Kaunas University of Technology

Faculty of Electrical and Electronics Engineering

Investigation of Adaptive pH Control System Based on Feedback Signal Statistical Analysis

Master’s final degree project

Bilal Butt

Project author

Prof. Dr. Vytautas Galvanauskas

Supervisor

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Kaunas University of Technology

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Bilal Butt

Project author

Prof. Dr. Vytautas Galvanauskas

Supervisor

Assist. Dr. Vytautas Gargasas

Reviewer

Kaunas, 2026

Kaunas University of Technology

Faculty of Electrical and Electronics Engineering

Bilal Butt

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Bilal Butt

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Bilal Butt. Investigation of Adaptive pH Control System Based on Feedback Signal Statistical Analysis. Master's Final Degree Project / supervisor Prof. Dr. Vytautas Galvanauskas; Faculty of Electrical and Electronics Engineering, Kaunas University of Technology.

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Summary

In this work to investigate the pH control system of a biotechnological process by using an Adaptive controller through feedback signal, using a statistical method in which the proportional gain is fixed and the integral time is adaptive by taking online measurement from the methods of moving average window, offset by measured and desired pH, and average absolute deviation to measure the pH signal. Then compare the results with the classical fixed PI controller, in which parameters are fixed, and this mathematical model is implemented on MATLAB Simulink software.

By successful implementation of this model from the result its easily observed that the proposed method overcome the limitation of classical PI controller and gives significant performance and better improvement in pH stability with less deviation and better disturbance rejection with the involvement of feedforward compensator which play also important role to improve the system performance and give better results also applied noise levels and calculate the integral absolute error values clearly that adaptive controller is much better then classical PI controller in all scenario.

Bilal Butt. Grįžtamojo ryšio signalo statistine analize pagrįstos adaptyvios pH valdymo sistemos tyrimas. Magistro baigiamasis projektas / vadovas prof. dr. Vytautas Galvanauskas; Kauno technologijos universitetas, Elektros ir elektronikos fakultetas.

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Santrauka

Šiame darbe siekiama ištirti biotechnologinio proceso pH reguliavimo sistemą, naudojant adaptyvųjį valdiklį per grįžtamojo ryšio signalą, naudojant statistinį metodą, kuriame fiksuotas proporcinis stiprinimas ir adaptyvus integravimo laikas, atliekant tiesioginius matavimus slenkančio vidurkio lango metodais, kompensuojant išmatuotą ir norimą pH, ir vidutinį absoliutų nuokrypį, kad būtų galima išmatuoti pH signalą. Tada rezultatai palyginami su klasikiniu fiksuotu PI valdikliu, kuriame parametrai yra fiksuoti, ir šis matematinis modelis įdiegiamas MATLAB Simulink programinėje įrangoje.

Sėkmingai įdiegus šį modelį iš rezultatų, lengva pastebėti, kad siūlomas metodas įveikia klasikinio PI valdiklio apribojimus ir užtikrina reikšmingą našumą bei geresnį pH stabilumo pagerėjimą, esant mažesniam nuokrypiui ir geresniam trikdžių šalinimui, įtraukiant tiesioginio ryšio kompensatorių, kuris taip pat atlieka svarbų vaidmenį gerinant sistemos našumą ir duodant geresnius rezultatus, taip pat pritaikius triukšmo lygius ir apskaičiuojant integralines absoliučios paklaidos vertes, aiškiai matyti, kad adaptyvus valdiklis visais atvejais yra daug geresnis nei klasikinis PI valdiklis.

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List of abbreviations

Abbreviations:

ANN Artificial Neural Network

ARMAX Auto Regressive Moving Average with Exogenous inputs

DEE Differential Equation Editor

DMC Dynamic Matrix Control

E. coli Escherichia coli

EKF Extended Kalman Filters

FOPDT First Order Plus Dead Time

GH Glycoside Hydrolase

IAE Integral Absolute Error

IMC Internal Model Control

IVF In Vitro Fertilization

MFA Material Flow Analysis

MPC Model Predictive Control

ODE Ordinary Differential Equations

OUR Oxygen Uptake Rate

PAT Process Analytical Technology

pH Potential of Hydrogen

PHAs Polyhydroxyalkanoates

PI Proportional Integral

PID Proportional Integral Derivative

PLS Partial Least Squares

QbD Quality by Design

ROS Reactive Oxygen Species

SQP Sequential Quadratic Programming

SVM Support Vector Machine

$\mathbf{T_i}$ Time integral

WMPC Wiener Model Predictive Control

Introduction

The biotechnological applications, an optimal physicochemical environment must be controlled for the quality, quantity, and safety profile of the product. Certainly, pH is generally considered to be one of the most significant factors for its direct impact on microbial activity, enzymatic activity, nutrient solubility, and metabolic processes.

Minor deviations in pH might cause discontinuities in reaction rates, thus leading to purity issues, contamination or failure of the process. The advent of advanced bioprocesses and the regulatory and quality control demand for these processes place an even greater demand for precise and adaptive pH control systems [1,2].

Traditional pH control strategies, such as PID (proportional, integral and derivative) controllers are widely used in reactors. However, these often fail to effectively control the dynamic and nonlinear nature of biological reactions, especially for continuous and fed batch or high cell density cultivations [3,4]. Also, they are not adaptive to responding to unknown disturbances or metabolic dynamics. Due to these consequences the development of adaptive and intelligent control has driven. Nonlinear adaptive controllers, with feedback and input output linearization, showed improved setpoint tracking and rejection of disturbance compared to PI/PID controllers for pH neutralization systems. [5].

In this work, we introduce a new adaptive control strategy using statistics (e.g., variance, skewness, patterns) of the feedback signals to dynamically update pH control parameters. It is different from a traditional set point control of the system, and it is adaptive to a dynamic change in the metabolic signals, resulting in a predictive and data driven manner. The addition of the statistical layer gives an extra degree of adaptability for the control and a representation of the inner mechanisms. During these research works, the study is anticipated to lead to the development of smart bioprocess control systems, in line with the worldwide trend of Industry 4.0 and digital manufacturing.

Background and Context:

Precise control of the pH of biotechnological processes is essential for the best yield and quality of the products and process stability. Many industrial bioprocesses, such as those for the manufacture of pharmaceuticals, fermented food, and biofuels, require precise pH control within small tolerances to retain good operating conditions and product consistency for many batches of production [2,7].

Additionally, the phenomena of microbial growth, varying buffer capacity, consumption of substrate, and formation of by-social product result in unpredictable process kinetics. Thus, static control laws with fixed tuning parameters often have poor performance, particularly in fed-batch and continuous operation modes, which typically involve fast-grade transitions and non-linear switching phenomena [3,8]. To overcome these limitations, adaptive and nonlinear strategies have been suggested, including input output linearization, model reference adaptive control (MRAC), model free adaptive control, neuro fuzzy controllers, and sliding model based hybrids [9].

However, there have been new developments in processing automation and data analysis that provide opportunities for more intelligent and responsive control systems. Among them, adaptive control strategies, including those with statistical feedback signal analysis, have been particularly popular. Adaptive pH controller works on a feedback system and statistical modelling to exploit real-time measurements to online tune controller parameters while using quantitative performance and multivariate tools to evaluate stability, control, and robustness [9]. For instance, [8] suggested gain-scheduling approach to tackle dissolved oxygen control in highly time-varying conditions by dynamically changing the controller gains according to the process measurements and it can be applied to pH control for similar process dynamics.

Further, statistical monitoring with feedback control enables the identification of variability, compensation for drift and projection of when the system will go out of control. This is especially important in systems with intrinsic delays, actuator limitations and/or nonlinear buffering effects, as in the case of microbial and enzyme systems [10,11]. State, rate and error history of such systems allows for tight control with little overshooting and oscillation.

The shift is the key factor for smart bioreactors systems and fed batch biomanufacturing in the new direction which required robust, industry 4.0 and independent possible ready solutions. To achieve such type of solutions we need to investigate predictive maintenance, digital twins, adaptive pH control and feed forward OUR based compensator required [12,13].

Problem Statement:

In Biotechnological processes the control of pH is very necessary due to its direct impact on microbial activities and quality of product. Nowadays bioreactors are highly nonlinear and time varying nature, and sensitive to disturbances, it's difficult for classical methods to solve these problems with fix parameters. The problem with these controllers is that they are not adaptable to the changing behavior of the system due to biological variation, buffer capacity changes, and operational variations from batch to fed batch and continuous operation. More advanced schemes, such as fuzzy logic or model predictive control, provide better performance, but tend to be complicated, require significant computation, and are not readily implemented in real-time for the relatively small capacity, less-automated installations.

In response to the above mentioned limitations, we present in this paper a new method for adaptive pH control that learns from feedback signals statistically. This contrasts with standard methods, which monitor and have considerations only for the state, variance, or error behavior of the feedback, as the feedback loop is not model based, using strict mechanistic models. Together, these allow for strong, real time control performance and, at the same time, significantly lower the tuning complexity and difficulties in implementation. Through the implementation of these plans directly into modern bioprocess workflows, this work is intended to close the loop between theoretical control methodologies and practical, scalable implementations in intelligent biomanufacturing environments.

Research Aim:

This research aims to investigate and evaluate a novel adaptive pH control strategy for biotechnological processes, based on statistical analysis of feedback signals, to achieve robust, real time regulation without requiring complex mechanistic models for calculating nonlinear equations, parameter estimation, online computation, and identification.

Research Objectives: The aim of this work is to:

1. To explore the constraints of traditional pH control strategies, especially PID control, in responding to the nonlinear and dynamic environment of bioprocesses.
2. To assess a proposed adaptive control system that uses statistical information from the feedback signal to enhance dynamic pH control.

3. Design on MATLAB and evaluate the control system's potential benefits and feasibility in contrast to the current widely used strategy (Classical PI) in terms of its ease of implementation, responsiveness and scalability.

1. Literature review

1.1 Importance of pH Control in Biotechnological Processes

In a biochemical system, pH expresses the measure of hydrogen ion (C_H^+) concentration indicating the alkalinity or acidity of solution. In past few years, studies on pH control via process engineering have boosted dramatically. Controlled pH systems are used widely in different industries like biotechnology, wastewater treatment, pharmaceutical and chemical industries [14]. Since hydrogen ions concentration governs the chemical reactions affecting the biological and physical properties of a system, making pH a critical variable in biochemical systems [15]. Cells and microorganisms are acclimatized to restricted pH ranges, slight changes disturb intracellular pH, which is responsible for enzymatic reactions, cell division, differentiation, homeostasis and mitochondrial localization [16]. When extracellular pH deviates, it causes cellular stress and impaired growth [16]. Industrial microbes like Corynebacterium glutamicum are affected by pH fluctuations as one of the most occurring stresses in massive fermentation, making it unavoidable to make pH homeostasis to survive in acidic or alkaline conditions [17].

Enzymes generally have very narrow pH ranges to work properly, slight deviation from these ranges triggers activity decline, which has urged substantial protein engineering efforts to broaden pH most favorable for industrial enzymes such as GH11 xylanases [18,19]. pH and temperature are identified as critical variables affecting yield like in propionic acid production [20]. Required pH for the germination spores by Aspergillus niger is pH>5 for citric acid production, in contrast, yielding phase depends on very low pH (~2) to favor best method, avoid competing acid formation and minimize contamination [21].

Low pH in citric acid production enhances metabolism, suppress infecting microorganisms and avoids unnecessary acids, simplifying and enhancing the product quality [21]. Stable extracellular pH is necessary for embryo health and development in IVF culture, in contrast, deviation in pH results in compromised development and adverse health effects in cell based processes [16].

Control and monitoring of pH is labelled as most crucial parameter across food, biotechnological and pharmaceutical industries. A slight deviation in pH value can cause massive, nonlinear changes in system behavior [15,22]. The titration curve nonlinearity, high sensitivity close to neutral value, variable buffering and time varying properties make pH control a highly challenging dilemma that must be settled for administrative compliance and process resilience [22].

1.1.1 pH and Product Quality and Safety

Enzymes used in industry typically operate in narrow pH ranges and small deviations from these pH values lead to a loss of activity and stability. However, process engineering is working hard to broaden these optimal pH range to provide best condition [18,19]. During GH 11 xylanase production, maintaining optimal pH is necessary for product spectra, elsewise deviated pH can cause poor breaking down of carbohydrates, off spectra products or weak bleaching in foods [19]. Similar restrictions apply in many enzymes driven processes, while poor pH handling results in decreased productivity and low conversion [18,19]. In Corynebacterium glutamicum, stress due to high or low pH (acidic or alkalinity) triggers reactive oxygen species (ROS) management, ion transport and membrane adaptation. Excessive stress can cause impaired metabolism and viability, compromising the fermentation of acids (amino and organic) [17]. Meiotic spindle durability, cell division and blastocytes formation IVF culture are way too sensitive to pH. Even a minute change (0.2 unit) can change intracellular pH and development [16]. Organic acid fermentation is highly sensitive to pH. There are two stages in propionic acid production with pH control (first 6.5 and then 6) significantly increasing substances [20]. In contrast, during citric acid production, first pH>5 for spore creation, then controlled acidification is required to support production [21].

By product formation and metabolic routing is controlled by pH. During Aspergillus niger citric acid fermentation, maintaining pH 3 inhibits gluconic and oxalic acids production, increasing yield, selectivity and recovery [21]. In propionic acid production, deviating pH leads to low yield and faster pH swings that are uncontrolled, especially when substrates like molasses and glycerol are used. Optimal pH enhances yield from 14.6g/L to 19.2g/L [20]. Minute change in pH while making cheese can effect casein matrix structure, moisture retention and solubility causing huge difference in texture and flavour. Poor managed pH produces crumbling, bitter and poorly melting cheese decreasing the process uniformity [23].

Impurities are controlled with pH regulation by biological as well as physiochemical pathways. Low pH enhances product quality by inhibiting undesired organic acids formation and suppressing contamination risks in citric acid plants [21]. pH dictates the protein solubility, accumulation and buffering properties in dairy products, which directly affects curd formation, whey formation and consistency of cheeses, yogurts and hydrolysates. Strict pH regulation are key components for consistent texture and functional characteristics [15,22]. To achieve uniform quality in dairy products and bioprocesses, real time pH monitoring is the key component [15,24].

In low pH and citric acid fermentations, operating outside perspective values can result in contamination by low acid tolerant organism or high yield of undesired metabolites, compromising the regulatory compliance and microbial safety [14,21]. Failure to maintain stable and suitable pH can result in permanent damage to oocytes and early stage embryo in IVF culture, causing damage to batch at cellular level [16]. Severe pH is considered as reason for corrosion and degradation of materials in process plants and effluent systems. Neutralization of pH before discharge (like 6-8) is necessary to avoid pipes damage, protect environmental receptors and aqua culture safety [22]. Controlling pH is very hard near neutrality due to severe nonlinearity of titration curves. Improper acid or base dosing results in pH swings leading to over neutralization, corrosive system and operational disturbance [22].

