Customized Adaptative Neuro-Fuzzy Approach to pH Control on a Stirred Tank Bioreactor

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Abstract*—Bioreactors are complex sets of tubes, sensors and actuators embodied in recipients of different shapes and sizes, used thoroughly in biotechnical and chemical investigative and commercial environments for hours on end. Stirred tank bioreactors are widely used and available globally, whose design is intentioned for in-batch and continuous operations. They serve as closed controlled systems for specific organic compounds reaction examination when treated with agitation changes and temperature shifts, as well as oxygen saturation and viscosity variation for both aerobic and anaerobic processes. In particular, the rapidness and magnitude at which a substance changes its associated pH affect its solubility and molecular structure, possibly reaching its denaturalization. Hence, analyzing and acting upon these systems pH, where several parameters interact with each other, is crucial for avoiding compound stressing and arriving to the desired products in addition to coherent investigation conclusions. The pH level management, commonly done manually by scientists, serves the purpose for applying fuzzy logic principles where historical data, as well as human expertise and experience, can be best utilized in designing the controller sets of inference rules and membership functions. Thus, this paper focuses on experiments design and proven tuned applications with limited microorganisms capacities of adaptative neuro-fuzzy process trained with custom genetic algorithms for automatic pH control in 5 litres stirred tank bioreactors, joined with practical comparisons between other control engineering formulations. While earlier related research focused on simulated reactions and theoretical control, this empirical procedure gives promising results on 10 seconds cycles of sensing and actuating, achieving an average 0.1 pH error margin on stability when utilized on an agitation and temperature controlled environment. This study provides scientists with an extendable and configurable procedure so to successfully and efficiently control pH on closed systems using an affordable master-slave micro-controllers architecture.

Keywords*—*fuzzy logic, automatic control, pH controller, bioreactor design, optimization engineering

I. INTRODUCTION

Bioreactors are meticulously designed and carefully manipulated closed systems, crucial for biotechnological and chemical procedures in both academical and commercial contexts [1]. Its research usages usually aim to analyze biochemical active organic compounds behaviour and response when affected by different cycles of natural conditions variations such as temperature [2], oxygen saturation [3] and viscosity [4]. Its main market-oriented utilization ranges from large scale production of consumables or custom alcoholic beverages and milk processing [5] to more contained and closely examined small scale on vaccines fabrication and proteins synthesis [6]. These systems standard capacity vary between contents of approximately 5 litres for investigation purposes and 200 litres for mass production [7]. This paper proposes and compares approaches to bioreactor pH control guided by classical and fuzzy logic, which are general and independent of the systems dimensions, but dependent on its substances concentrations.

Controlling the pH of compounds formed by microorganisms in a liquid medium is paramount for the proper study and analysis of the biomolecular processes that occur, as well as for the correct and expected nutrients development and biological functions availability [8]. Nonetheless, given the strict system requirements for accurate usage, this mandatory regulation mechanism needs to act in conjunction with other relevant controlled properties (e.g., external vest temperature, agitation rotor speed) whose variance produce changes on pH and vice-versa [9]. This intrinsic unavoidable feedback joined by the microorganisms behavior unpredictability demands generally complex solutions through classical means. Using fuzzy logic, however, trained human experience and deductive thinking can be emulated on a robust, reliable and efficient controller [10].

The presented approaches are tested with multiple compounds on bioreactors with working regular agitation speeds from 120 to 220 rpm for molecular oxygenation and temperature variation between 18 and 42 Celsius grads. Further sterilization ranges, i.e., microorganisms cleansing, are not considered for pH control.

Figure 1 shows the used system architecture and communication sequencing per cycle regarding devices related to pH control. It corresponds to a centralized master-slave structure where the master has the control logic of all regulatory properties of the system and the slave communicates and mandates over the peripherals sensor and actuators, consisting on one peristaltic pump for each acid and base drops.

