Kaunas University of Technology
Faculty of Electrical and Electronics Engineering

Investigation of Gain Scheduling Adaptive pH Control System for Microbial Cultivation Process

Master's final degree project

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Control Technologies (6211EX014)

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Declaration of Academic Integrity

I confirm that the final project of mine, Rajavishnu Rajkumar, on the topic „ Investigation of Gain Scheduling Adaptive pH Control System for Microbial Cultivation Process " is written completely by myself; all the provided data and research results are correct and have been obtained honestly. None of the parts of this thesis have been plagiarised from any printed, Internet-based or otherwise recorded sources. All direct and indirect quotations from external resources are indicated in the list of references. No monetary funds (unless required by Law) have been paid to anyone for any contribution to this project.

I fully and completely understand that any discovery of any manifestations/case/facts of dishonesty inevitably results in me incurring a penalty according to the procedure(s) effective at Kaunas University of Technology.

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Rajavishnu Rajkumar. Investigation of Gain Scheduling Adaptive pH Control System for Microbial Cultivation Process. 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

This thesis is about investigation of adaptive pH control of fed-batch microbial cultivation process. A nonlinear MATLAB/Simulink process model was implemented, with biomass concentration, hydrogen-ion concentration and reactor volume as state variables. Using this model, a PI controller and gain-scheduling adaptation laws were implemented to enhance the control performance in time-varying operating conditions. The following controller types were compared: fixed PI controller, gain-scheduled controller with measured reactor volume and substrate feed flow, gain-scheduled controller with measured substrate feed flow and constant average reactor volume, and gain-scheduled controller with measured reactor volume and estimated substrate feed flow.

Simulation results indicated that gain-scheduled controllers outperformed fixed PI controllers. The gain-scheduled controllers had lower tracking error and better disturbance rejection. The controller that used measured reactor volume and substrate feed flow had the smoothest response with the lowest overshoot, while the controller that used measured reactor volume and estimated substrate feed flow had the lowest tracking error. Simulations with Gaussian measurement noise added to the measurements demonstrated that the gain-scheduled controllers were still better at low and medium noise levels, but at the highest noise level there were no significant differences between the controllers because the response was dominated by the measurement noise. In conclusion, the results indicate that gain-scheduled PI control is an effective approach to pH control for fed-batch microbial cultivation.

Rajavishnu Rajkumar. Stiprinimo numatymu pagrįstos adaptyvios pH valdymo sistemos, skirtos mikrobiologiniam kultivavimo procesui, tyrimas. Magistro baigiamasis projektas / vadovas prof. dr. Vytautas Galvanauskas; Kauno technologijos universitetas, Elektros ir elektronikos fakultetas.

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Santrauka

Šiame darbe nagrinėjamas adaptyvus pH reguliavimas periodiniame su pamaitinimu mikrobiologiniame kultivavimo procese. Buvo įdiegtas netiesinis MATLAB/Simulink proceso modelis, kurio būsenos kintamieji yra biomasės koncentracija, vandenilio jonų koncentracija ir reaktoriaus tūris. Naudojant šį modelį, buvo įdiegti PI reguliatorius ir stiprinimo numatymo adaptavimo dėsniai, siekiant pagerinti valdymo kokybę kintančiomis sąlygomis. Buvo palyginti šie reguliatorių tipai: fiksuotų parametrų PI reguliatorius, stiprinimo numatymo reguliatorius su išmatuotu reaktoriaus tūriu ir substrato tiekimo srautu, stiprinimo numatymo reguliatorius su išmatuotu substrato tiekimo srautu ir pastoviu vidutiniu reaktoriaus tūriu bei stiprinimo numatymo reguliatorius su išmatuotu reaktoriaus tūriu ir apskaičiuotu substrato tiekimo srautu. Modeliavimo rezultatai parodė, kad stiprinimo planavimo reguliatoriai veikė geriau nei fiksuoto PI reguliatoriai. Stiprinimo numatymo reguliatoriai turėjo mažesnę sekimo paklaidą ir geresnį trikdžių kompensavimą. Reguliatorius, kuris naudojo išmatuotą reaktoriaus tūrį ir substrato padavimo srautą, turėjo sklandžiausią atsaką su mažiausiu perreguliavimu, o reguliatorius, kuris naudojo išmatuotą reaktoriaus tūrį ir apskaičiuotą substrato tiekimo srautą, turėjo mažiausią sekimo paklaidą. Modeliavimas su Gauso triukšmu, pridėtu prie matavimų, parodė, kad pagal stiprinimo numatymą veikiantys valdikliai vis tiek veikė geriau esant žemam ir vidutiniam triukšmo lygiui, tačiau esant didžiausiam triukšmo lygiui reikšmingų skirtumų tarp valdiklių nebuvo, nes atsake dominavo matavimo triukšmas. Apibendrinant galima teigti, kad rezultatai rodo, jog pagal stiprinimo numatymą veikiantis PI valdymas yra efektyvus pH reguliavimo metodas, taikomas periodiniuose su pamaitinimu mikrobiologiniuose kultivavimo procesuose.

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Objective of the research

This study focus on the creation of a MATLAB/Simulink model of a fed-batch microbial cultivation process and explore the efficacy of gain-scheduled adaptive pH control

To meet the objective, the following tasks will be carried out:

- Literature review,
- MATLAB/Simulink implementation of the model,
- PI and gain scheduled PI controller designs,
- Comparison and simulation of system A (fixed PI controller), system B (gain scheduling with known reactor volume and known substrate feed flow), system C (gain scheduling with known substrate feed flow and known average reactor volume), and system D (gain scheduling with known reactor volume and known substrate feed flow)Performance based on IAE total, IAE transients, and overshoot,
- Noise influence analysis,
- Results and conclusions.

The aim of the study is to identify the best pH control policy in the fed-batch process under investigation. The role of time-varying process conditions, rejecting disturbance and resistance to measurement noise are given special consideration.

The key parameters to be used in the research include reactor volume, feed flow of the substrate, growth of biomass, concentration of hydrogen ions, as well as the controller adaptation strategy.

The purpose of the study is to demonstrate whether gain-scheduled PI control can do a better job in the pH regulation than a traditional fixed PI controller and which of the studied systems provides the best overall results.

Introduction

The modern scheme of the biotechnology is significant in addressing the issues in different areas like medicine, pharmacy, agriculture and environmental engineering. Another role of bioengineers is to create new biotechnological solutions, as well as to optimize and control the microbial cultivation processes which facilitate large-scale production. The success of process control strategies particularly in the pharmaceutical and bioprocess industries, where the products are complicated and can be extremely valuable, is a determining variable in influential productivity, quality and consistency of the production [1].

Biotechnology is necessary to solve different problems and issues in the modern world. The growth of microorganisms such as Escherichia coli, Saccharomyces cerevisiae or CHO cells to form proteins, enzymes and secondary metabolites demands close control of environmental factors such as temperature, pH, dissolved oxygen concentration (DOC) and nutrient feed rates. Although fixed setpoint tracking systems are capable of holding some physical parameters using classical control strategies such as PID, they are frequently inappropriate in dealing with the dynamic and nonlinear characteristics of biological systems [2].

The Microbial processes are defined by the dynamic fluctuations, growth dependent behaviour, and the metabolic change. Moreover, biological reactions are very particular to the provision of important nutrients and trace elements that should be strictly controlled to prevent problems such as overflow metabolism or nutrient deficiency. Dynamic nutrient feeding can significantly increase productivity in fed batch processes but there is still significant difficulty in determining the best feeding strategies because real time sensor capabilities are limited and there are nonlinear relationships among the process variables [3].

In order to cope with these difficulties, the bioprocess models are employed to evaluate and forecast the internal condition of microbial systems. These models are unstructured kinetic models, which are adequate in the case of unlimited growth, to more complicated structured models that consider cellular regulation and heterogeneity. Despite being simple, unstructured models are unlikely to work well when cells are nutrient limited or entering product formation phases, which necessitates the use of adaptive control strategies [4].

Within this set of statements as consideration, gain scheduling algorithms have been proposed as a possible approach with subsequent adaptation and controller parameter modification based on operating parameters like biomass concentration or the rate of growth. Adaptive control of the nonlinear and the dynamic systems can be achieved using gain scheduling. It is easy to implement and less complex than full model based controllers like Model Predictive Control (MPC) yet is more responsive and superior to a simple controller. Constant parameter PID controllers do not live up to their promises in their inability to react to system dynamics and biological disturbances in the real world in industrial applications. Gain scheduling is the best solution, as it provides a flexible and scalable outcome, improving the stability and efficiency. It is a blend of the strength of classical control and flexibility required by the modern bioprocesses [5,6].

Thus, precise regulation of technological parameters like pH is critical in ensuring the best growth and production conditions, especially in dynamic batch and fed-batch processes where traditional controllers might not work [7].

The aspiration of this thesis is to investigate the use of gain scheduling algorithms for pH control of model microbial cultivation systems in order to improve the process adaptability under various conditions and compare the efficiency.

1.1. Overview of Main Industrial Processes and the Importance of pH Control

1.1.1. Major Biochemical/Biotechnological Processes in Industry

The Fermentation processes are widely used in the industries like food production, biofuel generation, and biochemical manufacturing. The pH conditions are essential to maintain the microbial activity, ensuring of high productivity and specific product outcome as per requirement. The deviations from ideal pH can significantly reduce the yield and product quality in the fermentation process [8].

The controlled fermentation processes are important to the industrial enzyme production. Precise control of the pH is critical for enhancing enzyme yield and quality, biopharmaceutical processes such as production of recombinant proteins and vaccines, and enzymatic activity, stability and specificity are highly sensitive to pH. Precise pH control is critical to ensuring protein stability, bioactivity, and regulatory compliance, which directly impact therapeutic efficacy and safety [9,10].

