and more appealing products. Therefore, the tobacco industry is the believed to be the single largest challenge to the WHO FCTC implementation (1).

Similar to the WHO FCTC, the model for obesity control may also face those challenges. The first one is the difficulty to enforce restriction on the advertising and promotion of unhealthful food and beverage. As foods and drinks are essential to people, and are much more complicated than tobacco products, it is hard for governments to enforce bans on the advertisements of some particular foods, and restrict people's choices. The second main challenge is the food industry. Food companies, especially multi-national food companies, which are believed to have more power and influence than tobacco companies, will consistently act against rein and regulations in order to maximize profit. The third one is that such a model may adversely affect food availability due to the expensive and heavy handed legal restrictions (7). Therefore, the model to control obesity faces even more challenges and needs to be considered more carefully when draw the lessons from the WHO FCTC.

Although facing many challenges and difficulties, some achievements have been made at current stage. Firstly, the WHO Global Strategy on Diet, Physical Activity and Health (GSDPAH) was endorsed by the World Health

Assembly in 2004. The Strategy has mirrored the measures in the WHO FCTC, including the integrated economic approach, more effective labeling and package measure, tighter marketing and promotion control, and intensive educational campaign (25). It encourages all the Parties to make efforts and closely cooperate with other countries and organizations to deal with the issue of obesity. It is believed to be a big stride forward in constituting a model to restrain the market availability of unhealthful food for obesity control. Besides, under the pressures from governments and organizations, some multi-national food and beverage companies, including *Krafts* and *Pepsi*, have made compromise to different degrees. For example, Krafts announced that it would not only eliminate the trans-fatty acids and improve the nutritional content of its food and beverage products, but also stop marketing towards children (4). These achievements possibly indicate a good start and a bright future for the model to restrain the market availability of unhealthful food for obesity control.

However, a promising start does not indicate a smooth process and a favorable outcome. Some difficult points could still not be ignored. First, the GSDPAH has comparatively weak restriction force on the governments and public actors, and could only take measures in more tender forms such encourages and suggestions instead, let alone for the ambitious food and drink companies. Second, implementing the price and tax measures could possibly incur the public opposition and other technical problems. Third, the unhealthy food is just one of, rather than all of, the contributing factors for obesity; while other factors, such as unhealthy lifestyle and the lack of exercise, leave a very small space for governments to control by mainly implementing economic approach and advertisement-banning regulation. Last, unlike the desire for tobacco, the desire for food, including the high-energy and high-fat food, is probably the deep and instinctive human nature, and thus make the obesity problems more complicated. Therefore, governments could hardly walk in the fine line when controlling obesity problems to a considerable degree.

VI. CONCLUSION

In conclusion, although the policies included in the WHO FCTC could not be adapted for controlling obesity

wholesale, the WHO FCTC can indeed constitute a model to constrain the market availability of unhealthful foods and beverages for obesity control. The WHO FCTC has successfully controlled tobacco use, and the key measures, which are economic approach, educational strategies, labeling measure, restrictions on marketing as well as clinical invention, can be applied to restrain the market availability of unhealthful foods in order to control obesity. However, not all the foods are lethal, the issue of obesity control may be more complicated than tobacco control. Governments and organizations should cooperate globally and closely, and apply those measures comprehensively to create synergy in order to better control obesity. Though the potential model for obesity control may face some challenges such as the difficulty of implementation and obstruction of food industry, it has already made some achievements at current stage; for example, the WHO Global Strategy on Diet, Physical Activity and Health has been endorsed, which indicates that the future of the model for obesity control will possibly be bright.