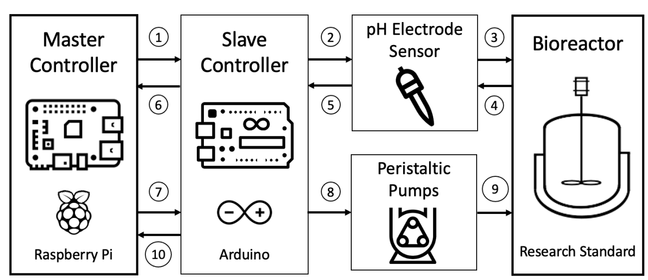

Figure 1. Proposed architecture and sequencing of control system.

This paper proceeds with a brief review of related bioreactor control literature followed by considerations of relevant preliminary experiments necessary for particular system understanding. Then, it focuses on proposed classical, fuzzy and neuro-fuzzy perspectives on pH control in order to later compare its testing results and applications.

II. Literature Review

Bioreactor design's research and analysis is a discipline whose beginnings date back several decades while being continuously encompassed and updated with evolving practices and techniques in its search for generality, scalability and efficiency [11]. Indeed, recent viral outbreaks not only promoted the technical relevance of the biotechnological field but also demanded sophisticated tuned precision and fault tolerant equipment to fulfill the increasing vaccines requirements [12].

Currently, the majority of bioreactor control observations consists on specification and hierarchical delineation of interested magnitudes sets whose regulation may provide greater dominion over part of the system processing. These properties are then subjected to traditional ON-OFF or PID controls (usual for agitation and temperature procedures) [13], as well as neural networks on supervised reinforcement learning algorithms [14]. Albeit useful in practice, these perspectives stand as too complex to the general public, with little availability for further customization.

Contemporary remarks on bioreactor pH control remain traditional variations of classical loop stresses on particular fermentation compounds using stepwise aggregation procedures [15] and/or CO_2 sparge feedback commands [16]. Although tested optimal within their specific environment and processes, these studies depict certain lack of generality and flexibility for more broaden and global scenarios.

Recent related researches on fuzzy control of bioreactors describe specialized designs of a predictive model and fuzzy supervisory controllers for anaerobic processes [17], as well as adaptive PI controller with fuzzy-based parameter selection for fed-batched procedures [18]. Although these methodologies are innovative, they are focused on simulated reactions of scarce microorganisms types with theoretical specifications.

III. Preliminary Experiments

This section focuses on initial experimentation with selected peripherals and associated operational fault managements, necessary in every control design. The proposed procedure also requires a historical analysis and abstraction of the system's time evolution over iterated pH homogeneous variation.

A. Peripherals Examination

The utilized glass two-electrode sensor measures pH with a precision of 0.002 in the entire range 0-14 at usual aforementioned conditions, with reference electrode fixed at 6.86 [19]. It communicates with slave controller using a communication module through I^2C data protocol, industrially used between integrated circuits on environments with little signal interference [20]. This enables additional automatic functionalities of connectivity check and calibration verification.

The low-pressure electrical peristaltic pumps are integrated with DC engines and generates drops of tested approximate 69μL through silicon tubes of 1 cm diameter [21]. These are activated by slave controller using dual h-bridge motor drivers and Pulse Width Modulation (PWM) as shown in Figure 2.

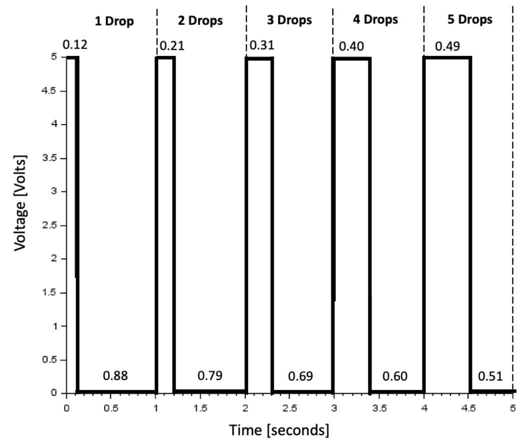

Figure 2. PWM signaling to peristaltic pumps for 1 to 5 drops expulsion.

Thus, sensors and actuators are commanded using affordable Arduino slave controllers, which are connected to a Raspberry Pi master controller where the procedural control decisions are defined. Master and slaves controllers communicate through Modbus ASCII serial protocol [22], which redundantly corroborates message information on both ends. This system design enables the usage of multiple sensors and actuators with a correspondent latency increase.