1.1.2 Challenges of pH Control in Real Bioprocess

In bioreactors pH management is inherently difficult because system is highly non linear, time varying and sensitive to perturbation, not only just because of controller design choice [20,24]. pH neutralization shows S-shaped titration curve, extremely sensitive near neutrality. A minute change is acid, or base flow can change pH by one unit [22]. Yield of the process depends on the complete medium composition. In other words, the titration curve is not well defined and changes over time for multicomponent liquid medium [20].

Fig. 1. shows the titration curve of HCl, it shows how much base should be added into the solution. In bioprocesses, pH control is challenging because the underlying neutralization and buffering behavior is strongly nonlinear. S-shaped titration curve is exhibited by the acid base system, so process gain changes exponentially across the pH range, small base additions near the equivalence point can cause large pH spikes, whereas the same addition in a buffered region has minor effect [22].

In real fermentation broths, multicomponent buffers and weak acids disturb the titration curve and make it a time varying function because of changing composition [22].

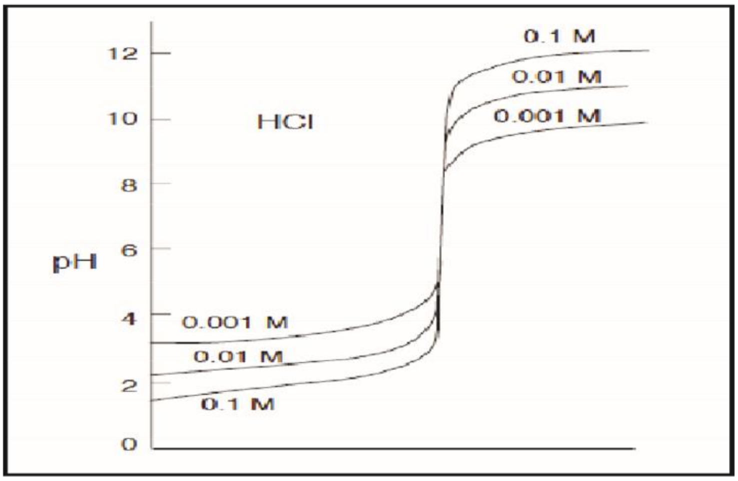

Fig. 1. Titration curve of HCl at different stages [22].

Bioprocesses also demonstrate time varying dynamics, biomass growth, substrate depletion and product accumulation contributing to change in buffer capacity and effective process gain over the batch or fed batch trajectory [20]. Intracellular pH is maintained in microorganisms through ion exchangers and transporters, and hence metabolic activity and production of acids and bases show dynamic responses to pH disturbances and control actions [17]. Real time and accurate measurement is very difficult. pH depends on temperature, dry matter content, ionic strength and gas content, so the measured value can drift with process conditions even at constant true proton activity [15]. Electrodes are sensitive to temperature, pressure, fouling and aging, leading to noise and sensor drift that require frequent calibration and compensation [14,21].

From a control design perspective, nonlinear nature, time varying gain and dead times of pH processes make simple linear controllers inadequate [22]. The process is extremely sensitive near the equivalent region and tuning that is best at the beginning of the batch and can be too aggressive later in the batch, and tuning that is robust at high biomass may be sluggish at startup [22]. Furthermore, the titration curve and dynamic characteristics of the process are not well understood for complex, multicomponent broths and they vary as the culture grows, so that controllers must deal with structural uncertainty [22,24].

1.1.3 Industrial relevance of pH control in Bioprocess

pH is a fundamental control variable across fermentation, cell culture, environmental treatment and food processing, directly influencing productivity, product quality and safety [25].

Citric acid is produced by the fermentation of Aspergillus niger, low pH is essential during production phase (~2) to maximize the citric acid accumulation, inhibit contamination and prevent by products like gluconic and oxalic acid formation [21]. If during the process pH is not properly maintained, citric acid yield drops, contaminating organisms growth and downstream recovery become more costly and difficult [21]. Temperature and pH are most important variables to produce propionic acid, propionic acid fermentation shows same sensitivity. Poorly handled pH results in feedback inhibition by acid, decreased titers and production of undesired products like butyric acid [20].

Many industrial enzymes operate under strict pH conditions, matching enzyme pH to process pH is essential for activity and stability [19]. As shown in **Fig. 2.** Xylanases are used in pulps, baking juice clarification, pharmaceutical and biorefineries. Pulp bleaching requires thermo-alkaline xylanases (pH>9), while baking and juice clarification requires acidic pH [19]. If pH of the process is mismatched with enzyme pH, catalytic activity drops steadily, making the process uneconomical [15,19].

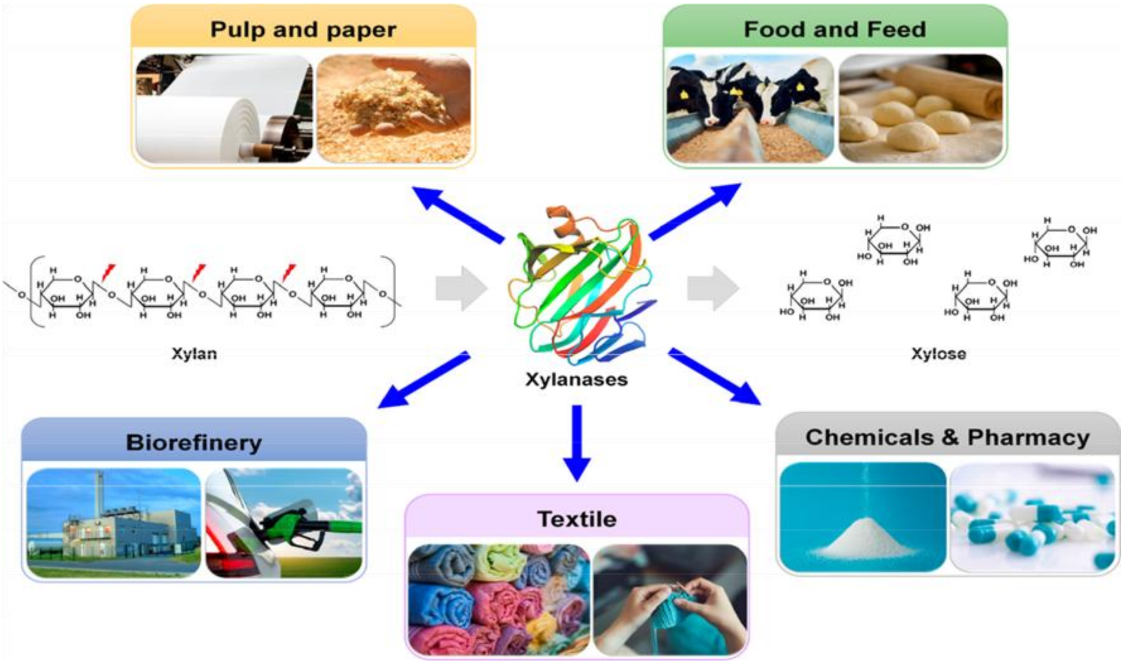

Fig. 2. Application of xylanases [19].

In industrial production of amino acids and organic acid fermentations with Corynebacterium glutamicum, pH fluctuations are frequently occurring stress. The organism struggles with multiple homeostasis mechanisms to counter the high and low pH stress [17]. Poor management of pH control results in oxidative stress, ion imbalance and growth inhibition, decreasing the product yield at industrial scale microbial fermentation [17]. pH shock strategies show that controlled pH disturbances can increase yield but uncontrolled shock decreases viability and productivity [25].

In mammalian IVF and embryo culture, extracellular pH firmly controls meiotic spindle stability, cell division, enzyme activity and blastocoel formation [16]. Suitable and stable culture medium pH is considered crucial for embryo health. If pH deviates, intracellular pH regulation is perturbed, leading to impaired development and decreased IVF success rate [16]. Biotherapeutics production in bioreactors depends on strictly controlled culture conditions. Modern bioreactor control strategies endorse strict pH monitoring and control as vital component for process performance, productivity and viability [24]. Inadequate control on pH, these systems result in low product quality and process variability, which is not acceptable in pharmaceutical production [24].

For wastewater treatment and pretreatment for biotechnological processes, pH neutralization plants are standard units [22]. Effluents must be discharged at pH range 6–8 to safeguard the aquatic life and minimize corrosion, poor pH management results in environmental damage, regulatory noncompliance and compromised downstream biological treatment [22]. As neutralization system is highly nonlinear and hard to control, advanced strategies are being developed to maintain effluent pH in strict limits [22].

In dairy processing, pH is a strictly controlled parameter, used as a contamination marker as well as controller of product properties in cheese, yogurt, fermented beverages and protein hydrolysates [15]. Chinese baijiu fermentation uses lactic acid to acidify the fermentation environment to prevent spoilage and impart characteristic acid taste, too much acid makes the wine too sour, while too little acid leads to poor taste and spoilage risks [14].

1.1.4 Consequences of Poor pH Control in Bioprocesses

Optimal pH is essential for cell culture and microbial growth, optimal pH lies in narrow window, slight deviation from optimal limits results in low biomass growth and decreased metabolic activity as intracellular homeostasis may fail [16,20]. During organic acids production, inconsistent pH may lead to low yield and productivity, conversely properly handled pH can increase titers significantly [20]. Likewise in citric acid production, hydrogen ion concentration is part of unusual nutritional conditions required for overproduction, disruption of these conditions results in low citric acid accumulation and compromised metabolism [21]. Poor pH management can transfer metabolic pathways resulting in production of undesired products, such as by changing flux through enzymatic steps in carbon metabolism [16,25]. Even a tiny pH fluctuation for an instance can cause large, irreversible changes in culture performance, decreasing the reproducibility in batches and minimizing growth [22,24].

Inadequate pH management typically enhances acid base consumption because controllers over correct against large deviation on a steep titration curve in highly nonlinear neutralization system [22]. Consequently, this increases resources consumption in reagents, utilities and downstream neutralization, since more chemicals and energy are required to bring the process back within normal limits [22]. In many plants, the lack of non-robust control of pH levels dictates the process to be brought back into specific conditions through manual intervention of the operators, therefore increasing the manpower requirement and possibility of human error [24].

Since pH regulates the process equilibrium, protein stability and microbial composition, unstable operation results in uneven product quality, including instability in titer, impurity profile and performance [17,23]. In IVF processing, a slight deviation in pH affects embryo developmental competence, and in dairy processing, pH deviation affects textural and functional properties of milk products, demonstrating how narrow suitable pH range can be [15,16]. Under severe excursions, cultures may lose viability or become contaminated, which can result in batch failure and loss of material [14]. Decreased yields, prolonged batch times, supplementary reagents and repair activities results in higher operating costs resulting in motivation for adopting more advanced and robust approaches to pH control in bio-therapeutic and fermentation processes today [24].

1.2 Bioreactor Operating Modes and Their Industrial and Control Implications

Different operational modes (batch, fed batch, continuous) can be used to define the time profile of the addition and removal of substrates and products in the process, leading to different substrate availability, growth environment and process dynamics [26]. Mode selection influences substrate profiles, growth rate, product yield and the extent of difficulty required to maintain pH, dissolved oxygen and other variables [27]. For adaptive pH control strategies, fed batch is specifically important due to high industrial relevance with strong time varying dynamics [27].

1.2.1 Batch Operation

In batch mode, reactor is filled with medium and culture at beginning and vacated at the end of farming [28]. Batch mode offers straightforward operation and sterilization; therefore, it is mostly used in laboratories and in some industrial fermentations where quantity and productivity demands are moderate [28]. The closed nature of system diminishes contamination risk during the operation and simplifies the control, making it suitable for high value and sensitive products [29]. From control perspective, batch systems are fundamentally simple, but conditions are time varying as nutrients are consumed, products and by products accumulate and pH drifts as metabolism progresses [30]. Varying conditions result in nutrient limitation, product inhibition and low productivity due to downtime between batches [31]. However, control strategies are implementable because volume is constant and no feed flow driven disturbances occur [30].

1.2.2 Fed-Batch Operation

In fed batch process, substrate is introduced during cultivation resulting in an increase in volume over time while effluent is eliminated at the end of process [27]. By customization of feed rate and composition, fed batch allows control of nutrient supply, suppression of substrate inhibition and achievement of high cell densities and product titers across different bioprocesses [27]. Fed batch strategy is widely used in industrial fermentations (like lactic acids, PHAs and vaccines) to enhance the productivity and engineer growth product formation relationship [30,32]. Control effects are significant. Variation in biomass concentration, change in volume and time varying metabolic states create nonlinear and varying dynamics, making pH maintenance and other controls challenging [27]. Feeding strategy disturbs pH by both direct (via feed composition and base addition) and indirect (through changing metabolic rates) ways, making controller performance poor if adjustments are invariant [33]. These characteristics make fed batch more prone to disturbance, model incompatibility and unobserved heterogeneities, however, it also makes it a precious benchmark for advanced or adaptive control methods [27].

1.2.3 Continuous Operation

In continuous operation mode, fresh medium is continuously added while culture broth is continuously withdrawn at the same volumetric rate, ideally maintaining a steady state for substrate, biomass, and product concentrations [31]. This results in high spacetime yields, effective equipment utilization and bulk production campaigns with consistent product quality when a stable steady state is maintained [29]. Continuous operation is more suitable for process intensification and long-term production of vaccines, biopolymers or fuels [31].

However, continuous systems are more susceptible to contamination, failure and long term genetic or physiological drift, demanding strict monitoring and control to maintain stability [29]. Although steady state operation may facilitate the control of pH theoretically (as set point and loads are constant), disturbances occurring continuously, gradual fouling and variation in parameters may still present regulation problems over extended campaigns [31].

1.2.4 Comparison of Operational Modes

Batch fed batch and continuous operation are different from each other in complexity, productivity and control conditions which make them suitable for advanced pH control.

In batch mode, nutrients are introduced at beginning of process and volume remains constant, so process dynamics are controlled by intrinsic microbial growth and product formation with relative mass balances and control structure [28]. Complexity of the operation and control difficulty are minimal, making batch suitable for screening and kinetic studies, however productivity is restricted due to downtime for filling, sterilization, cultivation and by inhibitory metabolite buildup toward the end of the run [32]. This model provides moderate flexibility as set points can be changed between batches but not within a run. Risk of contamination is minimal because the culture is not continuously fed. Nevertheless, the relative homogeneity and simplicity of the dynamics make batch less challenging, and hence less informative for the assessment of pH control and adaptive algorithms, particularly in the assessment of the response to rapid changes [31]. The issue of scalability is well established industrially but it may make the problems of mixing and pH gradient more severe [31].