REFERENCE

- [1] Lien, G. and DeLand, K. (2011) Translating the WHO Framework Convention on Tobacco Control (FCTC): Can we use tobacco control as a model for other non-communicable disease control? *Public Health*. Vol.125:12:847-853
- [2] Haslam, D., and James, W. (2005) Obesity. *Lancet*. 366 (9492):1197-1209
- [3] Barness, L., Opitz, J, and Gilbert-Barness E. (2007) Obesity: Genetic, molecular, and environmental aspects. *American Journal of Medical Genetics Part A*. 143A(24):3016-34
- [4] Daynard, R. (2003) Lessons from Tobacco Control for the Obesity Control Movement. *Journal of Public Health Policy*. Vol.24, No.3/4:291-295.
- [5] OECD Factbook 2013. www.oecd-ilibrary.org/sites/factbook-2013-en/12/02/03/index.html?itemId=/content/chapter/factbook-2013-100-en [Accessed June 20, 2014]
- [6] Yach, D., Hawkes, C., Epping-Jordan, J. E., & Galbraith, S. (2003). The World Health Organization's Framework Convention on Tobacco

- Control: implications for global epidemics of food-related deaths and disease. *Journal of Public Health Policy*, 24(3/4), 274-290.
- [7] Mercer S., Green L., Rosenthal A., Husten C., Khan L., Dietz W. (2003) Possible Lessons from the tobacco experience for obesity control. *American Society for Clinical nutrition*. 77 (suppl): 1073s-1082s.
- [8] World Health Organization. (2003) *Framework Convention on Tobacco Control*. Geneva: WHO Press.
- [9] US Department of Health and Human Services. (2000) Reducing tobacco use: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centres for Disease Control and Prevention, National Centre for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health.
- [10] Yach, D. et al. (2003) The World Health Organization's Framework Convention on Tobacco Control: Implications for Global Epidemics of Food-Related Deaths and Disease. *Journal of Public Health Policy*. Vol.24, No.3/4:274-290
- [11] Jacobson, M. and Brownell, K. (2000) Small taxes on soft drinks and snack foods to promote health. *American Journal of Public Health*. Vol. 90, No. 6:854-857
- [12] Cash SB, Sunding DL, Zilberman D. Fat taxes and thin subsidies: prices, diet, and health outcomes. *Acta Agric Scand, Section C - Econ* 2005; 2: 167-74.
- [13] Kuchler F, Tegene A, Harris JM. Taxing snack foods: what to expect for diet and tax revenues. *Agric Info Bull* 2004; 8: 1-11.
- [14] Kuchler F, Tegene A, Harris JM. Taxing snack foods: manipulating diet quality or financing information programs. *Rev Agric Econ* 2005; 27: 4-20
- [15] Smed S, Jensen JD, Denver S. Socio-economic characteristics and the effect of taxation as a health policy instrument. *Food Policy* 2007; 32: 624-39
- [16] Santarossa JM, Mainland DD. Employing an environmental taxation mechanism to reduce fat intake. In: Chern WS, Rickertson K, eds. *Health, nutrition and food demand*. Oxford: CABI Publishing; 2003. pp. 223-45.
- [17] King, S. (1999) Price Discrimination, Separation and Access: Protecting Competition or Protecting Competitors? *Australian Journal of Management*. Vol. 24, 1: pp. 21-35.
- [18] Codex Alimentarius. (1991) General Guidelines on Claims.
- [19] Yang G and Hu A. (2011) *Tobacco control and the future of China*. Beijing: The Economic Daily Press.
- [20] Wan, X., Ma, S., Hoek, J., Yang, J., Wu, L., Zhou, J., & Yang, G. (2012). Conflict of interest and FCTC implementation in China. *Tobacco control*, 21(4), 412-415.
- [21] WHO/FAO Expert Consultation. (2002) *Diet, Nutrition and Prevention of Chronic Diseases*. WHO Technical Report Series 916.
- [22] Schar E, Gutierrez K, Murphy-Hoefer R, Nelson D. (2006) *Tobacco use prevention media campaigns: lessons learned from youth in nine countries*. Atlanta, GA: US Department of Health and Human Services. Centres for Disease Control and Prevention, National Centre for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
- [23] World Health Organization. (2011) *WHO report on the global tobacco epidemic warning about the danger of tobacco*. Geneva: WHO Press.
- [24] World Health Organization. (2010) *Work in progress in relation to Article 9 and 10 of the WHO Framework Convention on Tobacco Control*. Report by WHO'S Tobacco Free Initiative. Geneva: WHO Press.
- [25] World Health Organization. (2004) *WHA Resolution 57.17 Global strategy on diet, physical activity and health*. Geneva: World Health Assembly.