Proper pH control is crucial for efficient microbial metabolism and reduction of impurities, which is particularly important in biological wastewater treatment processes such as anaerobic digestion and denitrification for enhancing treatment efficiency and process sustainability [11].

1.1.2. Importance of pH Control

1.1.2.1. Impact on Product Quality and Yield

Accurate pH regulation directly influences the microbial growth, enzymatic activities, and metabolic processes therefore its influencing product quality, yield, and consistency. For example in this article the author studies have shown [8] that sharp pH control through adjusting feed gas ratios in the bio methanation processes significantly enhanced methane yield by maintaining stability within the methanogenic process.

1.1.2.2. Influence on Process Stability and Safety:

Correct pH management provides stability of the process and safety in operation. In the production of aqueous electrodes, for instance, the inclusion of a pH control in the process prevents possible corrosion of the aluminium substrate which may affect the performance of the electrode and its operation safety [10].

1.1.2.3. Challenges of Maintaining Optimal pH

Maintaining at a stable and optimum pH value has a number of difficulties such as limitation of buffer capacity, reagent expense and consumption, and interactions with the microbial community. For example, during sludge fermentation to produce short chain fatty acids (SCFA), gradual pH adjustment is beneficial but must be properly managed to balance changes in the microbial

community with potential inhibitory effects [3], and likewise in the hydrogen based autotrophic denitrification processes the essential of the pH control between acidic (HCl) and CO_2-based has given a significant impact on microbial dynamics and overall process efficiency [11].
Overall, precise and specific range pH control remains essential in various areas of the biochemical and biotechnology industries to ensure product quality, performance stability, and economic sustainability.

1.1.3. pH control

Modifying the pH level plays a crucial role in maintaining product quality and minimizing equipment corrosion within the controlled system. Properly applied pH regulation conserves the reagents needed for pH management. pH level regulation is applicable in multiple areas:

- In biotechnology the pH control is applied to the cultivation of microorganisms and metabolism [12].
- In the chemical industry for the salt crystallization processes [13].
- In surface treatment processes, efficient for theremoval of paints and varnishes, the hardness of nickel coatings, and selection of the brightness of nickel coatings.[14].
- In fermentation processes for the regulation of fermentation time and the growth of the organisms in fermentation processes [15].
- In pharmaceuticals, for studies on body reactions, stability and efficacy of formulations [16].
- For water softening, purification processes - pH neutralization reactor and other related applications [17]

1.1.4. Titration Curve Nonlinearity

The nonlinearity in terms of pH control problem arises from the measurement and chemistry of pH scale.
The logarithmic of pH is define as,

$$pH(t) = -log_{10}(C_H)) \tag{1}$$

The equation states that understanding of pH measurement to changes in hydrogen-ion concentration C_H is strong and current pH value of nonlinear function.

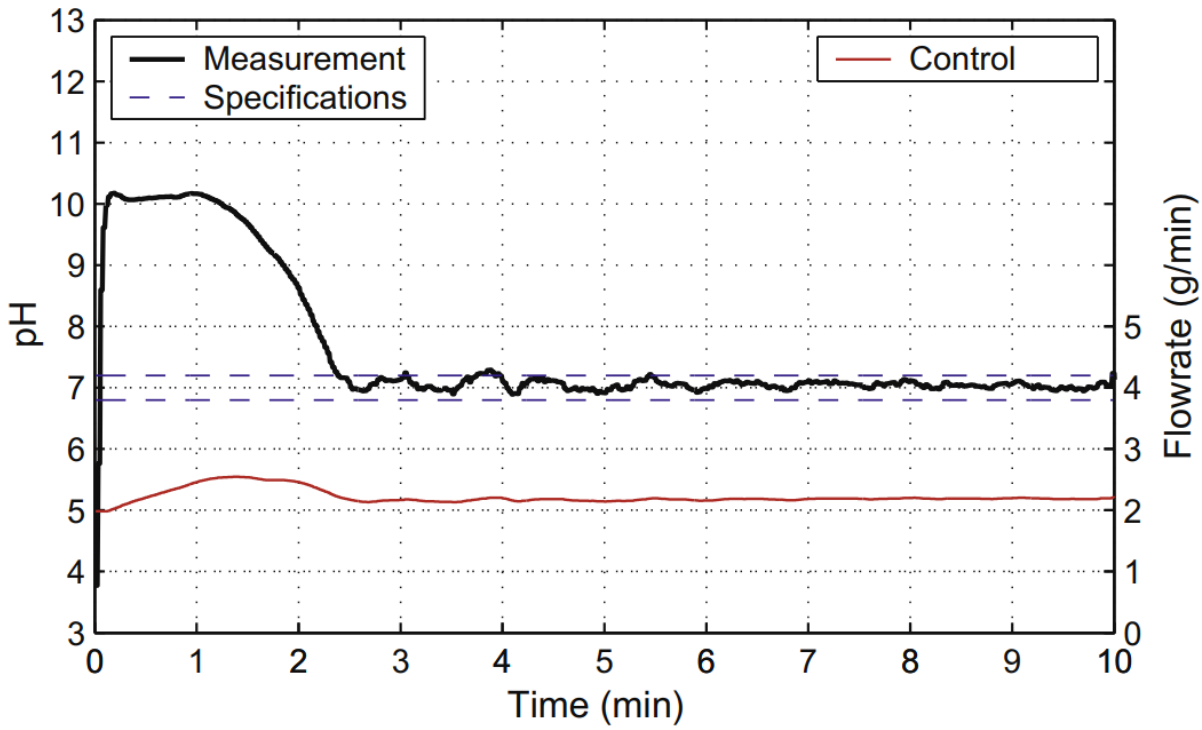

Fig. 1 observation of the pH [18].

This quantitative property (a small change in CH leads to a correspondingly large change in pH) characterized this effect quantitatively and showed the pH neutralization process to be a demanding nonlinear control benchmark precisely because nonlinearity in measurement is compounded with nonlinearity in process dynamics - a compounding that is most extreme in the near-neutral range most relevant to biological applications as shown in the Fig.1. This is the basic observation of the process control engineering that can be applied directly to the problem of bioreactor pH control [18].

The practical implication of this to control design is that a linear controller with a desired pH operating point will have an effective loop gain that change both with the pH setpoint and with the process dynamics across the titration curve, regardless of the state dependent dynamics, and both effects on the loop gain must be considered simultaneously [19].

1.1.5. Instrumentation Constraints in Fed-Batch Systems

Gain-scheduled and model-based adaptive control strategies vary the parameters of the controller according to the present process state, and thus, they also depend on the precision and dependability with which the scheduling variable measurements are acquired. In real fed-batch cultures, process measurements are considerably less available and of lower quality than in simulation studies.
The actual growth rate and biomass concentration, which are the two variables that directly cause the disturbance of hydrogen-ion production, cannot be directly measured using standard instruments and have to be estimated using software sensors or the off-gas analysis. These limitations in instrumentation imply that the performance in a real facility will be relatively poorer than in simulation studies, which assume perfect knowledge of the state, and it leads to the particular interest in reduced-instrumentation scheduling arrangements that are robust to not having the entire collection of ideally available measurements [20].

1.1.6. pH control for gain scheduling-based adaptive control algorithm

When selecting an adaptive control algorithm for pH control, the auxiliary variable measurement availability and mathematical knowledge need to be considered.

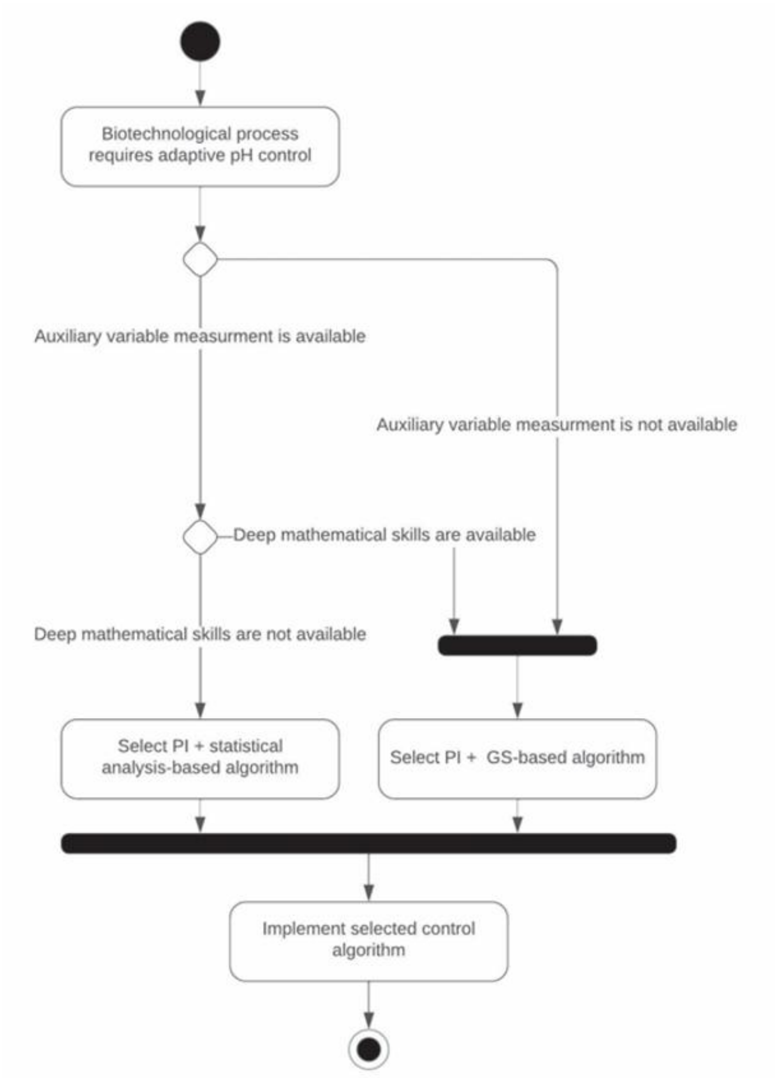

Fig. 2. pH adaptive control algorithm type selection.