Fed batch introduces substrate and other feeds during the process, feed addition and volume change become key engineered variables [27]. This adds to the complexity and difficulty of operation and control because substrate, pH, dissolved oxygen and osmolality must be managed in time-varying modes, but it also allows the achievement of high cell concentrations and productivities in PHA and viral vaccine production where fed batch outperforms batch and become real industrial choice [26,27]. Fed batch is flexible and feeding strategies may be chosen to match the kinetics of metabolism and product quality [27]. Risk of contamination is relatively higher than batch mode due to longer runs, still it is less than in continuous processes [32]. Intrinsically dynamic system in terms of varying volume, substrate and by product concentrations, results in significant and controllable pH perturbations from the addition of substrates and bases/acid, hence making fed batch an excellent choice for evaluating and stressing adaptive pH control strategies [27].

In continuous mode, fresh medium and effluent flows are balanced to ensure that volume remains constant while cells and products are continuously removed. This mode can achieve high time average productivity by inhibiting all nonproductive down time and keeping the culture in an optimal steady state [29,32]. Continuous cultivation enables flexibility for steady state studies including precise control of dilution rate and nutrient ratios to modify product composition and molecular weight [32]. However, complexity and difficulty are high for controlling this model due to requirement of many pumps and fittings, the need to maintain sterility over long periods of time and small disturbances can lead to contamination and changes in product composition, particularly in multistage cultures [32,34]. Risk of contamination is considerable in this mode due to the possibility of genetic deviation over long periods of operation [32].

1.3 Modeling Techniques for Bioprocess Control

Bioprocesses are extremely nonlinear, time varying and sensitive to operating conditions, conventional measurements and approximate tuning lead to poor control, particularly when core parameters (biomass, substrate and product) are unmeasurable and perturbations are occurring consistently [35]. Models are helpful in prediction, simulation and optimization of trajectories, tuning and design of controllers and exploration of design spaces that are costly to cover experimentally [36]. Relevance of the modeling approach depends on the existing knowledge (for example stoichiometry and kinetics), quality and quantity of data, since mechanistic models depend on knowledge while data driven and hybrid models depend on informative datasets [37]. Overall, there are three model classes used for bioprocess control and analysis, these are kinetic, data driven and hybrid model [37].

1.3.1 Kinetic (Mechanistic) Modeling

Mechanistic models are based on mass balances for biomass, substrates, products and in some cases gas liquid species, along with growth and reaction kinetics and physicochemical relations such as Monod type rates, yield coefficients and pH or oxygen transfer correlations [38]. State variables contain biomass growth rate, substrate consumption, product formation, volume dynamics and oxygen uptake, macroscopic Monod models are widely used to relate substrate and cell concentrations to growth and uptake [38]. These models are interpretable, equipped with information about internal process behavior and naturally suitable for model based control, sensor and optimization, since they can predict far more than the range of experimental data if the underlying conditions are well represented [37,38]. They demand comprehensive process understanding and well-designed experiments, missing mechanisms or shallow kinetics can lead to model mismatch and inappropriate predictions for complex biological systems [37].

1.3.2 Data-Driven Modeling

Data driven models are fundamentally predicated on measured input, output data rather than first principles equations, using tools such as regression, partial least squares, neural networks, support vector machines, Gaussian processes and machine learning approaches [37]. Data driven models are used when process physics is uncertain as they can manage complex nonlinear systems directly from operational data and can be implemented relatively quickly if sufficient data is available [37]. As an example, soft sensors based on spectroscopic data and chemometrics can estimate cell or substrate concentrations for advanced control without specific kinetic details [38]. Limitations of data driven models are dependent on data quality and coverage, poor estimation outside the training limit and lack of interpretability, which can inhibit root cause analysis and robust controller design [37]. In industrial bioprocesses, costly and time consuming experiments can limit the amount and diversity of available data, which can limit the safe operation of purely data driven models to a narrow range of operations [39].

1.3.3 Hybrid Modeling Approaches

Hybrid models, which combine mechanistic models with data driven models, are used for enhanced accuracy, robustness and predictions accuracy when incomplete information is available [39]. Widely used strategy is to retain first principles, mass balances and stoichiometry while using nonparametric or machine learning models for uncertain kinetics. In an industrial E. coli fed batch, a parametric dynamic model of a bioreactor was blended with an artificial neural network model defining biomass and product formation rates, providing an accurate description of productivity over broad ranges of temperature, pH and feed rate, and for Quality by Design (QbD) and Process Analytical Technology (PAT) development [40]. At industrial scale, deep neural network is combined with a refined kinetic model to predict time varying parameters in fermentation, substantially enhancing robustness and capturing complex temporal dependencies not depicted in the kinetic model alone [41]. Hybrid modeling approaches are considered as an enabling platform for Industry 4.0, QbD and PAT in biopharmaceutical processes, where data is limited but regulatory pressure for process understanding is high [39]. A generic hybrid EKF (extended Kalman filters) framework demonstrated that hybrid models used within extended Kalman filters can provide significantly more accurate soft sensor predictions for mammalian titer than PLS based (partial least squares) benchmarks, empowering real time monitoring, conditional feeding and automated decision-making [42]. Comparative analysis between mechanistic and hybrid models illustrates that, while mechanistic models benefit from previous knowledge and are less sensitive to which experiments are used for training, hybrid models can achieve higher accuracy when aided by informative design of experiments data, emphasizing that experimental design quality is more critical than quantity [37]. Likewise, hybrid state estimators based on mechanistic ODE models and data driven observation functions have yielded low noise state estimates suitable for advanced control in therapeutic protein processes [35]. On the other hand, hybrid models are complex to develop and validate, computationally heavier and require process knowledge and representative datasets [37,39].

1.3.4 Comparison of Modeling Techniques

Kinetic model is based on mass balances and physiochemical laws, used in ODE bioreactors. This model is easily Interpretable, predictive and compliant with model based control, but it requires strong prior knowledge and parameterization effort [38]. Data-driven model trains from process data (regression, ANN, SVM, system ID). This model can detect complex nonlinearities with small effort, but this model requires more data, prediction is not accurate and provides limited insight [37]. Hybrid model provides data-based corrections and interpretable as well as accurate, but this model is more complex and requires data and knowledge both [39].

1.4 pH Control Techniques in Biotechnological Processes

In bioprocesses, pH control is challenging due to nonlinearity of neutralization, process gain changes by orders of magnitude along the titration curve and bioreactor dynamics varies with biomass, substrate and sensor drift [43,44]. Consequently, a spectrum of controllers is used, from conventional PI/PID to adaptive, intelligent, MPC and feed forward structures [44,45].There are multiple types of electrodes for pH measurement such as conventional glass electrodes, metal electrodes and solid-state glass electrodes. Conventional glass electrodes is best for selectivity, stability and accuracy. Metal electrodes are used for food and medical products monitoring. Solid-state glass electrode is rugged [46].

1.4.1 Conventional PI/PID Control

The PI/PID controller calculates the actuator signal from a weighted sum of present error (P), accumulated error (I) and error rate (D), since derivatives enhance noise from glass or electrodes and on/off peristaltic pumps, PI is widely used in pH control [44]. At industrial scale, PI/PID are used because of their simple structure, low computational effort and direct execution in commercial bioreactor controllers [44]. When the pH loop can be estimated by a first order plus dead time (FOPDT) or ARMAX model, classical PID tuning (like Cohen Coon) gives good reference value tracking and minimal integral squared error in fermentation, as shown for Clostridium acetobutylicum pH regulation [45]. However, bioreactor pH systems are nonlinear and time varying, changes in titration curve increase as much as 10,000:1 near pH 7, changes in buffer capacity with feeding and biomass driven acid base production acting as a drifting disturbance [44]. As a result, a PI controller tuned for operating conditions may perform poorly in buffered regions yet outrun or oscillate close to neutrality, performance decreases further in long fed batch processes as process gain increases with biomass [43,**47**]. Comparative studies show that many advanced strategies including global linearization, generic model control, nonlinear IMC and adaptive algorithms can outperform fixed PID in more demanding pH processes [44,48]. Processes in which pH variations need to be closely regulated, conventional PID controllers do not work as process dynamics is not constant [49]**.** Hence, PI controller is a robust benchmark, but fixed parameters are insufficient in nonlinear and fed batch processes, demanding improvement through adaptive control rather than replacement.

1.4.2 Adaptive Control Methods

Adaptive controllers upgrade parameters online to adapt with changing process behavior. In pH control, strategies like gain scheduling, self-tuning PI, model reference adaptive control, nonlinear adaptive control and parameter tuning using error statistics are preferred [44]. Adaptive PI uses a prediction model to evaluate closed loop sensitivity to PI parameters and then automatically adjusts gains to satisfy time domain specifications; compared with standard PI, gain scheduling and globally linearizing control, this auto tuned PI produced significantly improved pH stabilization on a neutralization process [48]. In fed batch biochemical process pH control, an adaptive PI based on gain scheduling over a mechanistic model substantially minimized tracking error compared with a fixed PI, especially near the end of run when biomass induced acid production increases [43]. Nonlinear adaptive strategies are developed for laboratory scale neutralization units, input output linearization with indirect parameter estimation results in an adaptive nonlinear controller that turns down interruptions and buffering changes better than nonadaptive nonlinear control and a conventional PI [9]. In biotechnological cultivation, adaptive PI is used to control the specific growth rate in E. coli fed batch processes using an OUR based estimator as feedback, online OUR measurements to adjust the PI to time varying constraints and allow tracking of growth rate profiles [50]. These results demonstrates that adaptive control is most suitable in bioprocesses. Dynamics vary with biomass and substrate, disturbances develop during cultivation and fixed tuning cannot be optimal. Adaptive controllers offer enhanced robustness and disturbance inhibition, but they require choices about adaptation logic and poorly designed adaptation can destabilize the process [50,51]. Bioreactor aligned approach is adaptive PI based on statistical analysis of the controlled signal, in which variation in other statistics of the pH trajectory trigger parameter adjustments to maintain dynamic performance under variable conditions [51].

1.4.3 Fuzzy and Intelligent Control

Fuzzy and intelligent controllers replace detailed mathematical models with linguistic rules, expert knowledge and approximate reasoning. Error and error rate are mapped to qualitative terms (small, large, increasing) in fuzzy logic and integrated through IF THEN rules to trigger control actions, while in contrast, neuro fuzzy and neural controllers acquire such information from data [44].

Fig. 3. shows block diagram of fuzzy logic system. The process begins with data, which is fuzzified in the Fuzzification stage. The data then are fed into interference, which applies a set of rules in knowledge base. Then, it goes to the defuzzification process to get a crisp output, which is used by the real system.

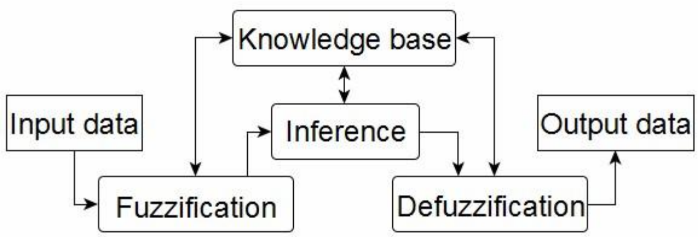

Fig. 3. Structure of Fuzzy Controller [44].

At laboratory-scale fermentation pH control, a fuzzy self tuning PI controller is implemented using digital peristaltic pumps. The design takes only pH error and its derivative as inputs, a fuzzy deduction mechanism generates a tuning parameter that updates PI gains online. In 2 L and 7 L reactors, this controller maintained pH within ±0.05 units regardless of varying volume and buffer capacity, establishing strong robustness to process changes [44,52]. Comparative studies on pH control denotes that fuzzy controllers can enhance the effective operating range on highly nonlinear titration curves, handle perturbations and can be implemented on modern hardware [44].

The MPC using a neural network is based on intelligent modeling and optimization, a feed forward neural network is trained using data from a PI controlled neutralization reactor and embedded in an extended DMC algorithm to attain better control of pH than the original PI controller without any prior first principle modeling [53]. These intelligent methods best fit for nonlinear, time varying bioprocesses and shown enhanced performance in experiments. Nevertheless, these approaches have some drawbacks like rule bases and tuning difficulties, validation issues in regulated industries and lower industrial acceptability compared to PI and MPC controllers [44,52].

1.4.4 Model Predictive Control (MPC)

MPC uses an explicit process model to predict future outputs over a finite horizon and computes suitable corrections by minimizing a cost function dependent on constraints. In pH control, both linear and nonlinear MPC approaches have been developed. Wiener models are comprised of linear dynamics in series with a static nonlinearity representing the titration curve, capturing pH nonlinearity with moderate modeling. A Wiener Laguerre model utilizing Laguerre filters for dynamics and a low order polynomial for the nonlinearity attained a variance accounted for of about 92% for a neutralization process and was used in a nonlinear MPC framework, as a result, controller better performed than linear Laguerre based MPC and enhanced SQP convergence while maintaining controllable complexity [54].

Fig. 4. show block diagram of linear MPC. The process begins with a setpoint y_{sp}, and compare with output $y_m$to detect an error signal. The error then goes through the controller G_c, which outputs a control signal u based on the disturbance. The control signal goes through the plant G_p, producing the output y_p. Also d_p represents external disturbance like noise or environmental changes.

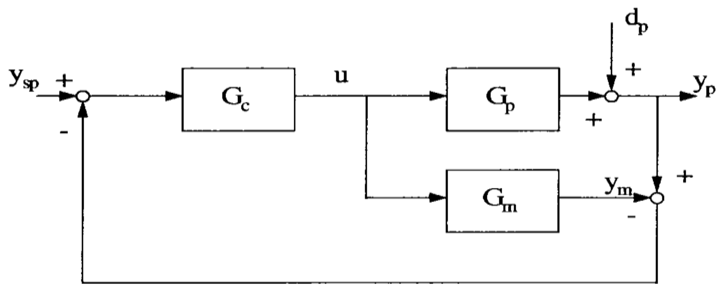

Fig. 4. Block diagram for linear MPC [55]

Experimentally, Wiener model predictive control (WMPC) was implemented to control pH neutralization process, comparing it with conventional PID control and linear MPC under constraints and modeling error. WMPC, using a cubic spline static nonlinearity and a step response dynamic model, resulted in improved tracking and disturbance rejection while instinctively handling output constraints. While providing the advantages of the linear MPC because the nonlinearity is effectively removed by optimization for the Wiener structure [55].

Neural network MPC are used as another nonlinear MPC option, a feed forward neural predictor, trained on PI controlled data is embedded into DMC to control pH, attaining enhanced performance than the training data PI controller without requiring explicit physical modeling [53]. Studies confirm the strengths of MPC such as handling of constraints, multivariable control, anticipation of modeled disturbances and enhanced performance on nonlinear systems [53].

However, the requirement of reliable models, computational facilities, software specialization and expert maintenance makes MPC model complex that might be considered excessive for control of a single pH process in many industrial bioreactors [50].

1.4.5 Feed-forward Compensation Strategies

Feed forward control executes corrective action from estimated disturbances prior to their complete effect on pH, which complements the feedback control action that reacts only after a disturbance has happened. In a pH system, disturbances arise from influent composition, changes in titrant concentration and biological production of acids or bases.