Effect of Chlorpyrifos Exposure during Development on Skeletal and Smooth Muscles in Juvenile and Adult Rats

Walaa Darwiche, Stéphane Delanaud, Veronique Bach, Jérôme Gay-Quéheillard
UFR de Médecine, PériTox, Périnatalité & Risques Toxiques,
UMR-I 01 Unité mixte INERIS,
Amiens, France
walaa.darwiche@u-picardie.fr
stephane.delanaud@u-picardie.fr
veronique.bach@u-picardie.fr
jerome.gay@u-picardie.fr

Wiam Ramadan, Wissam H. Joumaa, Hassan Khachfe
Université Libanaise, Faculté des Sciences,
Laboratoire de Physio-Toxicité Environnemental,
EDST, ER 017, Nabatieh, Lebanon
Lebanese International University, School of Arts and Sciences,
Department of Biological and Chemical Sciences,
Beirut, Lebanon
wiam.ramadan@liu.edu.lb, wjoumaa@ul.edu.lb,
hassan.khachfe@liu.edu.lb

Abstract—Chlorpyrifos (CPF) is a pesticide widely used in agriculture, commercial, and domestic applications. CPF acts in part through inhibition of acetylcholinesterase and thus can produce lasting effects on muscular system. However, the impact of chronic, low-dose exposure of CPF on mammalian muscles is poorly understood. In the present study, we examined in developing rats the effects of in utero and postnatal exposure to CPF, on contractile properties of the diaphragm, a respiratory skeletal muscle, and the digestive smooth muscles of the ileum. Wistar pregnant rats were administered by daily gavage from gestational day 1 to postnatal day 21 (PND21) with vehicle (control) or CPF at different doses: a low dose (1 mg/kg/d) and a high dose (5 mg/kg/d). At PND 21 and 60 the rats were sacrificed and both muscles of the ileum and the diaphragm were sampled for measurement. At PND60, there was a decrease in body weight of rats exposed to 1 mg/kg/d of CPF. Rats exposed to 5 mg/kg/d of CPF showed a lower body weight at all ages studied. In addition, CPF exposure increases the twitch tension of the diaphragm at PND 21 and 60. For the ileum, there was a significant increase in the twitch tension (g/ cm²) of the smooth muscle at PND21 in both groups. In conclusion, chronic prenatal and postnatal exposures to CPF affect the contractility of both the diaphragm and ileal smooth muscles. Further investigations are required to explain these increases in the contractility.

Keywords-Pesticide; chlorpyrifos; perinatal life; muscle contractility.

I. INTRODUCTION

Pesticides are unique contaminants in that they are intentionally released into the environment to elicit toxicity

in certain “pest” species. Unfortunately, a lack of selectivity often leads to problems of toxicity in humans and other non-target species. Organophosphorous (OP) pesticides are the major class of insecticides in the world today [1]. Poisoning with organophosphorous compounds is a global health problem. Organophosphorous compounds inhibit acetylcholinesterase resulting in accumulation of acetylcholine (Ach) and overstimulation of cholinergic synapses. Acetylcholine is an important neurotransmitter in both central and peripheral nervous system; in Central Nervous System (CNS), it is implicated in memory process and learning, and especially in muscle activity and vegetative functions; in peripheral nervous system (PNS), it is also implicated in the regulation of synaptogenesis [2]. The accumulation of the neurotransmitter acetylcholine causes hyperactivity in CNS and in neuromuscular junctions. Patients exposed to OP pesticides die mostly from respiratory failure and lung injury [3].

Chlorpyrifos (CPF), O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl)- phosphorothioate, was one of the most widely used OP insecticides in the U.S [1]. From 2000, all residential uses were banned. In the European Union, CPF is one of the widely used pesticides in agriculture with moderate toxicity with a rat oral lethal dose 50 (LD50) of 135-163 mg/kg [4].