B. Operational Considerations

Automatic sequential systems functioning over long periods of time demand in practice to define actions consequence of possible defects and events. Due to its overarching simplicity, procedures based on GEMMA framework [23] are structured for pH control, segmenting strategies as functioning, stop and failing processes shown in Figure 3.

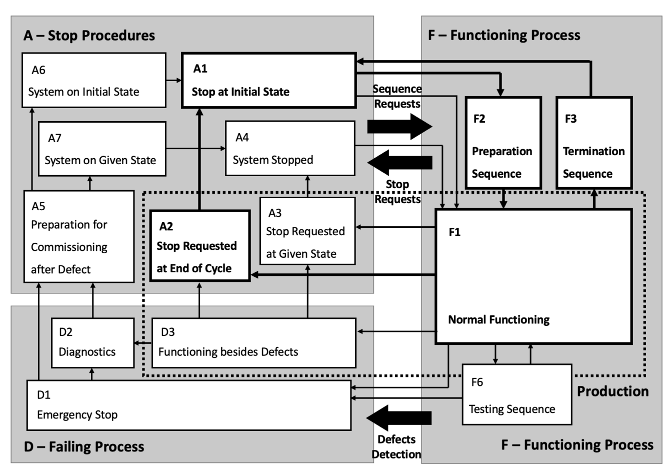

Figure 3. Depiction of automation processes based on GEMMA framework.

Predominant faults are classified as measurement defects, communication errors and actuators malfunction, all not mutually exclusive. Measurement defects are non blocker faults result of incorrect sensing that require message repetition. Communication errors are blocker faults consequence of bad frame reading or writing on a given endpoint, which obligate system stop and physical connector checking. Actuators malfunction provoke unexpected expulsions of acid or base drops, or none entirely.

Bidirectional communication between master and slave controllers, as well as with sensors, provides with acknowledgment notification possibility after each action, enabling repetitions or cancellations. However, communication with actuators remains unidirectional as there are no guarantees of consistent requested drops amount. This is considered on control logic, as incoherent system interaction generates corrective maneuvers on subsequent iterations.

C. System Analysis

The actuators interact with the bioreactor by the expulsion of standard acid HCl with pH 1.8 and base NaOH with pH 11.6, both on 70% concentrated solutions. When analyzing regular pH increments and decrements on organic compounds with constant homogenization, an immediate effect is identified on the pH measurement. Moreover, no apparent inertia is observed on the response as is illustrated in Figure 4, even when using multiple continuous drops. These factors cause that the usual working range is limited by the pH of acid and base expelled by actuators.

Considering these observations and given the need of prolonged continuous system functioning of days at a time, as well as the limited quantity of actuator solutions and engines life expectancy before replacement, extra requirements such as the usage of minimal drops with loose intervals over time are imposed.

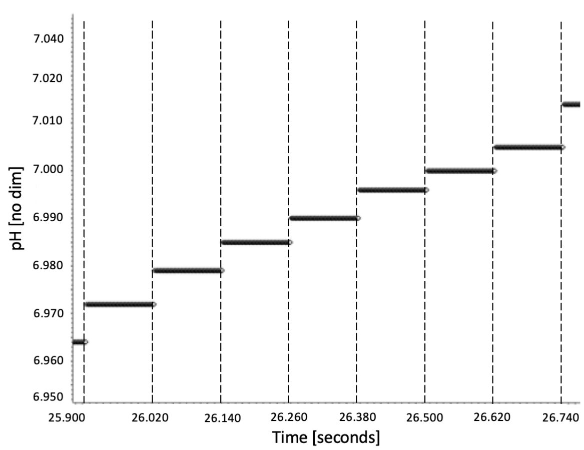

Figure 4. Incremental variation on pH result of periodic drop expulsions.