In Wiener modeling, a linearization of a neutralization process is obtained by using the inverse of the titration curve. A study suggested linearizing feedback and simple linearizing feed forward controller based on estimate of the inverse titration curve. Simulated results of a closed loop system demonstrated that combining feed forward control with a PI feedback substantially enhanced performance compared to linearizing feedback alone, if the inverse titration curve is correctly estimated [55].

In bioreactors, internal perturbations are caused by metabolic activity. A unified adaptive pH control model is suggested in which a standard PI controller is boosted by a statistical adaptation algorithm and an OUR based feed forward compensator. The feed forward part uses estimates of oxygen uptake rate to compensate for disturbances in biomass growth rate and biomass concentration that cause load disturbances, simulations show this combination improved control performance compared to fixed parameter PI control without additional hardware other than that required in industrial applications [51].

Feed forward compensation allows for fast rejection of disturbances and low pH variations when disturbances (such as OUR and inflow titrant) can be measured or estimated and modelled. Nevertheless, it is dependent on the quality of the disturbance model and cannot replace the need for feedback, which is required for offset removal and unmeasured disturbances [44].

1.4.6 Feed-forward vs Feedback Roles in pH Loops

In a pH control loop, feedback (PI or adaptive PI) and feed forward (for example OUR based compensation) play complementary roles. Feedback utilizes pH error, the difference between measured pH and the reference value and therefore reacts after a disturbance has induced a deviation in pH [44]. This makes feedback essential for offset removal and handling unmeasured or poorly characterized disturbances which cannot be predicted in advance. Therefore, feedback controller is key regulatory element of the loop [9].

In contrast, feed forward uses a disturbance signal such as OUR or flow rate, rather than pH error to execute a corrective action before the disturbance has fully influenced the pH [51]. It is suitable for predictable and measurable disturbances, where an adequate disturbance model exists [54]. Feed forward improves disturbance inhibition and minimizes pH excursions, but it cannot replace feedback model because it cannot address unmeasured loads and zero steady state error is not guaranteed [44]. Practically, feed forward is implemented as an addition to a PI or adaptive PI controller, providing compensatory action for known disturbances, while feedback loop provides better tracking of the pH set points and corrects any unmodeled effects [44].

1.4.7 Comparative Review of Control Techniques

Comparative studies demonstrate that PI/PID controllers are simplest and most widely used but their performance declines on highly nonlinear, time varying systems like pH neutralization [45]. Advanced models like adaptive, fuzzy, neural and MPC models improve tracking and robustness but demand more complex models, hardware, tuning and validation. In biotechnology, institutions are reluctant to adopt sophisticated algorithms due to validation challenges and requirement for operator friendly tools [45].

In fermentation process, traditional PI tuned on FOPDT or ARMAX models can be used to control pH, but its parameters are designed for set-point operating conditions, and do not account for changing biomass and buffer concentrations [45]. Adaptive and gain scheduling PI, both models-based and empirical, have led to drastic reduction of pH variations along with improvement of information quality at minimal additional cost, making them appealing additions to the existing industrial control system [30].

Fuzzy self-tuning PI controllers provide best pH maintenance and robustness at laboratory scale but their complex and case specific design and tuning obstruct transfer to industrial platforms [52]. Wiener and neural network MPC models provide better control quality and constraint handling on standard neutralization units, however modeling and computational effort make it best candidate for critical and multivariable applications but not for every standard pH loop [53,55]. Feed forward strategies such as inverse titration linearization and OUR based compensation enhance disturbance rejection when high quality disturbance measurements are available and they integrate naturally with PI and adaptive PI controllers [55].

A recently integrated adaptive pH control model adapted for bioreactors combines three components, (i) PI controller as core actuator, (ii) adaptation algorithm driven by statistical characteristics of the pH signal that updates controller parameters when loop dynamics change and (iii) OUR based feed forward compensator for biomass related load disturbances. Simulations demonstrated that this model enhanced pH control accuracy compared with a fixed parameter PI while requiring no extra hardware or new software, making it implementable in commercial controllers [51].

2. Methodology

2.1 Biotechnological Process Model Overview

The biotechnological process model employed in this work corresponds to a fed batch cultivation system where biomass growth, hydrogen ion concentration and reactor volume dynamically evolved with respect to time. The model is defined to account for the key biological and physicochemical phenomena affecting pH dynamics during pH cultivation, but it is also appropriate for use in control system design and simulation studies. This modeling approach is based on the framework introduced by Galvanauskas [43], which has been widely used in research dealing with bioprocess modeling and control.

The model is a collection of nonlinear differential equations for the growth of biomass, hydrogen ion balance and reactor volume dynamics. Biomass growth is influenced by the specific growth rate, dilution effects due to addition of feed and alkaline, whereas hydrogen ion concentration is influenced by the metabolic performance, dilution effects of feed and addition of base for pH control. As stressed by Galvanauskas [43], such a structured but simplified model is appropriate for the evaluation of control strategies, by retaining the properties of process dynamics without adding new complexity.

In addition to the fundamental state variables, the model consists in an algebraic expression for the oxygen uptake rate (OUR) which is related to metabolic activity within the culture. OUR is one of the important secondary process variables and is used later in this study as an auxiliary signal in feedforward compensation as described by Butkus et al. [51]. A differential equation block structure of all model equations is implemented in the Matlab/Simulink environment and enables us to couple directly with feedback and adaptive control algorithms.

2.1.1 Biomass Growth Model

The biomass growth model is used to describe the time dependence of the concentration of the microbial biomass in the fed batch bioreactor. Biomass concentration is an important state variable as it affects directly the metabolic activity, substrate consumption, hydrogen ion production and oxygen uptake rate. As demonstrated in this study that biomass dynamics are modelled and microbial growth as well as dilution effects resulting from liquid inflows. This formulation is based on the control oriented bioprocess modeling approach that was proposed by Galvanauskas [43].

The change in biomass concentration over time is given by the following differential equation by Galvanauskas [43,51]:

$$\frac{dx}{dt} = \mu x - \frac{F_s + F_{pH}}{V} x \tag{1}$$

where x is the concentration of biomass, and μ is the specific growth rate, F_s is the flow rate of the substrate feed, F_{pH} is the flow rate of alkali for pH control and V is the volume of the reactor.

The first term on the right-hand side is the growth of biomass because of microbial metabolism and is proportional to current biomass concentration and the specific growth rate. The second term provides for biomass dilution from the addition of substrate and alkali streams in the fed batch mode of operation. As the reactor volume grows with time, the effects of dilution become important and have a strong impact on the overall biomass profile. By ignoring the effects of dilution in fed batch models, unrealistic biomass results and poor control performance evaluations might be obtained, according to Galvanauskas [43].

This biomass growth model gives a realistic but computationally efficient model for biological dynamics and is suitable for analysis and simulation of the control system. The resulting biomass concentration has a direct effect on hydrogen ion generation and oxygen uptake rate, thus conducting biological growth behavior to pH dynamics of bioreactor.

2.1.2 Hydrogen Ion Concentration and pH Dynamics

The hydrogen ion concentration in the bioreactor is the key variable controlling the behavior of pH and is directly influenced by the microbial metabolism, feed dilution, and addition of alkali for pH control. In biotechnological cultivation processes, metabolic activity causes production or consumption of hydrogen ions, and in fed batch operation, the continuous volume changes have an impact on ion concentration and following the formulation proposed by Galvanauskas [43].

The dynamic behavior of the hydrogen ion concentration is given by the following differential equation [43,51]:

$$\frac{dC_{H+}}{dt} = (\alpha_1 \mu x + \alpha_2 x) + \frac{F_{pH}(C^0_{H+} - C_{H+})}{V} - \frac{F_s C_{H+}}{V} \tag{2}$$

where C_{H^+} is the concentration of hydrogen ion in the reactor, α_1, α_2 are model parameters associated with the metabolic hydrogen ion production, μ is the specific growth rate, x is the biomass concentration, $F_s$is the feed flow rate of the substrate, F_{pH} is the flow rate of the alkali, V is the volume of the reactor, $C^0_{H+}$is the concentration of hydrogen ion in the alkali solution.

The first term is for the generation of hydrogen ions with the metabolic activity of microorganisms. The second term considers the effects of dilution caused by the sum of the inflow of substrate and alkali streams. The third term is a model for the effect of alkali addition on the hydrogen ion concentration and is the main manipulated variable in pH control. As highlighted by Galvanauskas [43], this structure can successfully reproduce the current physicochemical effects on pH dynamics in fed-batch bioreactor.

The output of the process in terms of measurable pH is related to hydrogen ion concentration by the logarithmic relationship [43,51]:

$$pH = -10 log C_{H+} \tag{3}$$

This is a nonlinear transformation that adds a high sensitivity of pH to small changes in hydrogen ion concentration, which adds to the difficulty of pH control. As a result, it is important to properly model hydrogen ion dynamics for the evaluation and comparison of various pH control strategies.

2.1.3 Reactor Volume Dynamics

In fed batch processes of biotechnological cultivation, the volume of the reactor is not constant, but it grows with time as a result of continuous addition of liquid streams. Reactor volume dynamics are important to the overall process behavior because volume changes will directly affect the biomass concentration, concentration of hydrogen ions and dilution rates. Therefore, an explicit volume balance is necessary to accurately describe the time changing nature of the system.

The reactor volume is modelled in a simple mass balance based on incoming solution of substrate and alkali. The dynamic behavior of the reactor volume is described by the following differential equation [43,51]:

$$\frac{dV}{dt} = F_s + F_{pH} \tag{4}$$

where V is the reactor volume, F_s is the substrate feed flow rate and F_{pH} is the alkali flow rate (for pH control).

2.1.4 Oxygen Uptake Rate (OUR)

The oxygen uptake rate (OUR) is an important process parameter to express the metabolic activity of the microorganisms during the biotechnological cultivation. OUR is directly related to biomass concentration and growth rate and gives valuable information about the physiological state of the culture. In this investigation, OUR is considered as an auxiliary process output as a way to support the control analysis and feedforward compensation, which is described by Galvanauskas [43], and later used by Butkus et al. [51].

Biomass concentration and specific growth rate with algebraic function sum provide as oxygen uptake rate as [43,51]:

$$OUR = \beta_1 \mu x V + \beta_2 x V \tag{5}$$

where OUR is the oxygen uptake rate, $\beta_1 = 0.8646\ g/g$ and $\beta_2 = 0.0180\ g/g.h$ are model parameters, μ is the specific growth rate, x is the biomass concentration and V is the volume of the reactor.

The first term is oxygen consumption related to microbial growth while the second term is oxygen consumption related to maintenance and depends on the total biomass present in the reactor and formulation by Galvanauskas [43].

In the context of this work OUR is not only a process indicator but also an informative signal for control purposes. As has been shown by Butkus et al. [51], the OUR can be successfully applied in feedforward compensation to account for disturbances that are predictable in metabolic activities, thus contributing to better pH control performance in fed-batch bioreactors.

2.2 Types of Controllers

2.2.1 Fixed PI Controller

In this study, fixed proportional-integral (PI) controller is used as baseline control strategy for pH control in fed batch bioreactor. Fixed PI controllers are extensively applied in the control of biotechnological and chemical processes, because of their simple structure and the ease of implementation and satisfactory performance under nominal conditions. In the case of the bioreactor pH control, the PI controller acts on the alkali addition rate to minimize the difference between the measured pH and the desired setpoint.

The control action produced by the fixed PI controller is based on the control error for the pH control, i.e. the difference between the pH setpoint and measured pH value. The general PI control law is given as by from [56]:

$$u_{PI}(t) = K_r(e(t) + \frac{1}{T_i}\int e(t)dt) \tag{6}$$

Where u_{PI} (t) is the controller output (alkali flow rate), K_r is the proportional gain, T_i is the integral time constant, and $e(t)$ is the pH control error.

For the fixed PI controller both controller parameters K_r and $T_i$are constant during the whole cultivation process. The parameters are chosen so that they will present a steady pH control under nominal conditions and are not adjusted to variations of biomass concentration, metabolic activity or reactor volume. This type of fixed parameter control structure is often used as a reference in biotechnological control studies, such as the modelling structure as presented by Galvanauskas [43]. However, as discussed by Galvanauskas [43] and further demonstrated in the pH control study by Butkus et al. [51], the performance of fixed PI controllers may worsen in fed-batch bioprocesses because of the inherently time varying and nonlinear nature of biological systems. A level of increased pH fluctuations and reduced disturbance rejection capability can occur due to the altering process dynamics during cultivation.

It is emphasized that zero parameter adaptation or statistical feedback analysis and feedforward compensation are not used in the fixed PI controller. All the controller parameters are kept the same during simulation, and the controller is used only as a baseline to assess performance improvements that are achieved by the adaptive PI controller presented in the following section.

2.2.2 Adaptive PI Controller Based on Statistical Analysis

Motivation for Adaptive PI Control

In pH control bioreactor usage of Fixed PI controller is common because of its performance seriously influenced by the time varying character of fed batch biotechnological process. During cultivation, biomass concentration, metabolic activity, and reactor volume continuously change which leads to changes in process gain and disturbance characteristics. As discussed by Galvanauskas [43], such nonstationary behavior decreases the ability of fixed parameter controllers to maintain consistent control performance throughout the entire operation.

In the particular case of pH control, minor changes in hydrogen ion production due to metabolic changes or feeding actions can lead to large pH deviations because of the nonlinearity of the relationship between pH and hydrogen ion concentration. Butkus et al. [51] stressed the importance of considering that conventional PI controllers optimized for a given operating point can show increased pH fluctuations or slow disturbance rejection under changing process conditions during fed batch cultivation.

To overcome these limitations, adaptive control strategies are needed which can be used to adjust the controller behavior according to process observed variations. In this work, adaptation is done without the need for an explicit process model of the online system or parameter identification. Instead, the adaptive PI controller adjusts its integral action according to statistical properties of the pH feedback signal so that the controller can respond to the changes in process dynamics while keeping a simple and transparent structure suitable for the industrial implementation.

Structure of the Adaptive PI Control System

The adaptive PI control system proposed in this work is based on the principle of the adaptation of integral time constant (T_i) of the conventional PI controller based on statistical properties of the pH feedback signal. This system does not make use of a detailed process model or online parameter identification, which makes it suitable for real time implementation in biotechnological applications where model accuracy may not be so high and where computational resources are limited.

Fig. 5. The adaptive structure is intended to modify the integral action of the controller, based on the variability of the pH signal and the variations from the setpoint. The control law resembles that of the standard PI controller but with the modification that the integral time constant T_i will be updated depending on the statistics of the feedback signal by Butkus et al. [51].