As shown in the above Fig.2. gain scheduling-based adaptive control algorithm does not require any auxiliary variable measurement equipment, and it relies only on the controller input/output variables. The statistical analysis-based control algorithm requires a feed forward compensator which uses OUR values. Therefore, this method relies on external parameter measurement but does not require deep mathematical skills and process knowledge to develop the control algorithm

.

1.1.7. Industrial Importance that influences in terms of pH:

In the food and beverages, chemicals, petrochemicals, pharmaceuticals, power generation, paper and pulp, and textile industries, pH measurement and control play an important role in increasing process efficiency, quality assurance, and environmental protection. The Table 1. below shows the significance of pH in different industries. With the migration of bioprocesses from the lab scale to the plant level, there would be an exponential rise in the number of pH control loops within new facilities.

Table 1. The Importance of pH in the Process Industry [21]

Application	Processes and Aspects Affected by pH
Microorganism	Microorganism growth and metabolism
Bacteriology	Dough volume
Baking	Texture, color, and crusting
Brewing	Yield and extraction using mashing
Chemicals	Temperature for sterilization
Cleaners	Effectiveness and crystallization of salts
Dyes	Effectiveness and tint of intermediates
Electroplating	Nickel deposition
Fermentation	Fermentation time and alien organism growth
Gelatin	Water absorption
Pharmaceuticals	Stability and body reaction
Pigment	Composition and precipitation
Pulp and paper	Sizing and coating, and foaming
Sewage	Digestion of sugar and fats, and destruction of glucose
Sugar	Inversion of sugar
Textiles	Efficiency of most wet processes
Water treatment	Coagulation and softening processes

The elimination of unwanted biological entities and productivity of the genetic engineering entities depend on the accurate and effective measurement and control of pH. Cost of poor batches and equipment contamination would be worth millions of dollars in case of highly added-value products [21].

1.2. Operational modes of the bioreactor-scale biochemical/biotechnological processes

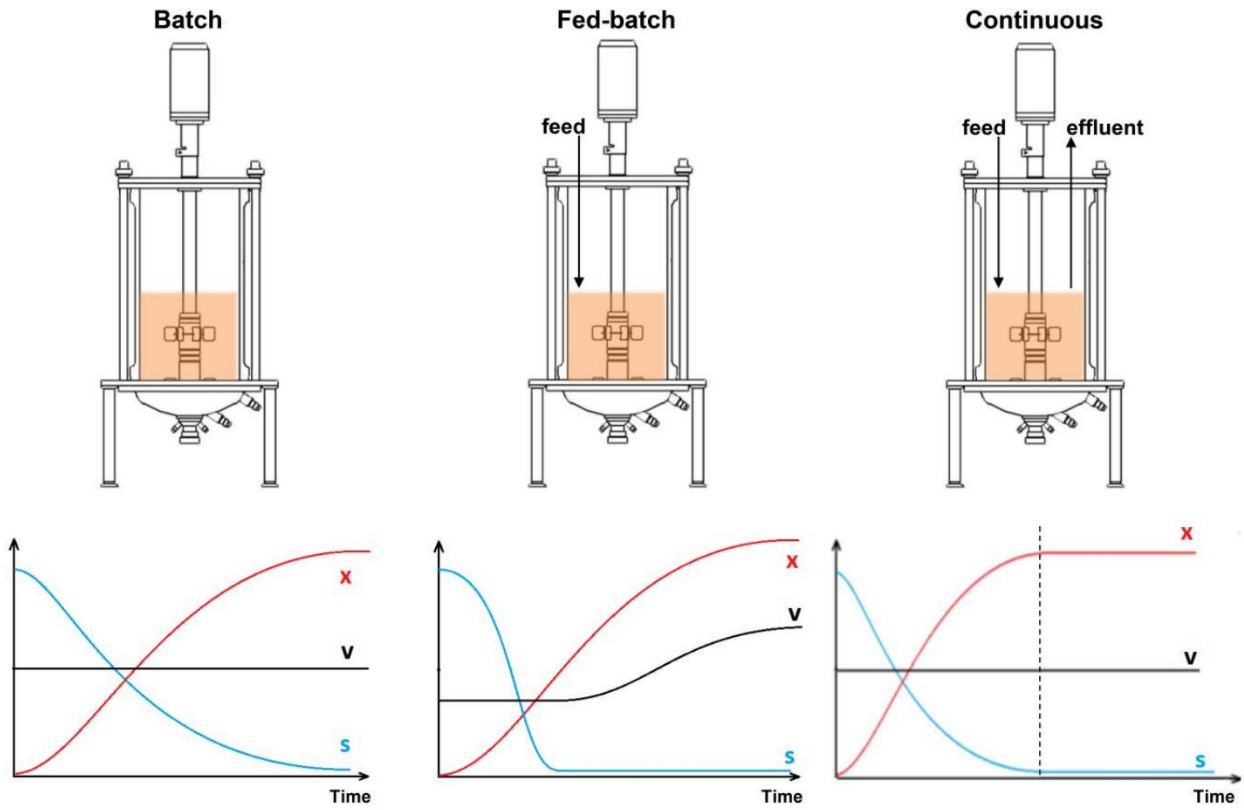

Fig. 3. Operational modes of the bioreactor-scale [21].

As shown in the Fig 3, the batch process, a fixed volume of medium is introduced into a microbial culture. As the microorganisms reproduce, they consume the resources in the medium and generate by the products, which progressively decelerates in their growth, ultimately resulting in the transition to the stationary growth phase all processes have a beginning and an end. A continuous process can be thought of as a long batch that can benefit from the automation of its start-up and shut down by the use of sequencing techniques and standards developed for batch operations. One important distinction between batch and continuous is that during the reaction or formation of product, the vessel discharge flow is zero for batch operations. For batch reactors where the reagent is consumed or for fed batch operations where the reagent and feeds are simultaneous, the response is self-regulating and many of the design techniques developed for continuous control and optimization apply.

For more traditional batch operations where the reagent and feeds are charged sequentially, the pH response is a ramp. This integrating response has profound implications as to control tuning and strategies. It is more critical than ever to minimize the reset action (maximize reset time) and maximize rate action to prevent overshoot. If the pH goes past the end point, the only way it can be corrected is by use of split ranged acid and base reagents. Often there is a dead band between the closing of one valve and the opening of the other valve to prevent cross neutralization, the pH response is integrating, and the pH loop will continuously oscillate across the split range point.

The use of an online pH measurement and one or more of the advanced batch control strategies listed in Table 2. below can reduce batch cycle time and improve consistency. If the starting pH is on a relatively steep part of the curve, then a temperature corrected curve can be used to calculate the charge required based on the change in mass ratio on the X axis (item 1). However, if the pH at the start of the reagent addition is on extremes where the conditions are harsh and the reagent ratio error is large, it is best to use a recipe number that was updated by the actual reagent used in the last best batch Item 2). A filtered and velocity limited rate of change of pH can be multiplied by the total time delay to provide a predicted pH that when compared to the desired point can provide an anticipation needed to prevent overshoot (item 3). Pulse width and amplitude modulation of the pH controller output can mimic the titration method used in the lab (item 4). Finally, inline pH control of a high recirculation flow can provide a smooth transition to the end point if the localized high reagent concentrations do not trigger side reactions, damage cells or crystals, or corrode recirculation piping and nozzles (item 5). The inline pH control set point is remotely set by a batch pH controller with its reset turned off when the batch pH approaches the end point. What works best may be a combination of an initial charge just short of the end point based on items (1) and (2) and then a combination of items (3) and (4) or (5) to make a trim adjustment [21].

Table 2. Advanced Batch pH Control Technique

Item no.	Advanced Batch pH Control Technique
1	Automatic calculation of charge from temperature corrected titration curve
2	Automatic partial correction of charge based on last best batch
3	Automatic end-point prediction and shutoff based on rate of change of pH
4	Pulse width and amplitude modulation of a proportional-only controller output
5	Cascade of batch pH to inline pH control of a high recirculation flow

1.3. Modelling techniques of the bioreactor-scale biochemical/biotechnological processes

1.3.1. Mechanistic/ Kinetic modelling model development

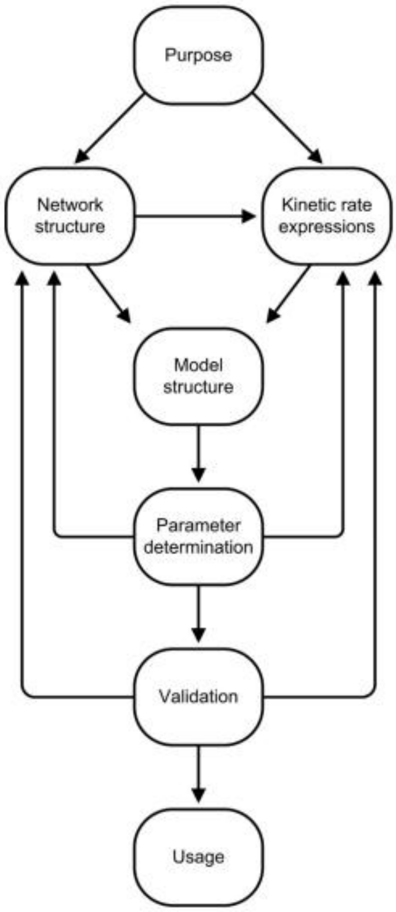

Fig. 4. Kinetic modelling model development [22]

The example schematic in the Fig.4. shows and highlights a modular approach to developing the models, involving network structure design, selection of kinetic rate expressions, parameter, model validation, and reduction.