The addition of a buffered solution as an intent to maintain the pH level at a certain value provokes the natural differentiation of the system response into zones, distinguishable for the steepness of the pH variation. Figure 5 illustrates this,

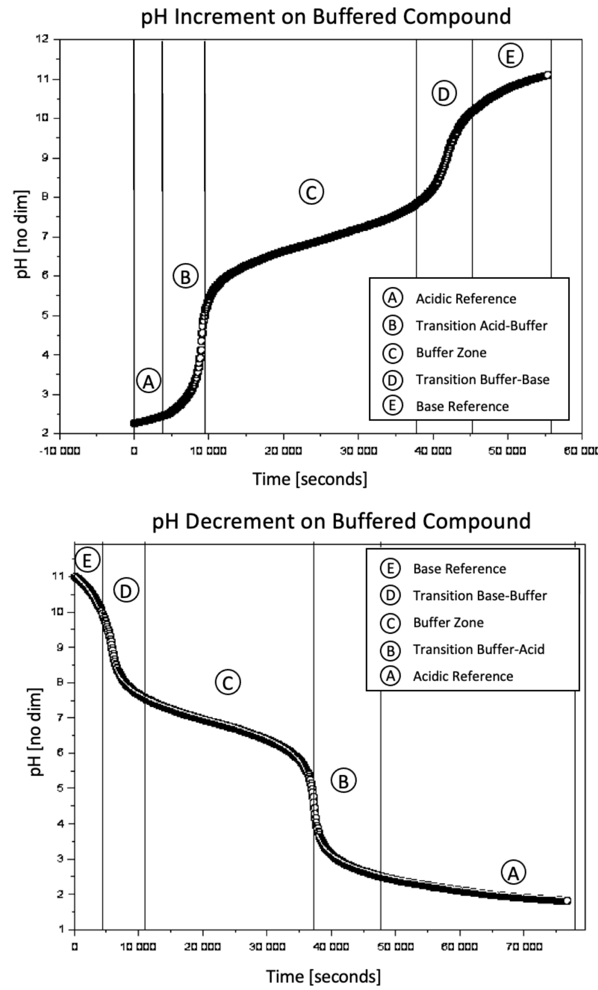

Figure 5. Variations of pH using three drops in a buffered KH_2PO_4 solution of *Streptococcus Thermophilus* in lacteus medium, with zones distinctions.

where five distinct zones are defined and named based on the nearness to buffer control or border limits and transitions between each state, for separate increments and decrements. These temporal behaviour is performed for traditional buffers KH_2PO_4, $C_2H_3NaO_2$, $C_2H_4O_2$ and $Ca_3(BO_3)_2$ on sets of 1, 3 and 5 continuous drops, resetting the system setup for each iteration. In order to avoid excessive compound waste, this analysis can be miniaturized on smaller recipients with same conditions and adequate substances concentration.

Several limitations are also required for consideration. First, bioreactors are usually used nearing maximum capacity with relevant compounds, and exceeded inclusions of actuator solutions are undesirable. Second, the system is needed for prolonged continuous system functioning of multiple days and it must endure limited quantity of actuator solutions and engines life expectancy before replacement. These imposes an extra requirement of minimal drops usage with loose intervals over time, granting a 6 to 10 seconds idle cycles in between consecutive control measurements and conditional expulsions of acid or base.

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IV. Control Observations

Previous experiences compendium and its analysis enables the structuring of custom classical, fuzzy and neuro-fuzzy controllers. These logic seek simplification and customization that fulfills requirements of counteracting biochemical reactions due to pH variations lesser than 0.2 per 10 seconds cycles.

A. Classical Controller

Given the observed non-inertial and immediate characteristics of pH permutations, a ON-OFF controller with decisions based on pH sensibilities and an error deadband for both increments and decrements of 0.05 from objective is used.

Figure 6 illustrates the general ON-OFF sequential logic, having as output the acid or base drops quantity to expel on system in the current control cycle.

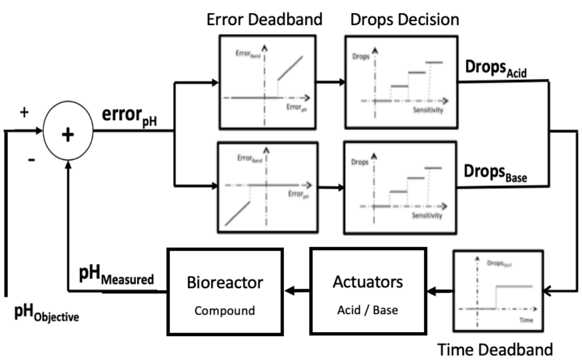

Figure 6. Diagram of utilized sensibility-based ON-OFF control logic.