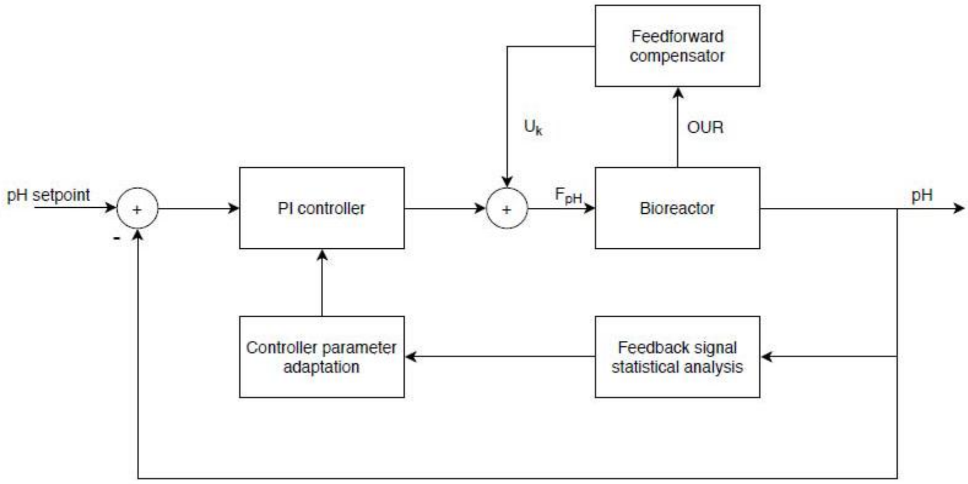

Fig. 5. Block Diagram of the Adaptive pH Control system [51].

For control law same general law will used by from equation (6) above mentioned

In statistical analysis feedback signal of pH, the T_i (k) integral time constantly updated at each step time.

Meaningful Components of the Adaptive PI Controller

— **Feedback Signal Statistics:** Analysis of the feedback signal (measured pH) by moving average, offset from the setpoint and average absolute deviation. This provides information on the stability and variability of the pH signal.

— **Adaptation of T_i:** The integral time constant T_i (k) is adapted based on the statistical analysis, based on a rule-based adaptation mechanism.

— **Rule Based Update Law:** If the variability or offset is greater than predefined values then T_i is reduced to make the controller more aggressive, and if T_i is greater the controller less aggressive and slow. Otherwise, T_i is not changed so that the control response is smooth.

The feedback signal analysis and statistical adaptation enable the controller to adapt to changing process situation such as biomass growth, the metabolic changes and substrate feeding. This structure provides large improvement in comparison to controllers with fixed parameters especially in processes with significant time-varying dynamics as shown by Butkus et al [51].

Statistical Feedback Signal Analysis

The ability of the adaptive PI controller is based on statistical analysis, in real time, of the pH feedback signal. Instead of issuing explicit process models or identification techniques, the system depends on statistical measures to monitor the changes in pH signal variability and setpoint offset. This approach leaves room for the integral time constant T_i of the controller to be adapted online, based on the observed behavior of the feedback signal.

The main statistical measures that will be used in this work are and used by Butkus et al. [51]:

Moving Average: Simple moving average is used to calculate the average pH value for a window of time. This provides a smoothed out estimate of the feedback signal and thus helps to determine the long-term trends and shifts in pH .

$$c_{ave}(k) = \frac{1}{n} \sum_{i=k-n}^{k-1} c_{el}(i) \tag{7}$$

Where n is the length of window and $c_{el}(i)$ is the measured pH at time.

Offset from Setpoint: The offset between the measured pH and the desired pH is calculated to detect slow deviations in the system. This is given by:

$$\boldsymbol{O_{ff\_set}(k) = c_{set} - c_{ave}(k)} \tag{8}$$

Desired pH setpoint calculated by c_{set}.

Average Absolute Deviation: By the pH signal and the average deviation calculated by the same window. This is useful in detecting an increase in the signal variability, which is typically a sign of disturbance or change of system behavior.

$$\boldsymbol{D_{abs\_ave}(k) = \frac{1}{n} \sum_{i=k-n}^{k-1} | c_{el}(i) - c_{ave}(k) |} \tag{9}$$

These statistical quantities are updated on every time step and applied on adjusting the integral time constant of the PI controller. By looking at the offset and deviation of the pH signal, the adaptive system knows when to make the more aggressive controller more aggressive (by decreasing T_i), or when to keep on doing what the controller is doing.

This statistical feedback-based adaptation technique has been proposed in previous works, e.g. Butkus et al. [51], which was found to be effective, in terms of improving the performance of the pH control system under different bioprocess conditions.

Rule-Based Adaptation of T_i

The most important of the adaptive PI controller is the rule-based adaptation of the integral time constant T_i. This adaptation is done based on the statistical analysis of the pH feedback signal, i.e., the offset from setpoint and average absolute deviation. By continuously monitoring these statistics, the controller changes T_i in real time to keep optimal performance of the bioprocess in spite of the time varying nature of the bioprocess.

Adaptation Rule

The adaptation of T_i is controlled by a simple and transparent rule which changes the integral action of the controller as a function of offset and variability detected in pH signal. The rule is as follows:

If the offset or the average absolute deviation is above predefined thresholds then the integral time constant T_i is decreased, in order to make the control more aggressive.

If offset and the variability are within limit, T_i is not changed so that the controller does not have a sudden spike performance due to small nonsystematic fluctuations.

The mathematical equation of the adaptation rule is the following by Butkus et al. [51]:

$$\begin{gathered} \boldsymbol{IF}\ |\ \boldsymbol{O_{ff_{set}}(k)}\ |> \boldsymbol{O}_{\boldsymbol{max}}\ \boldsymbol{OR}\ \boldsymbol{D_{abs_{ave}}(k)} > \boldsymbol{D}_{\boldsymbol{max}}\ \boldsymbol{THEN} \\ \boldsymbol{T_i(k) = T_i(k-1)\left(1 - a_1 O_{ff_{set}}(k)\right)}\ \boldsymbol{ELSE} \\ \boldsymbol{T_i(k) = T_i(k-1)} \end{gathered} \tag{10}$$

where a_1 is a tuning parameter, which controls the aggressiveness of the adaptation and $T_i(k-1)$ is the previous value of the integral time constant. This adaptation rule serves to make the controller more aggressive (lower T_i) when the system has a lot of drift or has more variation.

In case of neither the offset nor the variability being over the predefined thresholds, the controller keeps the last value of T_i, which ensures that the adaptation is smooth without unnecessary changes.

Benefits of Rule Based Adaptation

The rule based approach offers the following advantages:

- **Simplicity and transparency:** The process of adaptation is simple and does not require complex model identification and optimization algorithms.
- **Real-time responsiveness:** The adaptive PI controller is able to adapt to changes in process conditions quickly without being required to retune the controller manually.
- **Practical implementation:** The adaptation mechanism is easy to implement in the MATLAB/Simulink and is suitable for industrial applications where the computational resources and model accuracy may be limited.

This method of adaptive control without complete modelling of the process has been shown to be better than conventional fixed parameter controllers, particularly in bioprocesses where disturbances and process dynamics are constantly changing, as demonstrated by Butkus et al. [51] and Galvanauskas [43].

2.2.3 Feedforward Compensation Using Oxygen Uptake Rate (OUR)

In addition, feedback control, the adaptive PI controller includes feedforward compensation to improve disturbance rejection, in particular to predictable changes in metabolic activity. The Oxygen Uptake Rate (OUR) is one of the most important process variables that gives information about the metabolic state of the culture. Since OUR is a good function of biomass growth and substrate consumption, it is a good predictor of pH disturbances due to metabolic shifts.

Feed Forward Compensation Mechanism

The OUR based feedforward compensator is designed to predetermine pH changes due to metabolic activity in order to make proactive changes in the alkali flow rate by the controller. And the feedforward signal is generated as Butkus et al. [51]:

$$\boldsymbol{u_k = a_2 \,.\, OUR} \tag{11}$$

The feed forward term u_k is added to feedback control output $u_{PI}(t)$ .This offers the controller the chance to pre-emptively compensate for the impact of pH disturbance caused by increased or reduced metabolic activity which would be especially relevant in the early culturing phases where metabolic shifts are frequent and significant.

Benefit of Feedforward Compensation

- **Improved stability and disturbance rejection:** By using OUR it gives prediction of changes before pH deviations occur and improve the system stability
- **Reduced dependency on feedback:** By other additional information from OUR it reduces the dependency on feedback result overshoot and oscillation at large disturbances.

2.3 Implementation in MATLAB/Simulink

2.3.1 Fix PI Model

The upper **Fig. 6.** is model of Simulink is for Fix pi parameters and if exclude the PI controller from that then the model itself bioprocess model and then transfer to base model, attach different controller gain scheduling MFA and others so this was baseline model. And for making/designing we used different blocks like constant, function block to make logic or calculation and generate logic according to system requirements and using saturation and delay as required and set them on standard which are used for bioprocess modeling and using display and scope to view the values and graph plots.

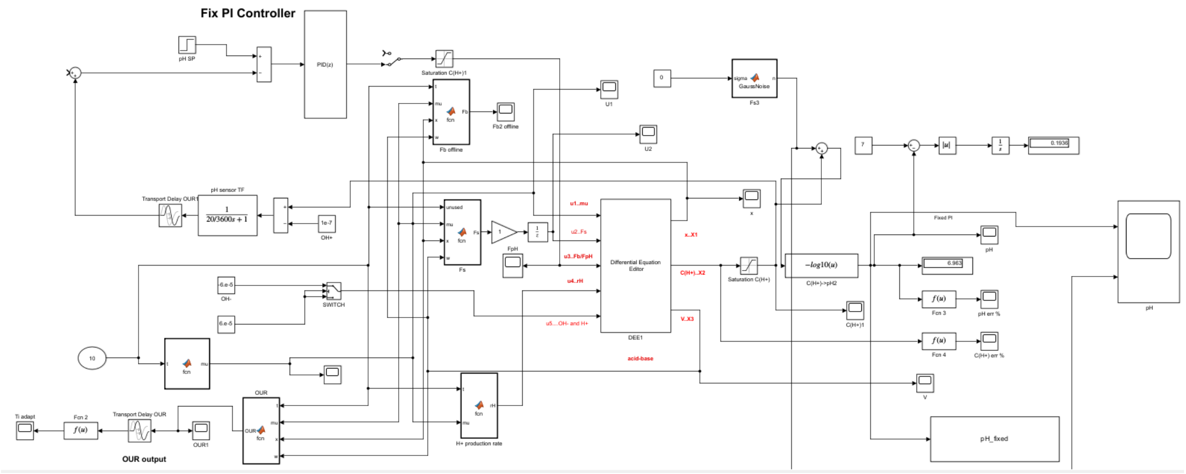

Fig. 6. Simulink Model of Fix PI Controller

2.3.2 Adaptive PI Model

The above Figure 7: Simulink model of the process developed represents a fed batch biotechnological cultivation process with adaptive pH control. The dynamics of the bioreactor are represented by a set of differential equations of biomass concentration, hydrogen ion concentration, and reactor volume, and from these parameters pH is computed as an output variable. A proportional integral (PI) controller is used to control the flow rate of the alkali and keep the pH at a constant setpoint. In the adaptive control structure, the proportional gain is constant, but the integral time constant is updated online based on statistical analysis of the pH feedback signal such as moving average, the offset from the setpoint and average absolute deviation. In addition, an oxygen uptake rate (OUR) based feedforward compensator is included in order to anticipate the metabolic disturbances due to biomass growth. The total control action is achieved by the summation of the feedback and feedforward contribution and is applied to the bioreactor model. This structure enables the controller to adapt to the process dynamics and disturbances, which are time varying, therefore pH can be controlled better than a PI controller with fixed parameters.

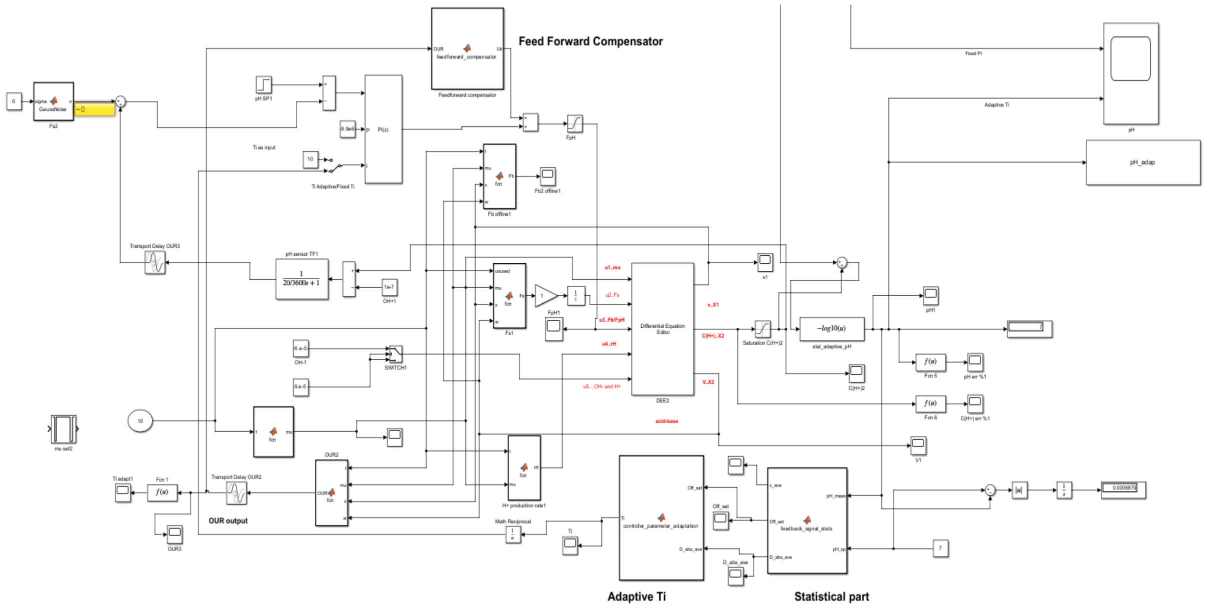

Fig. 7. Simulink Model of Adaptive PI Controller

DEE Block (Differential Equation Editor)

The below **Fig. 8.** DEE is used for implementing the dynamic process model of fed batch bioreactor. It shows the time variation of biomass concentration, hydrogen ion concentration and volume of the reactor using mass balance equations. As a balance of microbial growth and dilution effects, Biomass growth is simulated and hydrogen ion dynamics consider metabolism acid production, dilution, and alkali neutralization. The volume of the reactor is increased due to the addition of substrate and alkali. This model is the foundation for a simulation environment that is used to assess the fixed and adaptive pH control strategies.