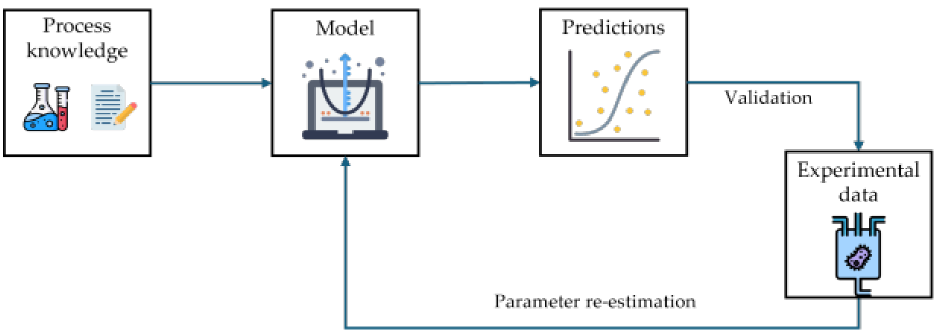

Fig. 5. Schematic of mechanistic model development [23]

The Fig. 5. represent kinetic modelling is the fundamental method for investigating and optimization of biochemical and biotechnological processes. As explained kinetic models provide a mechanistic representation of cellular metabolism by describing dynamic changes in metabolite concentrations over time, based on the enzyme kinetics, reaction stoichiometry, and environmental inputs, Table 3-4 is defined what type of model along with their characteristics and influence parameter of microorganism under which typical [23].

Notably, the kinetic models are enabling prediction of the microbial behaviour under varying process conditions, which is critical for the supporting advanced control strategies, such as gain-scheduling or adaptive pH regulation in the microbial cultivation. Despite challenges of parameter uncertainty and model complexity, kinetic modelling remains a key element for rational bioprocess control and cell factory design [22].

Table 3. Type of model [23]

Type of Model	Characteristics	Advantages	Disadvantages
Unstructured	• Biomass as black box, • Balanced growth approximation, • Mass balances and kinetic equations.	Description of the physical aspects of the process	Potential over-simplification of biomass-product dynamics
Structured	• Biomass as a multi component organism, • Cell growth based on interaction of intracellular components, • Metabolic flux equations.	Suitable to model complex systems (metabolic networks)	Extensive parameter identification (metabolomics)

Table 4. Microorganism and its type of Model

Microorganism	Type of Model	Studied Parameter
Aspergillus oryzae	Unstructured	Agitation and aeration
Bacillus subtilis	Unstructured	Oxygen supply
CHO cell	Unstructured	Temperature shift
E. coli	Unstructured	Overflow metabolism
E. coli	Structured kinetic	Specific growth rate
Penicillium chrysogenum	Pooled metabolic model	Feeding conditions
Pichia pastoris	Structured kinetic	Growth and recombinant protein production
Saccharomyces cerevisiae	Unstructured	Ethanol production
Zymomonas mobilis	Unstructured	Glucose and xylose co-fermentation

1.3.2. Data-Based modelling with case study integration

The data driven modelling techniques are mostly used in biotechnological processes due to the complexity, nonlinearity, and variability of biological systems. Differing from traditional first-principle models, data-based models utilize the historical and real-time process data to create predictive and diagnostic tools without requiring detailed biochemical equations. Karim et al

demonstrated the application of artificial neural networks (ANN), the principal component analysis (PCA), and the multiway PCA (MPCA) in real industrial fermentation scenario.
One of the significant examples involved using the ANN to predict product yield based on input variables like the dissolved oxygen, glucose concentration, agitation speed and optical density.
By using sensitivity and partial correlation analysis, the researchers were able to identify and eliminate the less impactful inputs and improving the model efficiency without compromising the accuracy. Another case study showcased the use of the MPCA for monitoring batch to batch variation in recombinant of protein fermentation.
The model detected early stage process of the deviations linked to the increased glucose levels, abnormal base addition, and the reduced biomass growth, all of which indicated metabolic stress or reduced effectiveness.
In a fed-batch enzyme production process, MPCA was able to flag low-yield batches by detecting crucial intervals where deviations in DO and CO2 occurred. so, here are the examples shows and highlight how the data-based models serve as both predictive tools and fault detection mechanisms.
Their capacity to analyse large, multidimensional datasets and adapt to the changing conditions makes them particularly relevant for the integration into adaptive pH control systems and gain scheduling strategies, where as for the real time process state estimation is essential for effective bioprocess control [23, 24], the Fig.6 shows the schematic of data driven model development,

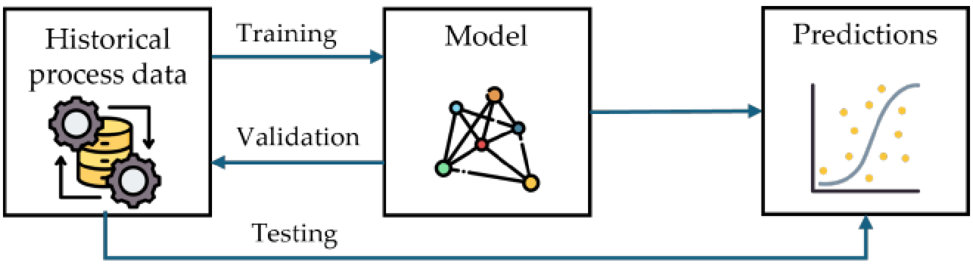

Fig. 6. Schematic of data driven model development [23]

- **Case Study 1**: ANN model trained to predict the protein yield and the sensitivity analysis reduced inputs from 9 to 7.
- **Case Study 2**: ANN used with a limited dataset and highlighted challenges in the modeling with small batch sizes.
- **Case Study 3**: MPCA identified faulty batches by tracking deviations in the glucose, DO, and OD.
- **Case Study 4**: MPCA used in the fed-batch enzyme production to the detect abnormal DO and CO2 levels indicating the process faults.

Table 5. Studied Parameter in data based modeling [23]

Microorganism	Type of Model	Studied Parameter	Main Findings
Bacillus megaterium	PCA	Fault detection	Real-time fault detection
E. coli	Neural Networks	μ-stat feeding control	Improved cell growth and protein production
E. coli	Reinforcement Learning	Feed rate control	Optimized product formation
Hybridoma cells	ML-PCA / ML-NMD	Reaction modeling	Parameter prediction with high accuracy
S. cerevisiae	Neural Networks	Temp. MPC	More robust temp. control
S. cerevisiae	Neural Networks	Monitoring	Similar results using online/offline data

S. cerevisiae	Gaussian process regression	Cycle time	Productivity improvement
Streptomycetes sp.	PLS	API production	Key variable identification

Table 6. Advantages and limitations of mechanistic and data-driven models [23]

Type of Model	Advantages	Limitations
Mechanistic	• Increased process understanding; • Suitable for process control and optimization • Model-based design of experiments (DOE)	• Time-consuming development • Requires extensive experimental validation • Needs intensive process knowledge
Data-driven	• Automatic model assembly • Real-time monitoring and fault detection • Low computational burden	• Poor extrapolation • Requires representative and reliable data • Limited for control and optimization

1.3.3. Hybrid modelling

Hybrid modelling has emerged to importance as a robust modelling in biochemical and biotechnological process modelling, particularly in fermentation based systems. According to Albino et al, hybrid models combine the interpretability and the extrapolation strengths of mechanistic that is white box models with the flexibility and adaptability of data driven that is black box methods.

This review highlights the growing importance of such models in on-line optimization, real-time monitoring, and scale up of fermentation processes. Mechanical or kinetic models are based on first-principle equations that is mass and energy balances, while the data driven models utilize historical process data through algorithms such as neural networks, PCA, or PLS regression. Hybrid structures are either parallel or serial where is designed to leverage strengths from both sides, enabling accurate predictions even in untested process conditions, and the fig.7. shows Schematic of the three ways to combine the two types of models that is Parallel, and Serial configurations

Applications range from prediction of the biomass and the product concentrations to advanced control strategies like feed optimization. Importantly, hybrid models are proven to enable model predictive control (MPC) and adaptive process management, and which directly aligns with gain scheduling pH control systems in the microbial cultivation. Their scalability and reduced data requirements make them ideal tools for digital biomanufacturing and bioprocess expansion [23].