The general idea, albeit compound specific, requires for significant drops expulsion on buffer zone (e.g., 5 drops for 0.02 variation) and considerably less on transition and reference zones (e.g., 1 and 3 drops respectively for same variation).

B. Fuzzy Perspective

An alternate broader approach is using fuzzy logic controllers, looking for a soft system response given ambiguous inputs and avoiding non-trivial mathematical modelling.

Figure 7 shows the global fuzzy control sequencing loop with the same drops amount parameter as decision output.

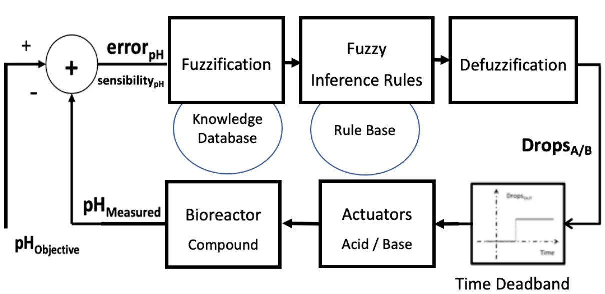

Figure 7. Diagram of proposed fuzzy-based control logic within the system.

In this case, input functions refer to error and sensibility, while output function allude to drops quantity expulsion for acid and base. Figure 8 exhibit a combination of triangular and trapezoidal membership functions that characterize fuzzy sets elements of both inputs expressed by linguistic variables result of a support fuzzification process, defining its universe of discourse. Through this method, a mapping of the crisp input values to the defined membership functions and truth values is performed. Then, these variables are used among max-min inference rules resulting in output linguistic variables, which conclude on the drops quantity after a defuzzification process guided by discrete centroid method, thus favoring the rule with the output of greatest area. In centroid defuzzification the truth values result of each rule are OR'd, i.e., the maximum value is used and the results are then combined using a centroid calculation.

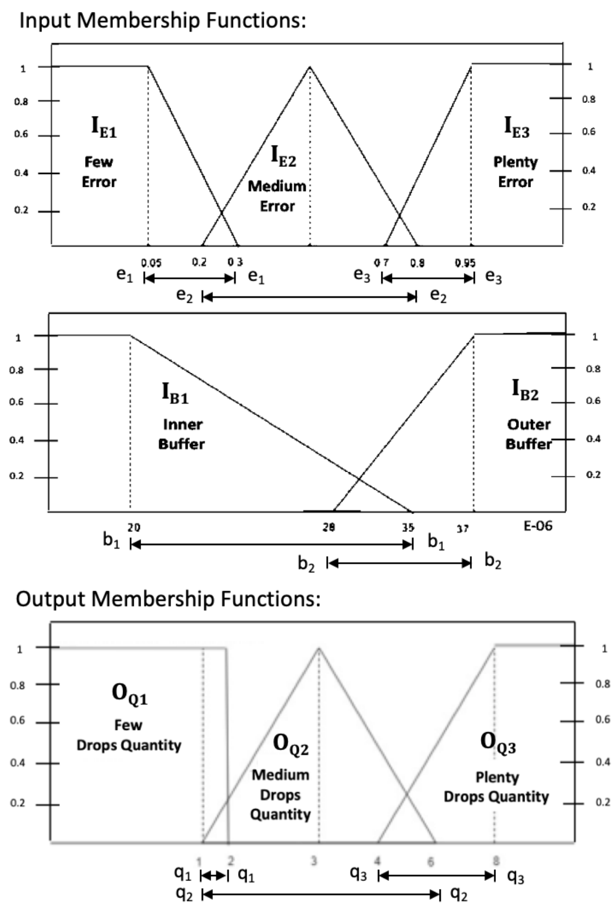

Figure 8. Fuzzy knowledge database, with membership functions definitions and linguistic variables indications.