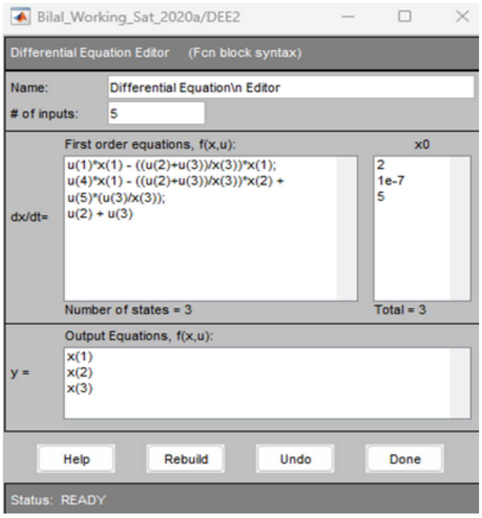

Fig. 8. DEE Block

Input

Table. 1. Input parameters of Differential Editor Block

Inputs. No.	Represent Name
u (1)	Specific growth rate μ
u (2)	Substrate feed flow rate F_s
u (3)	Alkali flow rate F_{pH}
u (4)	Initial biomass and hydrogen ion concentration parameters (α_1, α_2)
u (5)	Hydrogen ion concentration in alkali stream C_{H+}^{0}

Output

Table. 2. Output parameters of Differential Editor Block

Outputs. No.	Represent Name
x (1)	Biomass concentration x
x (2)	Hydrogen ion concentration C_H^+
x (3)	Volume of reactor V

Biomass

By using the equation (1) the right hand side of the equation is written for differential equation editor

u (1) *x (1) - ((u (2) +u (3))/x (3)) *x (1);

Hydrogen ion Balance

By using equation (2) the right hand side shall be written as for DEE block as below

u (4) *x (1) - ((u (2) +u (3))/x (3)) *x (2) + u (5) *(u (3)/x (3));

Volume Balance

By using equation (4) the right side written for DEE block as below

u (2) + u (3);

Initial Conditions

- x $(1)_0$ = 2 g/L
- x $(2)_0$= 1×10^{-7} mol/L (= pH 7)
- x $(3)_0$= 5 L

Controller Tuning Parameters

The Table 3 represent the parameters values which are used in simulations work.

Table. 3. Tunning Parameters Values

Sub Model	Parameter	Value/Units
Fixed PI	K_r	-2 x 10^6 (L/h)/(mmol/L)
	T_i	0.1 h
	T_s	0.001 h
Adaptive PI	K_r	-9.9 x 10^6 (L/h)/(mmol/L)
	T_{i0}	0.07 h
	$T_{i,\, min}$	0.03 h

	$T_{i.\ max}$	0.12 h
Adaptation	a_1	0.25
	O_{max}	0.0001 pH
	D_{max}	0.0015 pH
Statistics Block	Window width = n	54 s
	Window samples N	15
Feed Forward	a_2	7.75×10^{-4} L/g

3. Results

3.1 Process Model Graphs

The biomass concentration profile in the 10 h fed-batch cultivation process is shown in **Fig. 9.** The concentration of biomass rises towards the end of the run, showing high net cell growth. This is nonlinear with comparatively slow growth rate in the initial phase and comparatively rapid rate of biomass accumulation in the later phase. As an example, the biomass attains only around 8 g/L after 3 h, whereas it reaches almost 42 g/L after 7 h and nearly 100 g/L after 10 h. Even the slight decreases in slope can be observed near 1 h, 3 h, 5 h, 7 h, and 9 h, which are associated with the temporary decreases in specific growth rate implemented. In general, this number shows that the process load grows significantly later in the cultivation process, which is why there are higher demands on the pH control in the later cultivation phase.

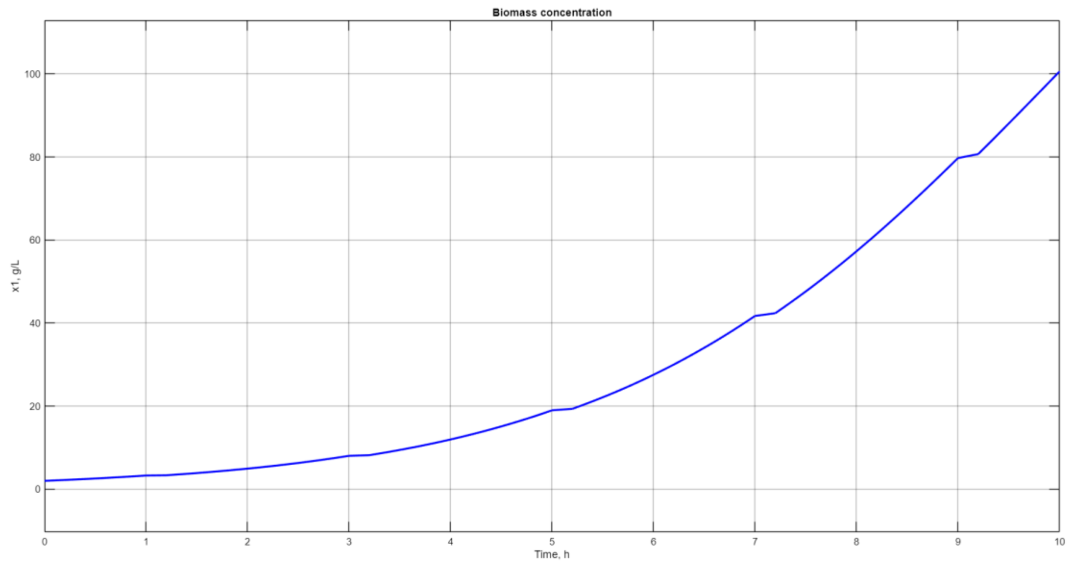

Fig. 9 Biomass concentration

Fig. 10. represents the profile of hydrogen-ion concentration at various times during the fed-batch cultivation process. This concentration is maintained in the same manner centered around 1.0x10^{-7} mol/L which is the pH setpoint of 7, which confirms that the controller puts the process close to the desired operating condition. Minor temporary deviations can be observed, mostly at the imposed disturbance times of 1 h, 3 h, 5 h, 7 h and 9 h. These deviations are slightly bigger in the later cultivation stage which is an indication of the growing process burden as biomass accumulates. The overall change of C_{H+} is not so large, though, which indicates that the controlled variable was successfully controlled during the simulation.

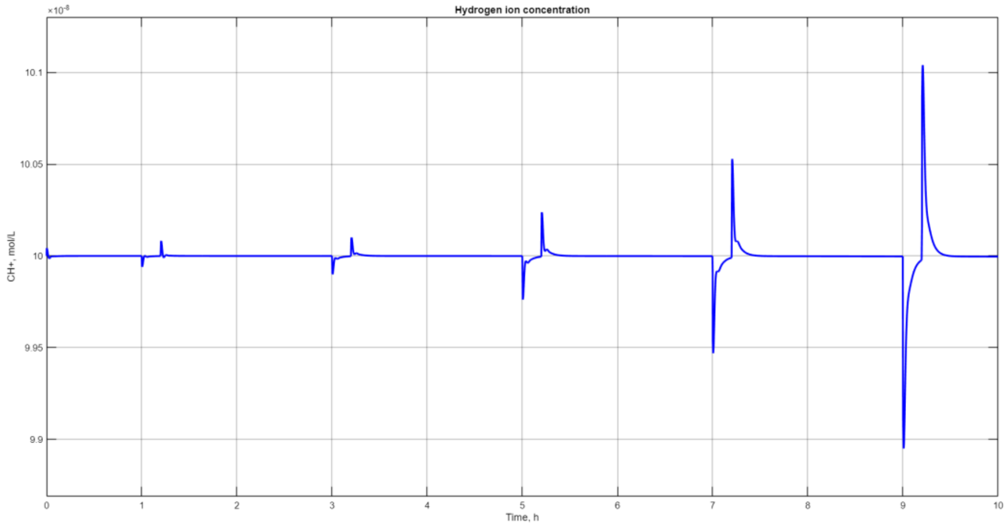

Fig. 10. Hydrogen ion concentration

Fig. 11. shows the alkali feed flow rate F_{pH}, which is the manipulated variable of the pH control loop. The amount of alkali addition required at the beginning of growth is very small and it is progressively increasing with time as the concentration of biomass and its metabolic activity are rising. The control signal eventually reaches approximately 0.03-0.04 L/h at 5 h, approximately 0.1 L/h at 7 h and almost 0.35 L/h towards the end of the simulation. We find short downward deviations about 1 h, 3 h, 5 h, 7 h and 9 h at these times disturbance applied, which is associated with the temporary reduction applied to the specific growth rate. In general, the figure confirms that the load of the growing process is compensated by the growing alkali addition during the fed-batch run.

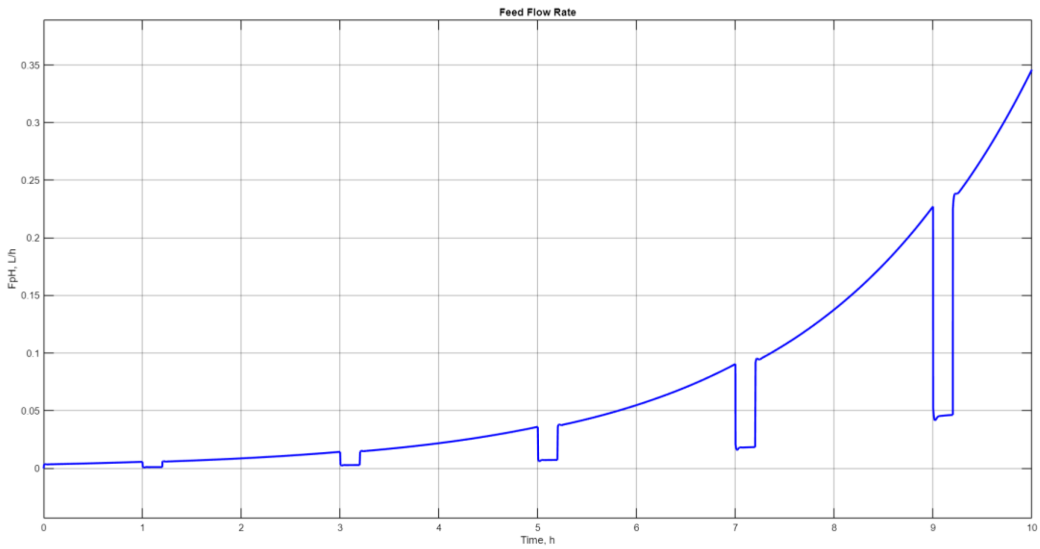

Fig. 11. Feed Flow Rate

Fig. 12. shows the plot of the adaptive integral time constant T_i through the cultivation process of 10 h. The parameter varies smoothly between about 0.070 h at the start of the run to around 0.0691 h at the end, showing a tendency of increasing the action of integral control gradually with the increase in cultivation load. At all times of imposed disturbance, that is, around 1 h, 3 h, 5 h, 7 h and 9 h, local changes in T_i are observed. The small adjustments are produced by the initial disturbances, and the more pronounced ones, produced by the late disturbances, are due to the increased sensitivity of the process when biomass accumulates. In general, the figure shows that the adaptation mechanism

adjusts the controller parameter online to react to the changing conditions of the process and repeated disturbances.

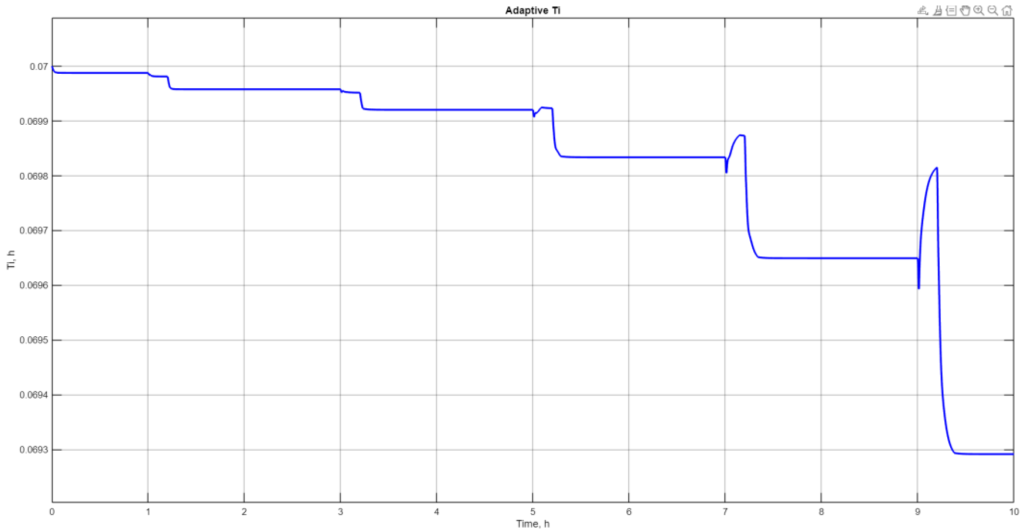

Fig. 12. T_i Adaptive

Fig. 13. shows the rate of oxygen uptake (OUR) during the 10 h fed-batch culture process. The OUR varies nonlinearly to nearly zero g/h at the onset of the run and to an approximation of 450 g/h at the end which shows a strong increase in the metabolic activity when the biomass is accumulated. As an example, OUR is only approximately 20 g/h at 3 h, then increases to about 50 g/h at 5 h, around 120 g/h at 7 h, and 290 g/h at 9 h. As can be seen, there is no doubt that the short-term decline in specific growth rate, which is imposed, leads to unambiguous temporary drops. The dips are more intense in the later phase since the same disturbance is acting on a system with far higher biomass concentration, and metabolic demand. Overall, this number demonstrates that OUR is an effective process load indicator that needs to be included in the feedforward compensation strategy.

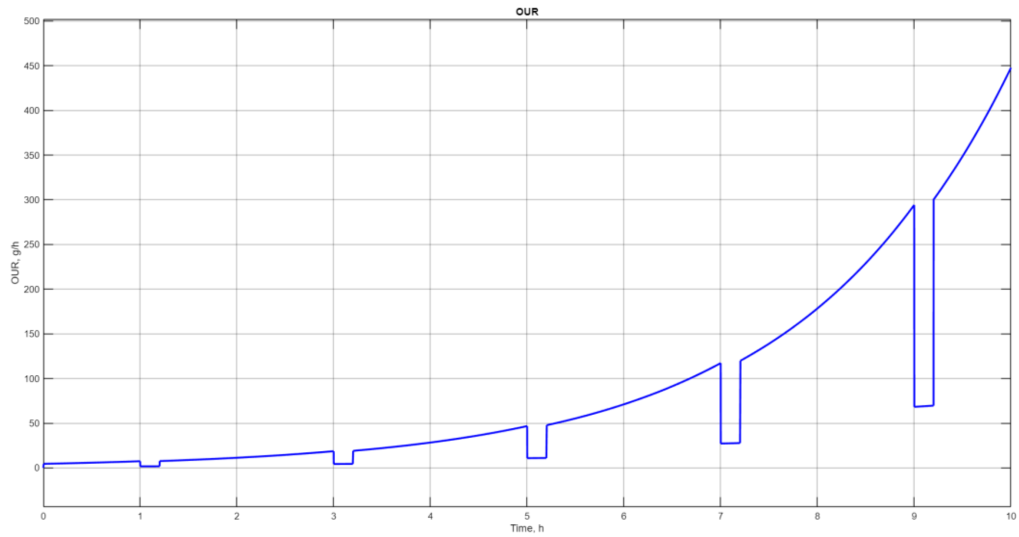

Fig. 13. OUR oxygen uptake rate

3.2 pH Graph

Fig. 14. shows the pH response of the fixed PI controller during the 10 h fed-batch cultivation process. The controller is set to hold the pH near the setpoint of 7 in the early stage, with only minor deviations about the disturbances at 1 h and 3 h. But the oscillations are greater with an increase in the process load. At around 5 h, the deviation is of the order of approximately 6.96 to 7.05 and at 7 h, the deviation is approximately 6.90-7.12. The maximum oscillation is found around 9 h where the value of the pH is found to increase to approximately 7.35 after which it decreases to about 6.80. These findings suggest that the fixed PI controller is less useful in the later stage of cultivation when the dynamics of the process are more challenging and when stronger rejection of disturbances is needed.