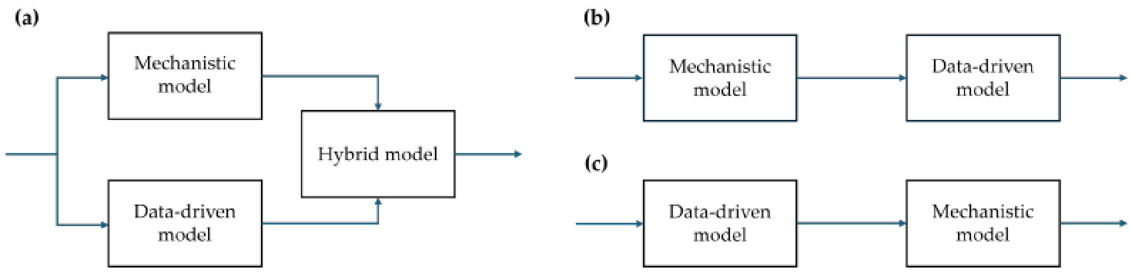

Fig. 7. Schematic of the three ways to combine the two types of models (a) Parallel configuration.(b,c) Serial configurations [23]

1.4. Control techniques in bioreactor-scale biochemical/biotechnological processes

1.4.1. Conventional PI/PID Control in Bioprocess Systems

1.4.1.1. Industrial Prevalence and Rationale

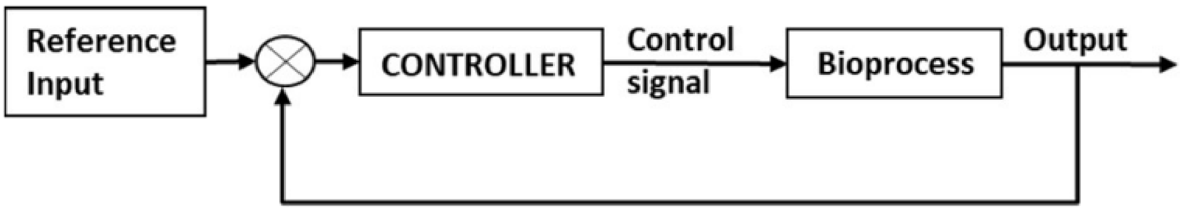

Fig. 8. General schematic PI/PID Control in Bioprocess Systems [38]

The Fig.8. is the general schematic PI/PID Control in Bioprocess Systems, although there is plenty of evidence that fed-batch bioprocessing is characterized by significant dynamics, PID regulators still dominate the area of process control implementation in industrial-scale fermentations and cultures. This tendency is certainly not caused by lack of awareness about alternative technologies but rather by a number of advantages that have yet to be replicated by more sophisticated solutions. PI and PID controllers are highly convenient to implement due to their low computational demand, full compatibility with DCS platforms provided by leading vendors, comprehensible for process engineers and quality assurance personnel, compliance with current submission practices and years of empirical validation within industry applications. In case of pharmaceutical manufacturing, where every control system change should be approved according to change control and validation guidelines, transparency of PI controllers becomes a valuable advantage that is hard to achieve with other types of regulation [24,25].

As far as pH control is concerned, use of the PI controller with no derivative term is common industry practice. Derivative terms amplify the measurement noise of electrochemical pH electrodes in the fermentation environment, producing unacceptable peaks in the output of the alkali flow rate regulator that destabilizes the control loop and leads to additional reagent usage. An integral component of the PI regulator compensates for steady-state offsets from a disturbance in the form of a constant hydrogen ion production rate, which is the primary goal of the pH regulation at steady state periods of growth [24,25].

1.4.1.2. Performance Deterioration Over the Batch Cycle

There lies a fundamental issue inherent to fixed parameter PI control of fed-batch bioreactors, in the sense that while the controller parameters will stay constant, the characteristics of the process will keep on changing. The use of any PI control requires a tuning at a certain operating point based on

an implicit assumption of a stationary linear plant with some defined process gain and time constant. During a fermentation process, the volume changes, biomass grows, and the growth rates change, resulting in a discrepancy between the gain and time constant of the plant compared to the design values used for the controller, hence degrading closed loop performance predictably.
This has been quantified by experimental observations, In the reviewed paper in real fermentations of E. coli cells for the expression of recombinant proteins, the integral of absolute error (IAE) obtained using fixed parameter PID control was 0.1887 pH compared to an IAE of 0.0189 pH· obtained using gain-scheduled adaptive control, demonstrating an improvement in control quality of about one order of magnitude. The benchmark above, which stems from real bioprocesses instead of simulations, gives clear indication that fixed parameter and adaptive pH control differ substantially [26].

Predictable directionality of the degradation is another characteristic. At the start of the batch cycle, with small volume and large process gain, the same tuning is sufficient to have reasonable setpoint control. With an increase in volume, leading to low process gain, the same tuning will become insufficiently aggressive, thus resulting in slow response to any disturbance and large setpoint error at the time when the growth of bacteria plays a crucial role for the product formation. More aggressive tuning for medium volume will result in overshooting and unstable behaviour of the process at the start of the cycle due to sensitivity of the process [26,27].

1.4.2. Advanced Adaptive and Intelligent Control Approaches

Smart control techniques for bioprocesses seek performance improvement by considering nonlinear behaviour, constraints, and dynamics, which cannot be solved with fixed parameter PID or PI controllers. Some of the main categories of smart control techniques relevant to microbial pH control are neural network-based control, model predictive control (MPC), fuzzy logic control, reinforcement learning, and so on.[28].

1.4.2.1. Artificial Neural Network-Based Control

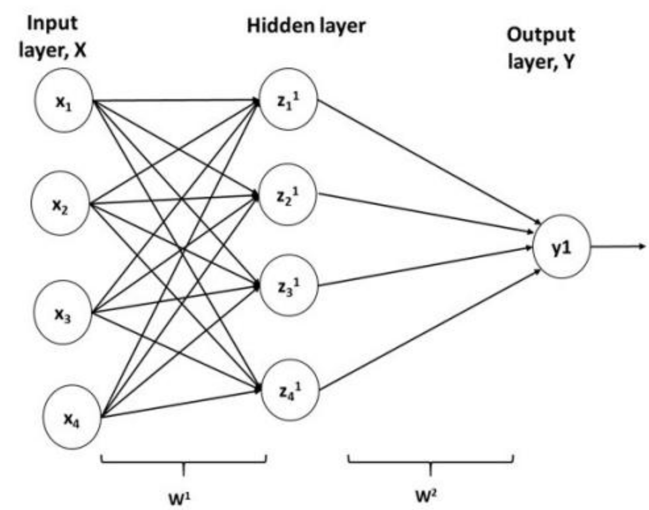

Fig. 9. Artificial Neural Network-Based Control [38]

As shown in Fig.9. Artificial neural networks have been used to approximate non-linear bioreactor behaviour and to design controllers by learning direct input-output mappings between system data [29] developed a controller for pH and dissolved oxygen regulation using an artificial neural network, proving that an inverse neural network model with adaptive correction can be used for effective set-point tracking in real fermentations. Recent developments focus on integrating neural models within an MPC structure in the referred paper used machine learning models to build MPC for cell culture, and the author of that suggested physics-informed neural networks to develop hybrid mechanistic-data driven models for predictive control. Although these works showed superior performance compared to traditional methods, ANN-based control typically involves obtaining sufficient datasets, is very process-specific, and produces opaque control schemes [29,31].

1.4.2.2. Model Predictive Control

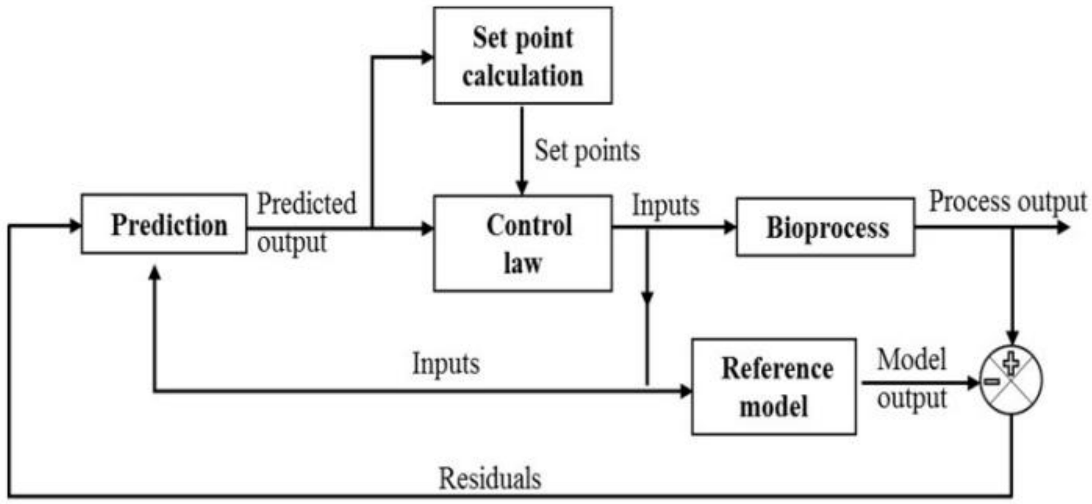

Fig. 10. Model Predictive Control [38]

In the MPC framework and Fig.10 is representative of it, a model-based approach is used wherein a dynamic process model is employed to estimate the process states ahead in time and then to generate control actions such that the future costs are minimized based on the estimated process states, with consideration of constraints on inputs and outputs [32].

In the case of fed-batch fermentation, model predictive control (MPC) has been shown to provide one of the most effective strategies for regulating the feed rate due to its ability to handle nonlinearities and constraints effectively [33].

Specifically, for pH related systems have proposed a nonlinear MPC strategy using a discrete-time NARX-Laguerre model of a pH neutralization process and shown the system's superiority over the conventional PID and adaptive PID controllers [34].

Moreover, the combined dynamic flux balance analysis and deep convolutional neural networks for constructing a hybrid model to design a model predictive controller for a fermenter, where it was shown to outperform other simpler model structures both in terms of prediction and control performance [35].

Additionally, physics informed neural networks can also serve as hybrid mechanistic-data driven surrogate models for bioprocesses in MPC design while respecting the physical consistency of the problem, in addition to their flexible approximation capabilities. However, as mentioned above, the success of MPC strongly depends on the accuracy of the model and accurate state estimation, otherwise, MPC will lose its performance advantages and may be computationally expensive.