People are regularly exposed to a wide range of pesticides which are food contaminants. Studies on chlorpyrifos showed that prenatal CPF exposure was associated with intrauterine growth retardation and decreased birth weight [5][6][7][8], developmental neurotoxicity [9][10][11] after prenatal exposure and it is also associated with high risk of lung cancer and leukemia among agriculture workers [12].

Recent investigations have focused on the determination of the mechanisms behind the age-related toxicity differences, since juveniles are more susceptible [13], and on the alterations resulting from repeated exposure during development. Moreover, there are numerous studies in

animals following acute [14] or chronic exposure to CPF [15] showing a significant inhibition of acetylcholinesterase activity in brain, diaphragm, liver, retina and blood cells and a decrease in muscarinic receptor (QNB) binding in brain, heart and retina during critical periods of development [16][17][18] or in adulthood [17].

Our objective was to investigate the effects of repeated gestational and postnatal exposure to CPF on the contractility of the respiratory muscle (diaphragm) and longitudinal smooth muscle of the ileum in Wistar rats and to determine the mechanism by which the contractility is affected. Such an investigation cannot be performed in humans. In this paper, we show the effects of chlorpyrifos exposure on body weight, survival rate, and the *in vitro* contractility properties of both diaphragm and longitudinal smooth muscle of ileum.

II. MATERIALS AND METHODS

The methods used in our experiments are summarized in the sections below.

A. Chemicals

Chlorpyrifos (O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl)-phosphorothioate, purity 99.8%) was purchased from LGC standards SARL (6, Rue Alfred Kastler, 83076, MOLSHEIM, France). It was dissolved in commercially available rapeseed oil (the vehicle) at dose of 1 mg/ml (for the CPF1 group) and 5 mg/ml (for the CPF5 group) in order to expose animals to 1 or 5 mg/ml/kg body mass/day. Other biochemicals were obtained from Sigma-Aldrich Chemical C (L'Isle d'Abeau Chesnes, 38297 Saint-Quentin Fallavier, France).

B. Experimental Design

Twelve female and 6 male Wistar rats (aged 8 weeks on arrival, body mass 250-300 g) were obtained from Janvier LABS (Le Genest Saint Isle Saint Berthevin, 53941 France). All animals were housed in cages in a controlled-temperature (23°C) room with a 12:12 h alternating light:dark cycle. They were maintained on a standard pelleted diet, with tap water ad libitum. After a 1-week acclimation period, females were mated with males and pregnancy was determined by the presence of spermatozoa in the vagina checked with a smear. After fertilization, female rats were individually housed in clean plastic cages and randomly assigned to a treatment group or control group. Pregnant rats were exposed by gavage from gestational day 1 (GD1) to the post natal day (PND21) at different doses: 1 mg/kg/d (CPF1) and 5 mg/kg/d (CPF5) vs vehicle. After weaning at PND21, pups were administered with the same doses of CPF until day 60 of age (PND60). Hence, pups were studied at two time points: weaning day (PND21) after gestational and lactational exposition and in adulthood (PND60) after further exposition to CPF in food.

C. Sample collection

At day 21, half of rats were euthanized with an intraperitoneal overdose of sodium pentobarbital (1 ml/kg; 200mg/ml solution) and muscles of both diaphragm and ileum were sampled for measurement of contractile properties. The second half of rats was weaned and administered with the same doses of CPF until day 60 of age (PND60). They were sacrificed and the contractile properties of their muscles studied.

D. Organ bath physiology

After euthanasia, the diaphragm and pieces of ileum were removed. Muscle strips were mounted in organ bath containing oxygenated Krebs solution at 37°C and pH 7.4. After 30min equilibration period, the ileal segments were stimulated by electrical field stimulation (EFS) (100 v- 32 Hz). For the diaphragm segments, fatigue was induced by application of a low frequency fatigue protocol consisting of supramaximal stimuli (2 Hz, 2 ms, 12 V) delivered directly to the muscle for 5 min for induction of fatigue.

E. Statistical analysis

Statistical analyses were performed with graphpad prism 5 software (graphPad software, Inc, San Diego, California). If groups were significantly different in a one-way ANOVA test, an impaired t test was then performed. Statistical significance is reported for the $p \leq 0.05$. Values were expressed as the mean \pm SEM.