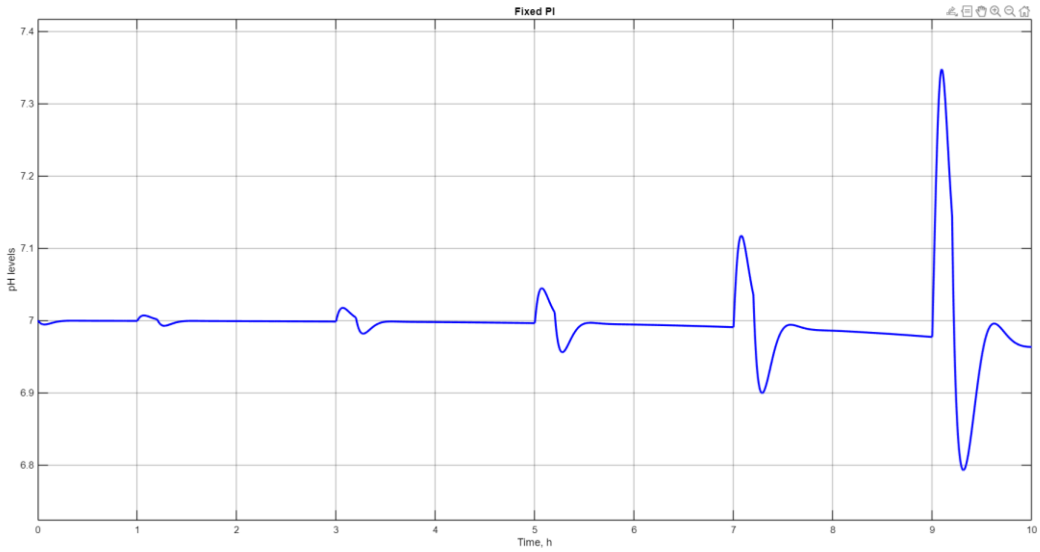

Fig. 14. pH response of Fix PI Controller

Fig. 15. illustrates the response of the adaptive PI controller to changes in pH over the duration of the fed batch culturing process (10 h). The adaptive controller ensures that the pH is maintained nearly at the setpoint of 7 throughout the entire run with only very small temporary deviations at the disturbance times around 1 h, 3 h, 5 h, 7 h, and 9 h. The pH is maintained at a relatively constant level of 6.994 to 7.004 even during the late stage where the process load is the highest. This is by far smaller than the variation in the peak to peak with the fixed PI controller. The outcome justifies the fact that the adaptive PI controller not only offers an excellent disturbance rejection ability, but also can manage to maintain stable pH regulation even when the fed-batch cultivation process is subject to time-varying dynamics. Overall, it confirms that adaptive PI controller is well tuned and can achieve accurate pH maintenance with minimum steady state error and robust dynamic performance.

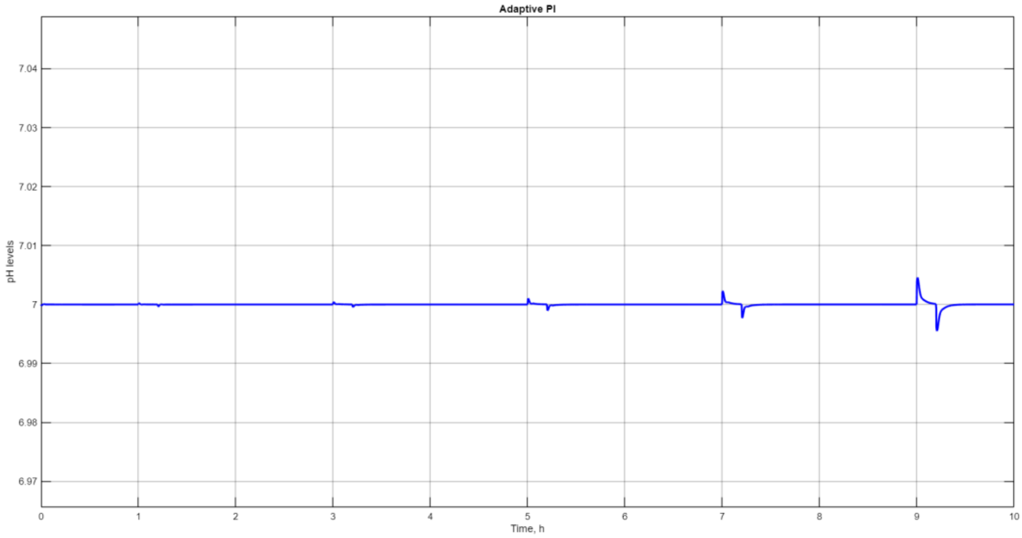

Fig. 15. pH response of Adaptive Controller

3.2.1 Comparison Fix PI Controller vs Adaptive PI Controller

Fig. 16. is the comparison of the pH response of the fixed PI controller and adaptive PI controller to the process of 10 h fed-batch cultivation. Both controllers work satisfactorily at the beginning stage, where the disturbances at 1 h and 3 h only cause small variations of the setpoint. The distinction between two responses however, the more the cultivation is done, the more the difference between these two responses becomes significant. At approximately 5 h, the fixed PI controller is already showing a distinct oscillatory transient whereas the adaptive PI controller is still kept within the pH 7 range. The fixed PI controller experiences severe overshoot and undershoot at 7 h and at 9 h in particular the pH ranges between 7.12 and 6.90 at 7 h and between 7.35 and 6.90 at 9 h. By comparison, the adaptive PI controller ensures that the pH remains within a very small range around the setpoint during the entire run with overshoot 0.0046 pH, undershoot 0.0061 and settling time is 0. These findings indicate that adaptive PI controller offers significantly improved disturbance rejection and robustness as compared to the fixed PI controller, in the later stage of cultivation when process load is the highest. And the other properties like overshoot, undershoot and settling time in mention in below **Table. 4.** at different hours disturbance applied.

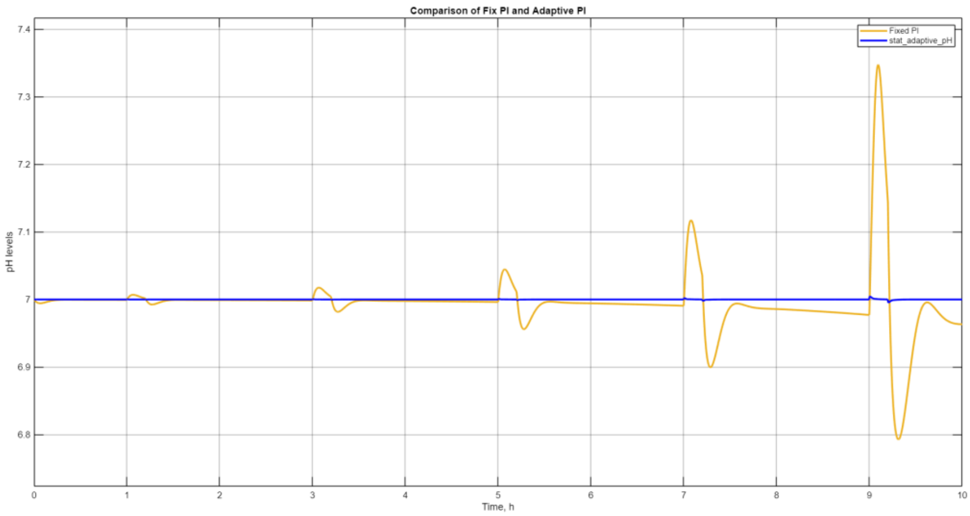

Fig. 16. pH response of Fix PI Controller vs Adaptive Controller

Table. 4. Dynamic performance of Fix PI Controller vs Adaptive PI Controller without noise

Disturbance at hours, (h)	**Fix PI Controller**			**Adaptive PI Controller**		
	Overshoot (pH)	**Undershoot (pH)**	**Settling Time, (h) (pH)**	**Overshoot (pH)**	**Undershoot (pH)**	**Settling Time, (h) (pH)**
1	0.00695	0.007415	0.000946	0.000177	0.000270	0.000946
3	0.01755	0.01829	0.000945	0.000435	0.000600	0.000900
5	0.04473	0.04405	0.000978	0.001035	0.001422	0.000978
7	0.11744	0.10060	0.2970	0.002309	0.003137	0.000978
9	0.34769	0.20734	0.4460	0.004581	0.006079	0.000957

3.2.2 Fixed PI Controller and Adaptive PI Controller Comparison under Gaussian Noise (levels)

3.2.2.1 Noise level σCH^{+}=1e-9 mmol/L

Fig. 17. shows a comparison between the response of the fixed PI controller and adaptive PI controller when the measurement Gaussian noise has amplitude 1x10^{-9} mmol/L is present. The adaptive PI response has slight noise-induced variations around the pH setpoint, but is tightly bounded around pH 7 throughout the entire simulation. On the contrary, the fixed PI controller has oscillations which become larger and larger as the cultivation continues. At the time of about 5 h, the fixed PI response has a range of about 6.96 to 7.05, whereas at the age of about 7 h, the range is between 6.90 and 7.11. The greatest oscillation is in the period around 9 h where the fixed PI controller rises to approximately 7.35 and then decreases to about 6.80. Although noise is present, the adaptive PI controller is able to maintain the pH within a small band around the setpoint and avoid the large overshoot and undershoot

of the fixed PI controller. These findings confirm that the adaptive PI controller still has the best disturbance rejection and control accuracy when operating under low-noise conditions. And properties like overshoot, undershoot and settling time mention in **Table. 5.** Results show that even under extremely low noise, adaptive PI controller outperforms the fixed PI controller in terms of stability and disturbance rejection, making it best choice for precise pH maintenance.

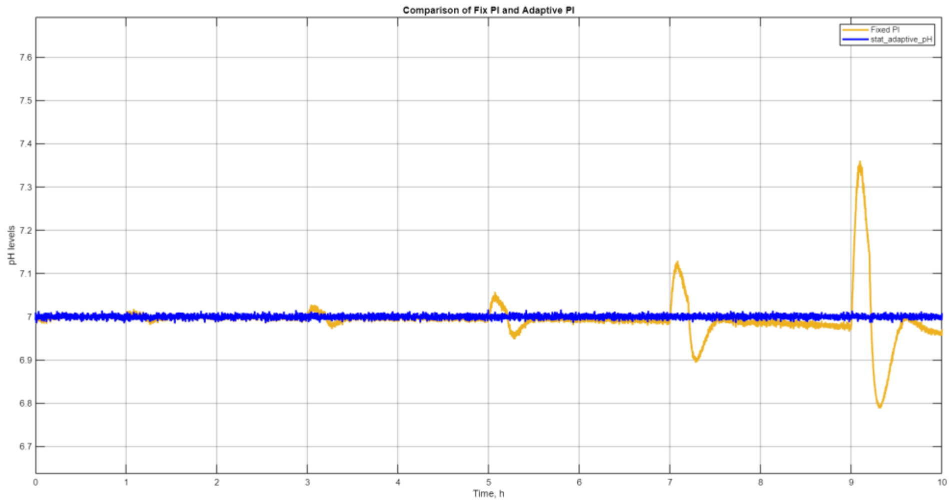

Fig. 17. Noise 1e-9 given Fix PI Controller vs Adaptive Controller

Table. 5. Dynamic performance of Fix PI Controller vs Adaptive PI Controller at noise 1e-9

Disturbance at hours, (h)	**Fix PI Controller**			**Adaptive PI Controller**		
	Overshoot (pH)	**Undershoot (pH)**	**Settling Time, (h) (pH)**	**Overshoot (pH)**	**Undershoot (pH)**	**Settling Time, (h) (pH)**
1	0.0179	0.0189	0.00099	0.0136	0.0152	0.00099
3	0.0281	0.0287	0.00088	0.0124	0.0140	0.00079
5	0.0575	0.0524	0.00011	0.0165	0.0142	0.00090
7	0.1295	0.1062	0.3100	0.0137	0.0142	0.00090
9	0.3608	0.2120	0.4550	0.0138	0.0145	0.00097

3.2.2.2 Noise level σCH^{+}=3e-9 mmol/L

Fig. 18. shows the behavior when the Gaussian Noise level 3x10^{-9} mmol/L is given to both Controllers. The adaptive PI response is shown to have continuous small-amplitude variations around

the setpoint as a result of the injected noise, but this remains tightly centered near pH 7 throughout the simulation. Conversely, fixed PI controller displays larger oscillations with the advancement of cultivation. At 5 h the fixed PI response changes to around a value of 6.96 to 7.05 and at 7 h it deviates between 6.90 and 7.11. The most extreme oscillation is in the area of 9 h where the pH varies to approximately 7.35 and then to nearly 6.80. The adaptive PI controller keeps the pH in a very small band around the setpoint and eliminates the huge overshoot and undershoot in the fixed PI case. And other properties mentioned in the **Table. 6.** below. The findings confirm the adaptive PI controller has the best disturbance rejection and control accuracy in the presence of noisy operating conditions.