1.4.2.3. Fuzzy Logic and Rule-Based Control

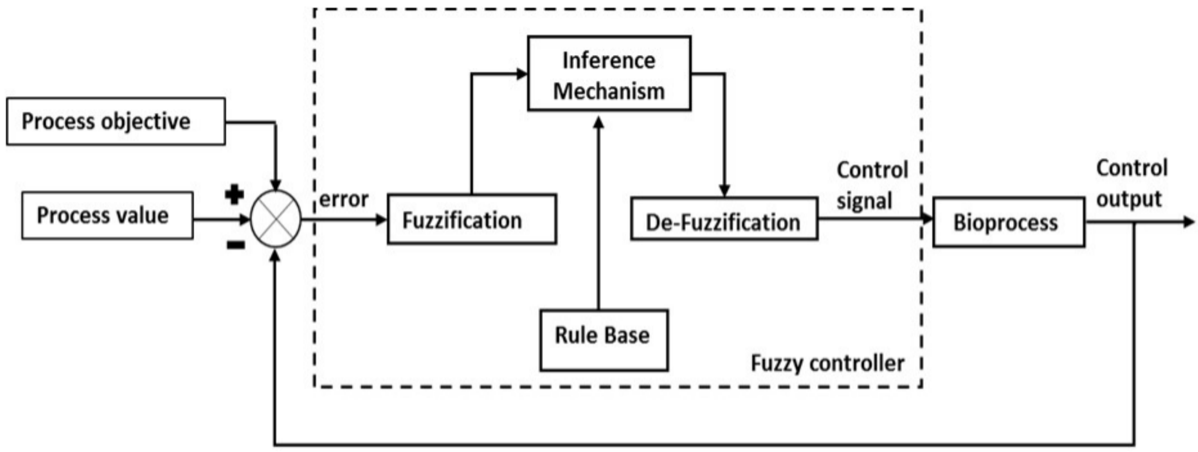

Fig. 11. Fuzzy Logic and Rule-Based Control [38]

Fig.11 illustrate schematic of Fuzzy Logic and Rule-Based Control, the use of fuzzy logic controllers has attracted considerable attention from researchers for regulating bioreactors since it allows incorporating the knowledge of the operators into linguistic if-then statements as well as coping with nonlinearities and uncertainties in the dynamics of the process without having an accurate mathematical model [36].

The application of industrial cases and simulation of fermentations and bioreactor operations shows that fuzzy controllers and fuzzily tuned PID regulators outperform conventional PID controllers, especially in cases where there are input multiplicities and high nonlinearities, providing faster responses in reaching optimal operation points. Type-2 fuzzy logic controllers have also been proposed to provide greater robustness to uncertainties that cannot be overcome by type-1 fuzzy logic controllers. At the same time, developing fuzzy controllers requires an adequate expert rule-base and tuning. Fuzzy and rule-based techniques do not offer the systematic approach provided by model-based techniques when it comes to the stability and performance of the controller design. This is a limitation to the usefulness of fuzzy approaches to complex control problems like pH control during fed-batch microbial cultivations [37,38].

1.5. Gain Scheduling

1.5.1. Conceptual Foundations

Gain scheduling is an organized methodology in nonlinear control in which a collection of linear controllers tailored to individual operating points is continuously tuned according to changes in the process dynamics with controller parameters parameterized as functions of some observable scheduling signal, For each instant at which ρ is fixed, the nonlinear plant is locally linearized and a controller is designed using any one of the linear methods like loop shaping, IMC synthesis, pole placement or even optimization. The gain-scheduled controller then computes online, turning the tough nonlinear control task into an easier task of solving several linear design tasks [39-40].

Control of the nonlinear systems is the fundamental challenge in modern engineering, particularly when the system dynamics vary significantly across different operating conditions. The commonly used solution is gain scheduling, a technique where multiple linear controllers are designed for specific operating conditions and merged as the system changes between them. Gain scheduling is the prominent in aerospace, automotive, and process control due to its ability to leverage linear control design techniques while handling certain nonlinearity functionalities.

However, the assumption that the combination of well designed linear controllers will perform adequately over the entire nonlinear operating space can be problematic. Therefore, comprehensive analysis of this method stability and robustness is essential. This session reviews two points, one that rigorously analyses the theoretical underpinnings of gain scheduling, and another that highlights its practical hazards and suggests remedies

1.5.2. Analysis of Gain Scheduled Control for Nonlinear Plants

The authors of the paper [41] perform basic research of the gain scheduling theory. Their work contains a formal investigation of gain-scheduled control systems designed for nonlinear plants and configuration is presented in Fig.12. They provide an analysis that confirms that the use of gain scheduling is not sufficient for achieving stable system behaviour.

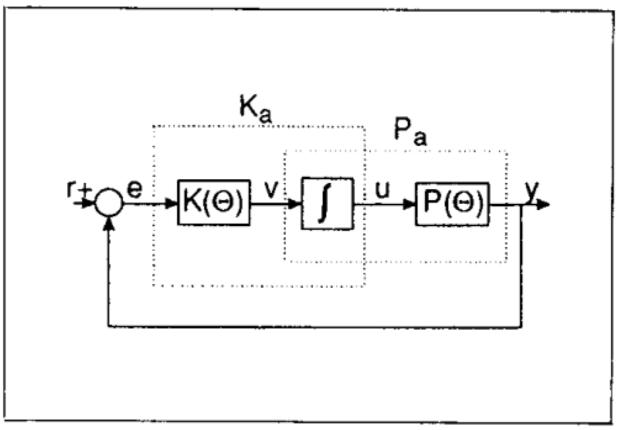

Fig. 12. Unity feedback configuration for command following [41].

Gain scheduling technique implies the design of linear controllers for several fixed operating points of a non-linear plant. In such a way, each linear controller corresponds to a different operating point and can be defined by a certain approximation of the plant. Controllers' schedules are based on a parameter related to the current operating condition of the plant. For instance, this parameter can be expressed as velocity, altitude or angle. It is often assumed that interpolating controllers results in the creation of a globally stabilizing controller. Nevertheless, as shown by the authors, this assumption is valid only under specific conditions.

The authors use Lyapunov analysis and linear matrix inequalities to find sufficient conditions for stability. This emphasizes that a correct selection of scheduling parameters is crucial since inconsistent transitions from one operating mode to another lead to undesirable system behaviour. Besides, gain-scheduled controllers should take into account the global dynamics of the system.
One of the main concepts presented in the paper is the concept of frozen time analysis. According to it, the dynamic condition of the gain-scheduled controller can be investigated assuming its scheduling parameter as fixed. Thus, the frozen time analysis provides a way to evaluate the actual real-time behaviour of the system [41].

1.6. Comparative Review of Existing Strategies and Research Gaps

The different control strategies discussed in this paper can be thought of as part of a continuous scale, comparing the potential for obtaining high-performance control in a closed loop to the difficulty of implementing this. PI control represents the strategy with minimal complexity as it does not require any modelling information, is easy to implement and tune, and has widespread regulatory approval but it cannot maintain consistent performance when faced with strong nonlinearity and time variation in bioprocesses. Full MPC with online model adaptation provides potentially optimal performance, but this method relies on accurate models, parameter estimation in real time, and online optimization making it difficult to perform in a typical industrial fed batch environment. ANNs make the task of modelling less difficult but need substantial amounts of data and cannot easily be verified where as fuzzy required except level rule based system without that it cannot be achieved systematic process

In terms of performance against various criteria like set point tracking, disturbance rejection, robustness against noise, model and data availability, complexity of implementation, and regulatory approval, each of these approaches is unique. While model predictive control (MPC) and artificial neural networks (ANN)-based controllers may yield excellent tracking behaviour and constraint satisfaction under simulated or laboratory conditions, their superiority over less complex techniques becomes marginal with the presence of model mismatch, data scarcity, and process variability. On the other hand, gain-scheduled PI lies in an advantageous middle ground because it needs simplistic models (like linearization of the hydrogen ion balance equation), low computational resources (only algebraic computations for tuning parameters), readily available instruments, and provides substantial improvement in pH regulation by orders of magnitude compared to a static PI controller [42].

There is no study that compares different gain-scheduling methods under the same conditions to determine their comparative outcomes. The effect of noise in the system is comparatively less discovered, previous research focuses on assessing system performance at a fixed noise value, with it being unknown how the performance would be affected by an increase in noise. The performance-instrumentation compromise for reduced instrumentation approaches (such as the use of average volume or substrate feed estimation based on alkali flow) has yet to be determined through systematic comparisons with the full instrumentation approach. Many simulation studies suffer from low reproducibility due to inadequate reporting of model equations, parameters, and implementation details.

1.7. Summary

The relevance of the topic of pH control as well as its specific challenges have been highlighted in this chapter and various control strategies from traditional PI/PID controllers to more complex intelligent control algorithms have been reviewed. The importance of precisely controlling pH both in terms of biology and regulatory process was shown while the characteristics of fed-batch processes including the nonlinearity and complexity of the system together with the instrumentations limitations rendered static PI/PID architecture inefficient.

Modern methods such as Model Predictive Control (MPC), Artificial Neural Network based (ANN) controller, Fuzzy logic and reinforcement learning offer high potential in theoretical studies, however, all of them require modelling efforts, computations or data and currently, they do not yet have enough maturity for practical use.

Gain Scheduled PI controllers have shown great potential in terms of simplicity, minimal modelling efforts and instrumentations needed, offering an order of magnitude better results compared to experimental pH control applications. Yet there were still shortcomings in terms of multiple configuration comparison, noise, and disturbances. The following chapters will fill those gaps via simulation results.