The conditional rule base is described as follows:

- IF$[(I_E = I_{E1} \wedge I_B = I_{B2})] \Rightarrow O_{Q1} = O_{Q1}^{acid} \vee O_{Q1}^{base}$
- IF$[(I_E = I_{E1} \wedge I_B = I_{B1})] \Rightarrow O_{Q2} = O_{Q2}^{acid} \vee O_{Q2}^{base}$
- IF$[(I_E = I_{E2} \wedge I_B = I_{B2})] \Rightarrow O_{Q1} = O_{Q1}^{acid} \vee O_{Q1}^{base}$
- IF$[(I_E = I_{E2} \wedge I_B = I_{B1})] \Rightarrow O_{Q2} = O_{Q2}^{acid} \vee O_{Q2}^{base}$
- IF$[(I_E = I_{E3} \wedge I_B = I_{B2})] \Rightarrow O_{Q2} = O_{Q2}^{acid} \vee O_{Q2}^{base}$
- IF$[(I_E = I_{E3} \wedge I_B = I_{B1})] \Rightarrow O_{Q3} = O_{Q3}^{acid} \vee O_{Q3}^{base}$

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The selection of acid or base drops expulsion is decided implicitly by the rules based on the error differential sign.

When processing these inference rules using max-min, if an AND relationship is specified, then their minimum value is used as the combined truth value, occurring analogously with OR relationships and their maximum value.

Given the carefulness needed for these systems variable conditions, traditional common practices for pH regulation are the manual addition of acidic and alkaline solutions. Thus, practical human experience is mandatory for the definition of mentioned placement and usual ranges of membership functions, as well as for distinguishing each linguistic variable and truth values. In consequence, the proposed solution is diagrammed by empirical methods using a trial-and-error approach on *Streptococcus Thermophilus*, *Escherichia Coli*, *Myxococcus Xanthus* and *Deinococcus Radiodurans* while testing grade fuzzification methods together with weighted-average and mean-max defuzzification processes.

C. Neuro-Fuzzy Approach

Another alternative consists in joining fuzzy logic with customizable learning methodologies, thus providing with adaptative responses over natural changes on system behaviour. In this case, again, input functions refer to error and sensibility, while output function allude to drops quantity expulsion for acid and base. This perspective, diagrammed in Figure 9, enables constant feedback between the fuzzy neural network and the genetic algorithm, which selects the amplitude sets $\{e_1, e_2, e_3\}$, $\{b_1, b_2\}$ and $\{q_1, q_2, q_3\}$ of the predefined membership functions based on historical pH variations with given buffer. Consequent permutations over neural formulations adjusts dynamic responses over persistent system modifications.

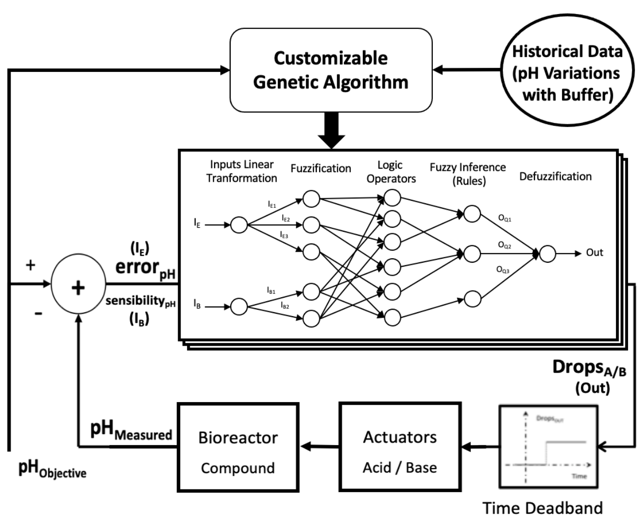

Figure 9. Neuro-fuzzy flow representation, including neural network iterations trained using a genetic algorithm helped by historical data.

Selected Mamdani-based feed-forward neural network is a 5-layer sequence with two inputs and one output that resembles aforementioned traditional fuzzy flow. Transitions from layers 1 to 2, as well as layers 4 to 5, contain [0,1] weights with equal average values in order to ensure symmetrical answer distributions on error input (I_E) and drops output (Out).