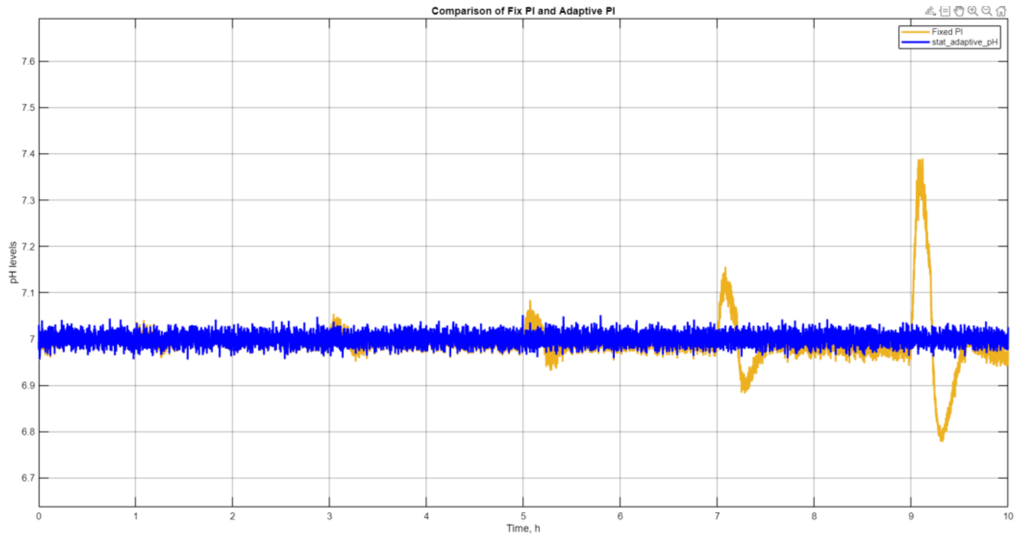

Fig. 18. Noise 3e-9 given Fix PI Controller vs Adaptive Controller

Table. 6. Dynamic performance of Fix PI Controller vs Adaptive PI Controller at noise 3e-9

Disturbance at hours, (h)	Fix PI Controller			Adaptive PI Controller		
	Overshoot (pH)	Undershoot (pH)	Settling Time, (h) (pH)	Overshoot (pH)	Undershoot (pH)	Settling Time, (h) (pH)
1	0.0422	0.0447	0.0011	0.0420	0.0442	0.0010
3	0.0546	0.0488	0.00099	0.0384	0.0406	0.00099
5	0.0843	0.0688	0.00096	0.0514	0.0413	0.00099
7	0.1558	0.1175	0.3340	0.0424	0.0414	0.000998
9	0.3897	0.2222	0.4560	0.0379	0.0420	0.000998

3.2.2.3 Noise level σCH^{+}= 5e-9 mmol/L

Fig. 19. shows the comparison between fixed PI controller and adaptive PI controller under the influence of Gaussian noise with variance level of 5×10^{-9} mmol/L. At this low level noise, system goes through minor fluctuations sufficient to evaluate sensitivity of controllers. Even at $5\text{x}10^{-9}$ noise level, the adaptive PI controller still beats the fixed PI controller similarly as in the case of $3\text{x}10^{-9}$. Although the adaptive response oscillates about the noise signal, the adaptive response is centred around the pH setpoint, when compared to the fixed PI controller, which oscillates about the disturbance times, especially later in the process. And other properties of both controllers mentioned in **Table. 7.** present below.

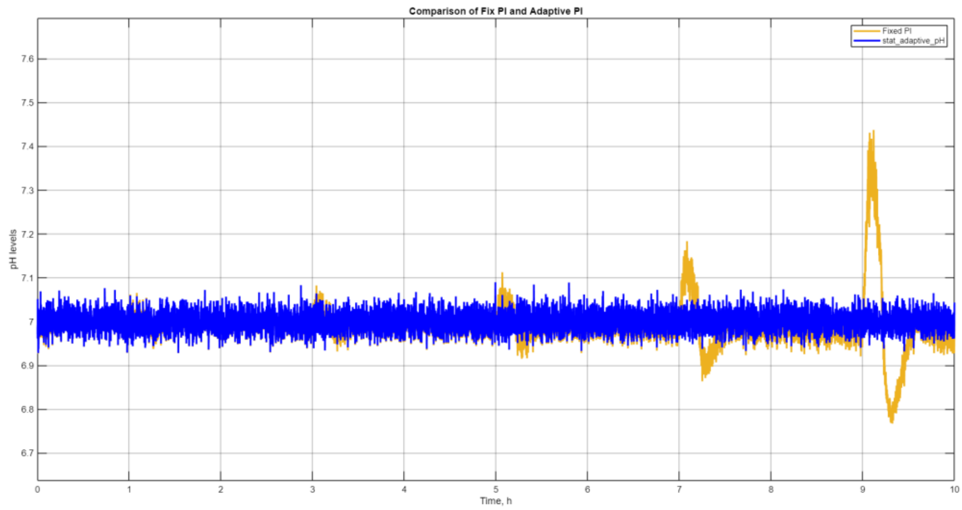

Fig. 19. Noise 5e-9 given Fix PI Controller vs Adaptive Controller

Table. 7. Dynamic performance of Fix PI Controller vs Adaptive PI Controller at noise 5e-9

Disturbance at hours, (h)	Fix PI Controller			Adaptive PI Controller		
	Overshoot (pH)	Undershoot (pH)	Settling Time, (h) (pH)	Overshoot (pH)	Undershoot (pH)	Settling Time, (h) (pH)
1	0.0810	0.0718	0.0011	0.0884	0.0713	0.0010
3	0.0858	0.0620	0.00099	0.0821	0.0657	0.00099
5	0.1128	0.0846	0.0700	0.0894	0.0668	0.00098
7	0.1837	0.1359	0.3610	0.0732	0.0668	0.00099
9	0.4376	0.2325	0.4650	0.0652	0.0670	0.00098

3.2.2.4 Noise level σCH^{+}=1e-8 mmol/L

Fig. 20. is used to compare the fixed PI and adaptive PI controller in a level of measurement Gaussian noise of 1x10^{-8} mmol/L. Large oscillatory deviations are still exhibited by the fixed PI controller, particularly about 7 h and 9 h when there is severe overshoot and undershoot. The adaptive PI controller even keeps the response centered around the setpoint and does not allow such large excursions. As a result, although the adaptive controller visually limits the large disturbance peaks, which the fixed PI controller does not, the increased sensitivity to noise leads to an increased cumulative error. Both controllers other properties are present in **Table. 8.**

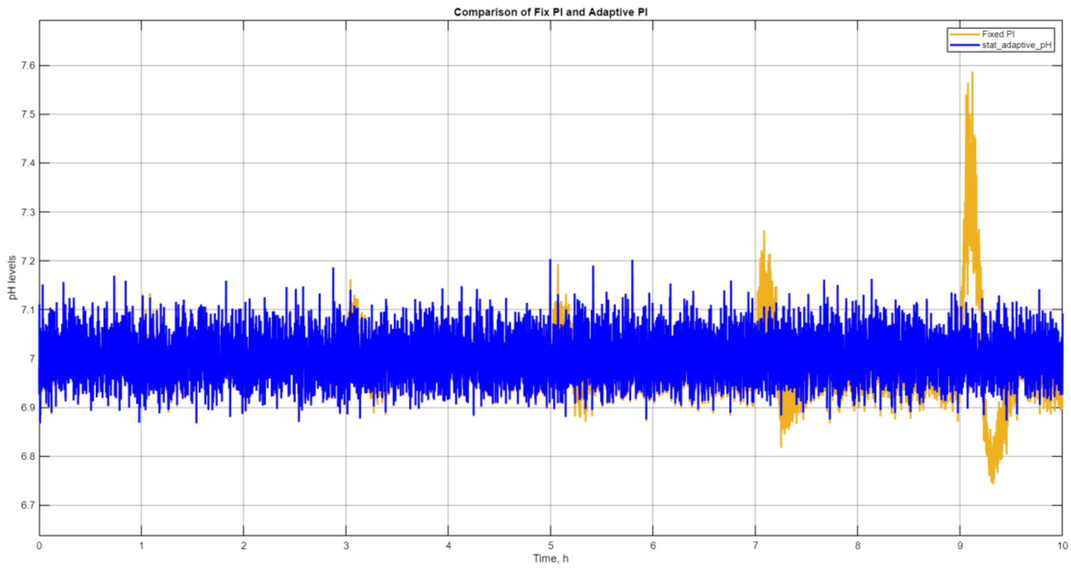

Fig. 20. Noise 1e-8 given Fix PI Controller vs Adaptive Controller

Table. 8. Dynamic performance of Fix PI Controller vs Adaptive PI Controller at noise 1e-8

Disturbance at hours, (h)	Fix PI Controller			Adaptive PI Controller		
	Overshoot (pH)	Undershoot (pH)	Settling Time, (h) (pH)	Overshoot (pH)	Undershoot (pH)	Settling Time, (h) (pH)
1	0.1582	0.1330	0.9860	0.1594	0.1326	0.9860
3	0.1625	0.1161	0.9980	0.1439	0.1227	0.9860
5	0.1941	0.1290	0.9950	0.2022	0.1247	0.9950
7	0.2627	0.1824	0.9820	0.1613	0.1248	0.9820

9	0.5871	0.2573	0.9980	0.1419	0.1267	0.7730

3.3 Integral Absolute Error

The Integral Absolute Error (IAE) is a performance index for the assessment of the accuracy of control systems. It is defined as time integral of the absolute value of the control error total accumulated deviation of controlled variable from its setpoint during a given period and general formulation as by [56]:

$$IAE = \int_0^T \mid e(t) \mid dt \tag{12}$$

where $e(t)$ is the control error and T is the evaluation time.

Lower IAE values are an indication of better control performance, lower deviation and faster disturbance rejection.

In this work, the Integral Absolute Error (IAE) is applied to quantify the performances of pH control of the fixed PI controller and adaptive PI controller. It is the sum of absolute deviations of bioreactor pH from the desired bioreactor pH setpoint (pH=7) for the total simulation time. Lower IAE values are indicative of better pH control, less overshoot and undershoot, and better rejection of disturbances under the time varying condition of fed batch processes. **Table. 9**. represents the comparison values IAE of Standard PI and Adaptive PI:

Table. 9. IAE of Fix PI Controller vs Adaptive PI Controller

σCH^+ Noise levels mmol/L	Fix PI Controller (pH)	Adaptive PI Controller (pH)
0	0.1936	0.0006879
1e-9	0.2033	0.03439
3e-9	0.2453	0.1033
5e-9	0.2977	0.1717
1e-8	0.4458	0.3455

Fig. 21. shows clearly by bar chart representation when different levels of noise are induced on both controllers. It observes that the Fix PI is less sensitive and accurate as noise level changing the behavior almost remains constant by checking the IAE values calculated in Table 3 as well. But the

Adaptive PI more sensitive and accurate which easily observed by IAE values and pH results as well which shows better stable performance than Fix PI controller.

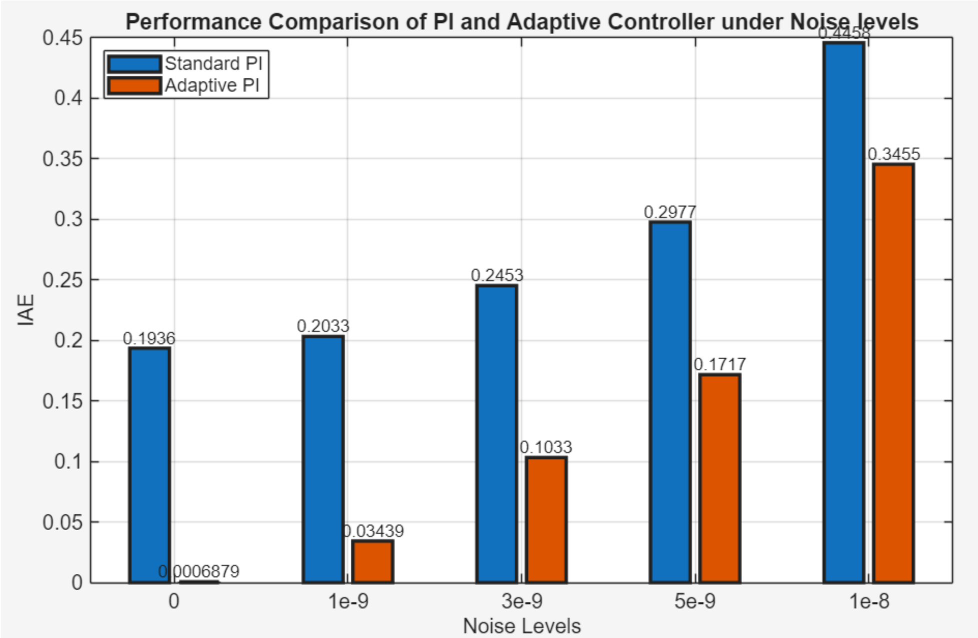

Fig. 21. IAE of Fix PI Controller vs Adaptive Controller

Conclusion

In this work, for the representative of a fed-batch biotechnological cultivation process, a nonlinear online time varying process model was successfully implemented by using the MATLAB/Simulink software.

1. A fixed parameter PI controller and an adaptive PI controller were designed and tested for pH control. Whereas the adaptive PI controller is also implemented by proportional gain fixed and integral time constant adaptive online on basis of statistical feedback signal of pH. The adaptation mechanism involved the moving average overtime offset from the setpoint and average absolute deviation of the pH signal, as well as an oxygen uptake rate (OUR) based feedforward compensator.
2. Simulation results clearly show that the fixed PI controller is satisfactory only under nominal conditions and has substantial overshoot, undershoot and oscillations when subjected to repeated disturbances in the specific growth rate. When there is no noise but on highest peaks disturbances at 7h and 9h overshoot 0.1174, 0.3477 of pH and undershoot 0.1006, 0.2073 of pH and settling time 0.2970 h, 0.4460 h. In contrast, the adaptive PI controller kept the pH much closer to the setpoint over the whole operation, on growth rate at 7h and 9h the overshoot 0.0023, 0.0046 of pH and undershoot 0.0031, 0.0061 of pH and settling time 0.000978 h, 0.000957 h. The increased performance of the adaptive controller is represented by much lower Integral Absolute Error (IAE) is 0.0006879 while fix pi IAE is 0.1936, which proves superior disturbance rejection and robustness.
3. When gaussian noise σCH^{+}= 1 x 10^{-8} applied to hydrogen concentration ions fix pi controller properties at growth rate on 7h and 9h, overshoot 0.2627, 0.5871 of pH, undershoot 0.1824, 0.2573 of pH and settling time 0.9820 h, 0.9980 h. On other side adaptive pi overshoot 0.1613, 0.1419 of pH and undershoot 0.1248, 0.1267 of pH and settling time 0.9820 h, 0.7730 h on 7h and 9h. And IAE fix pi is 0.4458 and adaptive pi is 0.3455. And more calculations and properties of both controllers are mentioned from **Table. 4.** to **Table. 9.**
4. Overall, the results confirm that statistical adaptation of the PI integral time constant, coupled with OUR based feedforward compensation, is indeed a very useful combination to improve pH control performance in fed batch bioprocesses. The proposed adaptive PI control structure is simple, computationally efficient and suitable for practical implementation, which makes it a reliable alternative to classical fixed parameter PI control for time varying biotechnological systems.

Future work

The next step is to enhance the adaptive control structure in order to adapt to process dynamics during the cultivation. Specifically, future research should explore other adaptive tuning methods, such as adapting other controller parameters in addition to the integral time constant. Given the large impact of the controller gain and the feedforward part, future work may involve the adaptation or simultaneous tuning of different control parameters to achieve more precise pH control over various operating conditions.

Another key area of investigation is the improvement of the feedforward and adaptation schemes. Our findings show that the feedforward component has an influence on the control action, whereas the feedback component is used for fine tuning around the setpoint. Hence, future research should look at better ways to choose or adapt the feedforward gain, and also to tune the statistical quantities in the adaptation law, such as the moving-window size, threshold levels, and sampling points.

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