2. Process Modelling and Simulink Implementation

2.1. Overview of the Process Subsystem

The fed batch microbial process is modelled in Simulink as a nonlinear dynamic plant with pH modelled using concentration of hydrogen ions C_{H^+}. The primary plant system is implemented within a block of Differential Equations Editor, and auxiliary MATLAB Function blocks are created to produce the necessary biological and operational outputs including rate of growth $\mu(t)$ substrate feeding rate $F_S(t)$ and hydrogen-ion production coefficient $R_H(t)$ The measured pH signal has sensor dynamics, transport delay, and measurement noise to simulate the realistic instrumentation.

2.2. State-Space Representation (Differential Equation Editor)

The choice of these variables was due to the fact that they represent the principal biological growth processes, the chemical growth processes associated with the pH, and the variable reactor volume that renders the fed-batch process nonlinear and nonstationary.
The plant uses three continuous states:

$$x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} = \begin{bmatrix} X(t) \\ C_{H^+}(t) \\ V(t) \end{bmatrix}$$

x - biomass concentration in the cultivation medium, g/l.
C_{H^+} - the concentrations of hydrogen ions,
V - cultivation medium volume, l.

2.2.1. Biomass balance, Hydrogen-ion balance, and Volume balance

The plant inputs are introduced in the Simulink model by the Differential Equation Editor block with five inputs.

$u(1) = \mu(t)$, is the biomass specific growth rate, 1/h,
$u(2) = F_S(t)$ is the flow of the feeding solution, l/h,
$u(3) = F_{pH}(t)$ is the flow of the alkali solution for pH control, l/h,
$u(4) = r_H(t)$ is the hydrogen-ion production coefficient,
$u(5) = CH0$ is the concentration of hydrogen-ions of the dosing stream.

The biomass balance explains the change in the concentration of biomass as a result of microbial growth and dilution as a result of the swelling reactor volume. The former is the growth of biomass by cell growth, and the latter is the decrease in concentration due to increase in volume. This equation (2) is necessary to describe the varying biological condition of process when fed batch is used.

$$\frac{dx}{dt} = \mu x - ((F_s + F_{pH})/V)x \tag{2}$$

So I have rewritten in DEE block as

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

The pH controlling equation is the hydrogen-ion balance. It takes into consideration hydrogen-ion generation relating to microbial activity, the effect of alkali dosing, and the effects of dilution due to the inlet flows, since pH is calculated based on the hydrogen-ion concentration, a minor variation in CH can cause significant pH variations.

It is against this reason that the state of hydrogen-ion needs to be numerically well behaved and positive during simulation.

$$\frac{dC_{H^+}}{dt} = (\alpha_1\mu \ + \ \alpha_2)x + \ F_{pH}(C^0_{H+} - C_{H^+})/v - (F_S C_{H^+}/v) \tag{3}$$

So, I have rewritten in DEE block as

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

(i.e. $u(4) = (\alpha_1\mu \ + \ \alpha_2)$),

Volume balance is the gain in reactor volume due to substrate feed and dose of alkali.

This equation (4) is more so significant since the effective process gain varies with time as the volume increases.

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

So, I have rewritten in DEE block as

$$u(2) \ + \ u(3),$$

Consequently, the response to the same control action may vary at various phases of the batch thus encouraging the application of gain scheduling. Fig. 13. Shows the DEE block and its execution in Simulink.

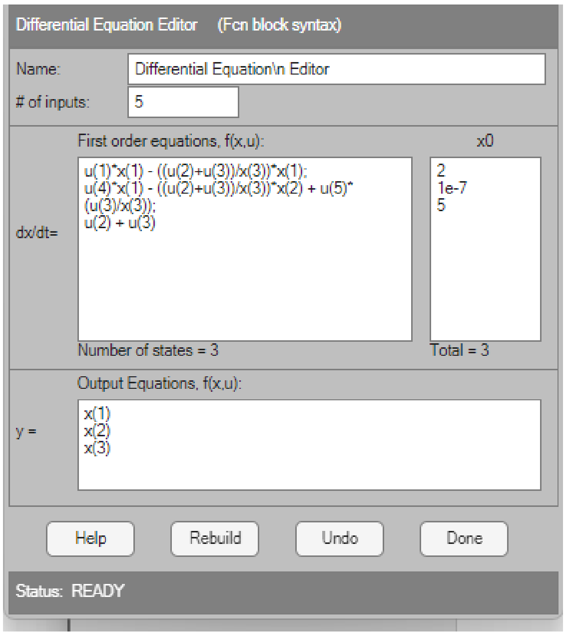

Fig. 13. The Differential Equation Editor block

The dosing term in this model is adjusted in such a way that the addition of alkali increases the C_{H^+}, which causes an increase in the pH. This will make the plant react with appropriate physical direction in base dosing.

Initial Conditions

The initial conditions are defined as:

$$X(0) = 2,$$

$$C_{H^+}(0) = 10^{-7}\frac{mol}{L},$$

$$V(0) = 5L$$

The initial conditions were chosen to represent the beginning of the cultivation process, with the initial hydrogen-ion concentration corresponding to a pH value close to 7. This not only ensures the simulation begins close to the desired operating region but also enables the controller response to be tested under realistic starting conditions.

2.3. MATLAB Function Blocks

2.3.1. Specific Growth Rate Profile with Disturbances (μ Profile)

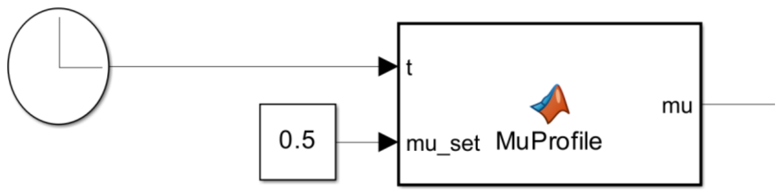

Fig. 14. μ Profile

On the block μ Profile as in Fig.14, it is an generating a time-varying specific growth rate $\mu(t)$ with periodic disturbances used to determine robustness of the controller.
The nominal value is:

$$\mu(t) = \mu_{set} \tag{5}$$

A 2-hour cycle is used to apply a repeating disturbance sequence during t ≥ 2.

$$\mu(t) = \mu_{set}/2 \tag{6}$$

This disturbance profile is characterized by periodic decreases in growth capacity (as a result of feeding or disturbances) and gives a challenging condition to assess adaptive gain scheduled control.

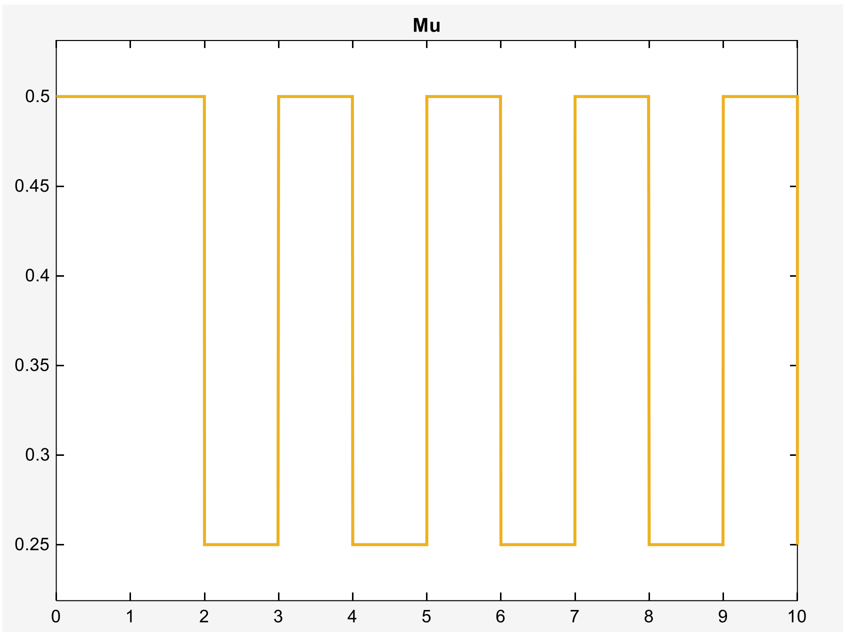

Fig. 15. Scope of μ Profile (X axis - Time(h), Y axis - $\mu(t)$)

Verified growth-rate disturbance trajectory $\mu(t)$ from Simulink scope (square-wave μ switching between 0.5 and 0.25 starting at t=2h) and it evidently observe in fig.15 scope of μ profile.

2.3.2. Substrate Feed Flow Model (F_S)

$$F_s = \mu_{set} xV/(Y_{xs} S_0) \tag{7}$$

Whereas the parameters used in the model,

$$S_0 = 450\ g/L,$$

$$Y_{xs} = 0.52\ g\ biomass/g\ substrate$$

The rate at which the substrate feed was introduced into the reactor $F_S(t)$ was modeled in terms of biomass and the volume of the reactor. This equation (7) makes the feed flow grow with the concentration of the biomass and the quantity of the liquid, which is comparable to the normal fed-batch feeding plans. The feed policy in this manner indicates the growing substrate demand of the growing culture.