A genetic algorithm is used for training and selection of adequate amplitude sets and neural network configuration on each t cycle iteration. Defined selection rules dynamically choose past contiguous iteration's sets as parents of future generations. Custom crossover rules linearly combine these parents using proportional [0,1] parameters $\{\alpha, \beta, \gamma\}$ based on historical data, as shown in below equations.

$$\begin{pmatrix} e_1^t & e_2^t & e_3^t \end{pmatrix} = \begin{pmatrix} \alpha_I & \alpha_{II} & \alpha_{III} \end{pmatrix} \begin{pmatrix} e_1^{t-1} & e_2^{t-1} & e_3^{t-1} \\ e_1^{t-2} & e_2^{t-2} & e_3^{t-2} \\ e_1^{t-3} & e_2^{t-3} & e_3^{t-3} \end{pmatrix}$$

$$\begin{pmatrix} b_1^t & b_2^t \end{pmatrix} = \begin{pmatrix} \beta_I & \beta_{II} \end{pmatrix} \begin{pmatrix} b_1^{t-1} & b_2^{t-1} & b_3^{t-1} \\ b_1^{t-2} & b_2^{t-2} & b_3^{t-2} \end{pmatrix}$$

$$\begin{pmatrix} q_1^t & q_2^t & q_3^t \end{pmatrix} = \begin{pmatrix} \gamma_I & \gamma_{II} & \gamma_{III} \end{pmatrix} \begin{pmatrix} q_1^{t-1} & q_2^{t-1} & q_3^{t-1} \\ q_1^{t-2} & q_2^{t-2} & q_3^{t-2} \\ q_1^{t-3} & q_2^{t-3} & q_3^{t-3} \end{pmatrix}$$

Customization attributes enable constant or evolutionary proportional parameters indication, as well as fixed or variable parents selection. Particularly, setting constant proportional parameters provide equal pondering on membership variations per cycle, while using evolutionary variations generates dynamic functions for reaching certain behaviour at a given point in time. Moreover, configuring fixed parenting promotes constant and stable considerations of parenthood relationships, while selecting variable parenting allows for suppressing or emphasizing set behaviours caused by expected disturbances. Both evolutionary proportional parameters and variable parenting involves preliminary optimization steps with specific distributions, which resolve primarily on fewer or lower buffer usage and consequent error in regime. Possible combinations of aforementioned approaches broaden the system's response and behaviour for a given experiment context, which might deliver further research and production possibilities for in-batch microorganisms growth. Furthermore, initial iterations are defined mirroring aforementioned traditional fuzzy perspective, thus aiming at overcome natural system hysteresis and early reactions. Seeking simplification, no specific mutation rules are currently determined or deemed necessary.

D. Results Comparison

Generalizing outcomes are complex for systems with non-identical repeatable experiences, even more when considering different combinations of input parameters values and process cycles through ever-changing environmental conditions. However, certain particularities can be observed for most use cases that enable objective control results distinctions.

Figure 10 shows examples of the system evolution with active pH controls that illustrates the comparable similarities between all the examined approaches.

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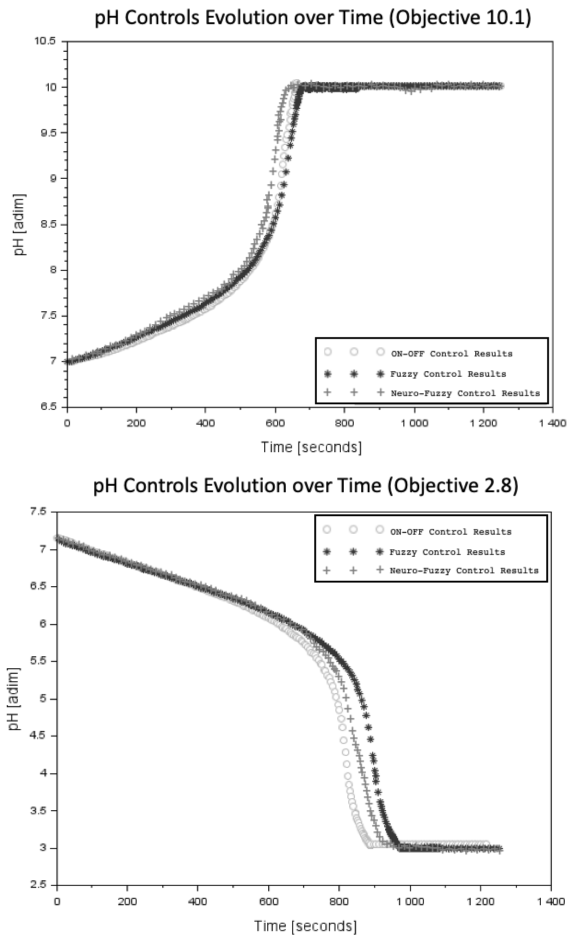