III. RESULTS

Our results obtained are exposed in the sections below.

A. Effect of CPF exposure on body mass and mortality of pups

Figure 1 shows that at birth and PND21 there was no difference in body mass of rats exposed to CPF1 compared to controls. However, at PND60, body mass of CPF1 rats was significantly decreased. Body mass of rats exposed to 5 mg/kg/d of CPF was significantly lower than control at birth, PND21 and PND60.

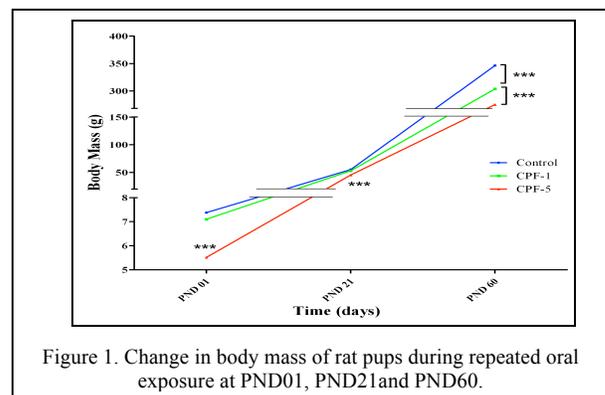


Figure 1. Change in body mass of rat pups during repeated oral exposure at PND01, PND21 and PND60.

It should be noted that deaths occurred essentially between PND01 and PND21 in pups exposed during in utero and postnatal periods to CPF5 (Table I).

TABLE I. NUMBER OF DEATHS OCCURING DURING REPEATED ORAL EXPOSURE TO THREE DOSES OF CHLORPYRIPHOS FROM PND01 TO PND21.

DOSES	Control	CPF-1	CPF-5
PND 01-21	0/25 (0%)	0/25 (0%)	13/32 (40%)

B. In vitro muscle contractility

At PND 21 and PND 60, the diaphragm shows a significant increase in twitch tension after oral exposure to CPF at doses CPF1 and CPF5, as depicted in Figure 2.

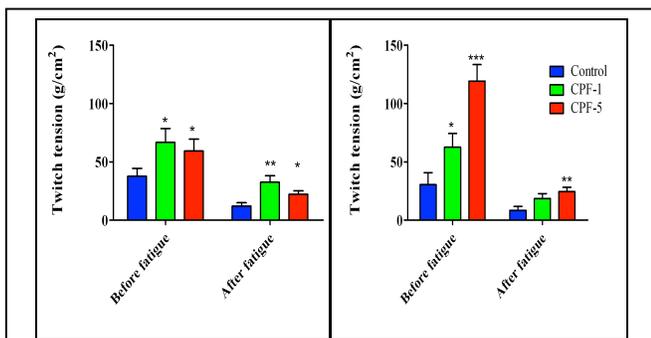


Figure 2. Twitch tension of diaphragm after oral exposure to CPF at PND 21 (2.a) and PND 60 (2.b). Values are expressed as mean ± SE (n=10/group) *significantly different from control (p<0.01).

However, only at PND60, the fatigability index was higher in CPF5 group compared to controls, as shown in Figure 3.

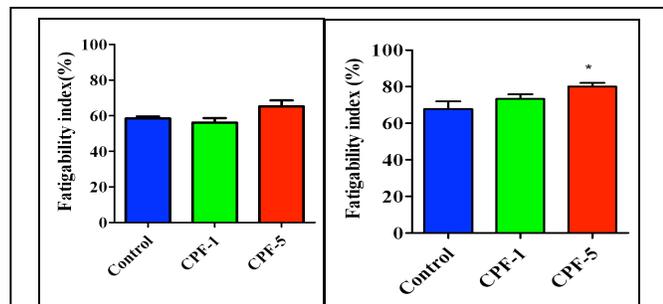


Figure 3. Effect of CPF exposure on fatigability of diaphragm at PND21 (fig.3.a) and PND60 (fig.3.b).

The EFS-stimulation of ileal segments of exposed rats showed a significant increase in the amplitude of contraction at PND21 and a significant decrease in the amplitude of contraction at PND60, as presented in Figure 4.