Figure 10. System response to pH controls at different objectives setpoints on *Streptococcus Thermophilus* solution with buffer KH_2PO_4.

According to these tuning and verification experiments results, the ON-OFF, fuzzy and neuro-fuzzy controllers stimulate the system to successfully reach pH levels with less than required 0.1 error margin without considerable overdraft nor oscillations when stationary for both increments and decrements. In fact, the fuzzy control gets to higher precision results than the classical control, i.e., closer to pH objective at regime, at a similar variation speed but at a greater transition time. This differentiation can be clearly appreciated on decrements and when a more extended pH variation is needed. Indeed, the fuzzy and neuro-fuzzy controllers are empirically more robust to noisy data caused by sensor malfunctions or circumstantial system behavioral spikes and levels reactions variations in setpoint vicinity in lesser approximation cycles quantities.

The neuro-fuzzy approach applied here defines balanced and constant proportional parameters while assuming fixed parents selection of three previous cycle iterations. As shown in Figure 10, it provides with sharper transition periods on both pH increment and decrement compared to traditional fuzzy perspective, with softer albeit slower adaptability changes and smaller divergences from objective. In particular, more accurate results with faster transitions can be obtained when setting evolutionary parameters along with same fixed parents selection, or variable parenting with extended preceding cycles considerations for further adaptability possibilities.

V. Conclusion

In this paper, three different approaches to pH control in bioreactors were proposed and its results compared through tuning and application of compounds with *Streptococcus Thermophilus*, *Escherichia Coli*, *Myxococcus Xanthus* and *Deinococcus Radiodurans* with standard actuators NaOH and HCl together with usual buffers KH_2PO_4, $C_2H_3NaO_2$, $C_2H_4O_2$ and $Ca_3(BO_3)_2$. Motivated by the natural relevance of pH property on the growth and survival of different microorganisms, and sought of general customized and flexible procedures for its control, all perspectives achieved an acceptable functioning with variable precision within the system characteristics and set requirements using affordable and scalable devices. Improvements related to diminishing transition times and increasing selection of membership classes can be further pursued for more meticulous or precise control and expanding current action ranges with additional limited drops quantities.

While the classical ON-OFF controller presented a more standard and direct logic sequence, the fuzzy and neuro-fuzzy propositions aimed at a more generic, customized and adaptable scheme to uncertain biochemical reaction changes with nonlinear behaviour. Due to its successful empirical testing and customization capabilities, the neuro-fuzzy approach is recommended to use on standard stirred tank bioreactors, with possible further investigation related to variants on other systems (e.g., other bioreactor types), as well as studied influence of different actuators concentrations and biological compounds characteristics (e.g., distinct buffers solutions and microorganisms combinations).

Potential real world use cases of this procedure involve commercial consumable fermentation and composition (e.g., milk derivatives preparation), as well as vaccine components concoction and manufacturing (e.g., antivirus processing for different animals) for small and large scale aerobic or anaerobic production. This is justified by the main dependence of the proposed procedure on compounds concentrations and independence of the system dimensions or capacities. Also, other academic use cases consist on studying certain microorganisms behaviour under stressing contexts in addition to genetic codes examinations, apart from traditional teaching and cultivation of recombinant DNA on proteins and bacteria. Thus, the complete process focused on reducing manual control and automating the simultaneous managing of multiple system properties, which is a contemporary trending practice on general bioreactors with long-term processes.

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