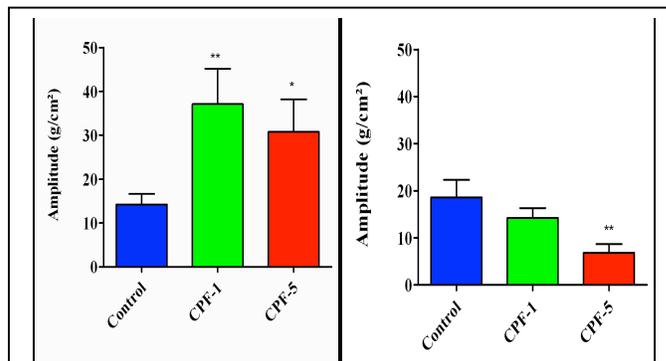


Figure 4. Contractility of ileal longitudinal smooth muscle at PND21 (fig.4.a) and PND60 (fig.4.b) in controls, CPF1 and CPF5.

IV. DISCUSSION

The data from this study show that in utero and postnatal chlorpyrifos exposure alters the contractility of diaphragm and smooth muscle of ileum. Organophosphorus (OP) insecticides elicit toxicity through inhibition of acetylcholinesterase, leading to accumulation of acetylcholine in the nervous system and consequent signs of cholinergic toxicity [19]. Our results show that perinatal exposure of rat pups to low dose CPF has an impact on growth, with lower body weight in CPF1 group at adulthood and in CPF5 group at birth, PND21 and PND60 as described by Mansour and Moussa [20].

This study was designed to investigate, for the first time, the effects of chlorpyrifos exposure from the first day of gestation to the post natal day (PND21) and to adulthood (PND60) on the contractility of diaphragm and smooth muscle of ileum. As expected, the exposure to CPF alters the contractility of diaphragm and ileal smooth muscle. At PND21 and PND60 the twitch tension of diaphragm was significantly increased in both CPF1 and CPF5 group. This can be explained by the inhibition of the acetylcholinesterase in the neuromuscular junction and will be confirmed by the dosage of acetylcholinesterase activity. Previous studies reported decreased acetylcholinesterase activity in diaphragm following repeated oral postnatal exposure to CPF from PND1 to PND21 [16] and in adult rats [14]. Furthermore, the fatigability index was higher in adult rats exposed to CPF5. This can be related to the protein content, the calcium intake or the neuromuscular junction structure. Further experiments are required to explain this increase. The amplitude of contraction of the ileal longitudinal smooth muscle of the ileum was increased in the rats exposed to both CPF1 and CPF5 doses at PND21. However, at PND60, the

amplitude of contraction was decreased in exposed group. This can be explained by the difference of administration of CPF: at PND21, rats were exposed to CPF in utero and via lactation; the chlorpyrifos is mostly detoxified by the organism of the mother. After weaning up to day 60, intestinal tract is directly in contact with CPF. Those features may provide an explanation for the difference observed between the two age groups.

V. CONCLUSION

The chronic, low-dose oral exposure to CPF from day one of gestation to postnatal day 60 alters the contraction of skeletal respiratory muscle, and longitudinal ileal smooth muscle in juvenile and adult rats. These effects could alter the respiratory pattern and the intestinal transit which will be investigated in future. These findings suggest that the pesticides exposure should be avoided as much as possible. The mechanisms that lead to the increase in the contractility have to be investigated. This change in the contractility of the muscle can be related to modification of the muscle structure including muscle fibers distribution, myofibrillar protein and/or RNA content. Thus, further investigations are needed in order to explain these muscle alterations.

REFERENCES

- [1] A. Grube, D. Donaldson, T. Kiely, and L. Wu. Pesticides Industry Sales and Usage 2006 and 2007 Market Estimates. Office of Chemical Safety and Pollution Prevention, U.S.Environmental Protection Agency. Washington, D. C. 2011.
- [2] M. Eddleston. "The pathophysiology of organophosphorus pesticide self-poisoning is not so simple," *Neth J Med.*, April. 2008, Vol 66, pp 146–148.
- [3] J. M. Lauder and U. B. Shambra, "Morphogenetic roles of acetylcholine," *Environ Health Perspect*, Feb. 1999, Vol.107 Suppl 1, pp. 65-69.
- [4] C. R. Worthing and S. B. Walker. The pesticide Manual, 8th ed., British Crop Protection Council Thornton Heath, U.K, 1987.
- [5] R. M. Whyatt et al. "Prenatal insecticide exposures and birth weight and length among an urban minority cohort," *Environ Health Perspect*, 112 (10), Jul 2004, pp. 1125–1132.
- [6] M. Levario-Carrillo, D. Amato, P. Ostrosky-Wegman, C. González-Horta, Y. Corona, and L. H. Sanin. "Relation between pesticide exposure and intrauterine growth retardation," *Chemosphere*, 55 (10), Jun 2004, pp. 1421–1427.
- [7] S. Dabrowski, W. Hanke, K. Polańska, T. Makowiec-Dabrowska, and W. Sobala. "Pesticide exposure and birthweight: an epidemiological study in Central Poland," *Int J Occup Med Environ Health.*, 16 (1), 2003, pp. 31–39.
- [8] D. B. Barr et al. "Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey," *Sci Total Environ*, 408 (4), Jan 2010, pp. 790–795.
- [9] P. Grandjean, and P. J. Landrigan. "Neurobehavioural effects of developmental toxicity," *Lancet Neurol.*, 13 (3), Mars 2014, pp. 330–338.
- [10] J. Flaskos. "The developmental neurotoxicity of organophosphorus insecticides: a direct role for the oxon metabolites," *Toxicol Lett*, 209 (1), Feb 2012, pp. 86–93.
- [11] V. A. Rauh et al. "Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children," *Pediatrics*, 118 (6), Dec 2006, pp. e1845–e1859.
- [12] W. J. Lee et al. "Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study," *J Natl Cancer Inst*, 96 (23), Dec 2004, pp. 1781–1789.
- [13] C. N. Pope, T. K. Chakraborti, M. L. Chapman, J. D. Farrar, and D. Arthun. "Comparison of in vivo cholinesterase inhibition in neonatal and adult rats by three organophosphorothioate insecticides," *Toxicology*, March. 1991, Vol 68 (1), pp. 51-61.
- [14] A. C. Nostrandt, S. Padilla, and V. C. Moser. "The relationship of oral chlorpyrifos effects on behavior, cholinesterase inhibition, and muscarinic receptor density in rat," *Pharmacol Biochem Behav*, 58 (1), Sep 1997, pp. 15–23.
- [15] S. Padilla et al. "Neurochemical effects of chronic dietary and repeated high-level acute exposure to chlorpyrifos in rats,". *Toxicol Sci Off J Soc Toxicol*, 88 (1), Nov 2005, pp. 161–171.
- [16] R. L. Carr, H. W. Chambers, J. A. Guarisco, J. R. Richardson, J. Tang, and J. E. Chambers. "Effects of repeated oral postnatal exposure to chlorpyrifos on open-field behavior in juvenile rats," *Toxicol Sci Off J Soc Toxicol*, 59 (2), Feb 2001, pp. 260–267.
- [17] H. Zhang, J. Liu, and C. N. Pope. "Age-related effects of chlorpyrifos on muscarinic receptor-mediated signaling in rat cortex," *Arch Toxicol*, 75 (11-12), Jan 2002, pp. 676–684.
- [18] J. R. Richardson, and J. E. Chambers. "Neurochemical effects of repeated gestational exposure to chlorpyrifos in developing rats," *Toxicol Sci Off J Soc Toxicol*, 77 (1), Jan 2004, 83–90.
- [19] B. E. Mileson et al. "Common mechanism of toxicity: a case study of organophosphorus pesticides". *Toxicol Sci Off J Soc Toxicol*, 41 (1), Jan 1998, pp. 8–20.
- [20] S. A. Mansour and A.T. Moussa. "Adverse effects of exposure to low doses of CPF in lactating rats," *Toxicol ind Health*, Vol 27, April 2010, pp 213-224.