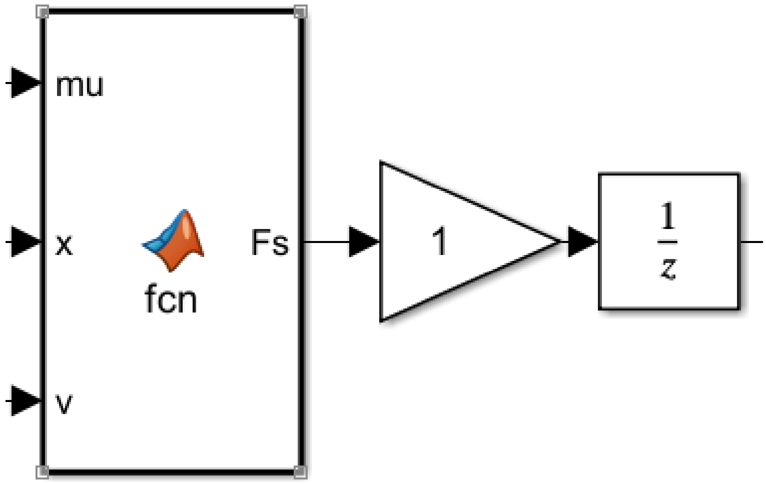

Fig. 16. substrate feed flow rate, F_S

The above Fig. 16 shows block (MATLAB Function) calculating substrate feed flow rate $F_S(t)$ based on $\mu(t)$, biomass $X(t)$and volume $V(t)$.

2.3.3. Hydrogen Ion Production Coefficient Model (H+ production rate)

The $rH(t)$, The hydrogen-ion production coefficient was modelled as a linear function of the specific growth rate. It is an indication of the presumption that the production of hydrogen-ions is based on the metabolic activity of the microorganisms. This simplified model is however adequate in assessing the impact of alteration of biological conditions on the performance of pH control.

$$rH(t) = (\alpha_1 \mu\ +\ \alpha_2) \tag{8}$$

2.3.4. pH Output Generation and Measurement Chain

Saturation and pH Conversion

The model models the pH indirectly by way of hydrogen-ion concentration. The pH value is computed by

$$pH(t) = -log_{10}(C_{H^+}) \tag{9}$$

The significance of this relationship is that it suggests that even minute changes in C_{H^+}, especially near 10^{-7} mol/L, particularly around can cause pH to vary. Thus, numeric stability (positivity and saturation of C_{H^+} is required in simulation.

Sensor, Transport Delay, and Noise

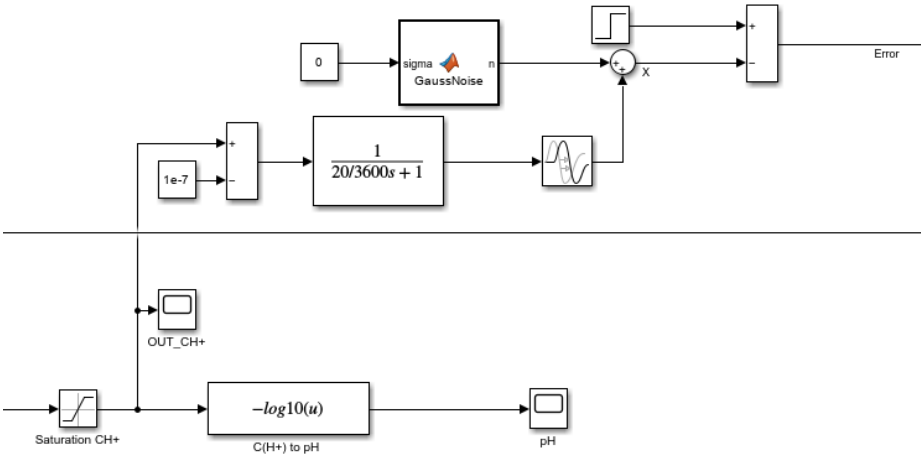

Fig. 17. Path of Sensor, Transport Delay, and Noise

The measured pH is passed through:
The sensor transfer function:

$$G(s) = \frac{1}{\tau_s + 1} \tag{10}$$

In the model $\tau_s = 20/3600$ hours (20 seconds), which corresponds to a realistic sensor time constant), a transport delay block to indicate further delay of measurement/transport with apply delay time=0.001.

The pH signal measured is contaminated by Gaussian noise to simulate sensor noise and test the control algorithm when the conditions are not ideal, Path of Sensor, Transport Delay, and Noise are show in Fig. 17.

2.3.5. Error Definition and Feedback Signal

The feedback signal is the measured,

$$e = C_{H^+}{}_{set} - C_{H^+}{}_{meas}$$

Were, $C_{H^+} = 1 \times 10^{-7}$, corresponding to the pH setpoint of 7.

When the positive error occurs that means that CH measured is lower than the setpoint and hence more alkali dosage is needed to increase CH. A negative error will mean that CH exceeds the setpoint, whereby the dosing action is expected to reduce. This sign convention is maintained all the way through the implementation whereby the counteracting action of the controller is meant to correct offset of the setpoint.

2.4. PI Controller Structure:

A PI controller is chosen because it is highly used in the control of industrial processes and its capability to eliminate steady-state error by the use of integral action. The PI control law is used in the form,

$$u(t) = K_c(e(t) + \frac{1}{T_i}\int_0^t e(\tau)\, d\tau) \tag{11}$$

Where $u(t)$, in controller output, $e(t)$ is the controller error, K_c is the proportional gain and T_i is the integral time constant. System A has a fixed parameter which is the case in both parameters, a standard fixed-tuned PI controller. In Systems B -D, the PI structure is maintained with the Kc and Ti being updated online based on gain scheduling rules. The uniformity of the controller structure across the systems will make sure that variations in performance are not mainly caused by the changes in the type of controller, but rather by the schedule strategy.

2.5. Gain Scheduling

The gain scheduling motivation in the process is that the fed-batch cultivation system is a nonlinear time-varying system.

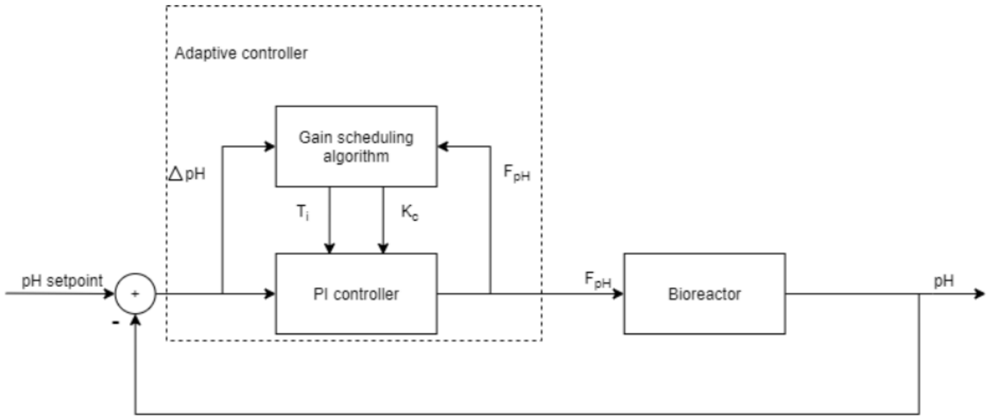

Fig. 18. Diagram of the pH adaptive control system

As shown in Fig.18, its illustration of the adaptive pH control system under study, which implements the adaptation algorithm which has the controller output and input signals as gain scheduling variables.
Some of the main variables that vary with time during operation include culture volume $V(t)$ which is increased by feeding and dosing, feed flow $F_s\ (t)$ which can change depending on the growth requirements, biomass $x(t)$ and growth rate $\mu(t)$. Since the variables are present directly in the hydrogen-ion balance equation, the effective process dynamics (gain and time constant), are not constant.

In a fixed PI controller, the parameters K_c and T_i are adjusted to one operating point (usually to an initial condition or a nominal point). Dilution rate $(F_s + F_{pH})/V$ can make or break the plant dynamics as the process progresses and the sensitivity of the alkali-concentration of hydrogen-ions to the alkali dosing can vary.

A typical PI controller having a fixed PI controller can have the following problem

- At other stages the controller can be overly aggressive, and the controller will give rise to oscillations or undue control action.
- Maybe at different stage the controller may become too weak, which results in slower setpoint tracking and increased disturbance rejection errors.
- The disturbance can trigger varying reactions at various times in a batch because of the varying volume and flow conditions.

This is dealt with by means of gain scheduling which adjusts K_c and T_i according to the operating point at the moment. In theory, at every time t the nonlinear process is locally parameterized by a simpler model the parameters of which may be represented in terms of measured variables.

Analytical scheduling formulas are then used to retune the controller such that when the conditions of operation vary the closed-loop response will be the same.

The proportional gain scheduling law is

$$K_c(t_k) = \frac{K_{Kc}V}{C^0_{H^+}(t_k)+C_{H^+}(t_k)'} \tag{12}$$

The shape of this expression indicates that the sensitivity of C_{H^+} to dosing by alkali depends on the dissimilarity among the concentration of the hydrogen-ion of the alkali stream as compared to the cultivation media. The effective process gain varies with this difference and hence the controller gain is varied. V(t) is used as the effect of dilution and mixing increase with volume: an identical dosing action produced a different effect in a larger volume than is produced in a smaller volume.

The integral time scheduling law is:

$$T_i(t_k) = \frac{K_{Ti}V(t_k)}{F_{pH}(t_k)+F_S(t_k)} \tag{13}$$

This phrase explains the high impact of total inlet flow on the speed of the process. The ratio $V/F_{pH} + F_s$The ratio is analogous to a dominant time constant of the dilution-driven dynamics: the larger the total inflow, the faster the dynamics will change, and the less time the controller integral time should have in order to be responsive. On the other hand, with a small inflow in relative terms to the volume, a slower process is to be expected, and a greater integral time is to be used to prevent excessive aggression of the integral action.

The tuning coefficients K_{kc}, K_{Ti} define the general aggressiveness of the scheduling. These coefficients were picked in this work to fit the reference design and subsequently checked by simulation to offer stable and reasonable closed-loop behavior.

2.6. MATLAB/Simulink Implementation (with Gain-Scheduling)

The Fig 19. Shows full MATLAB/Simulink model of the gain-scheduling adaptive pH control system for the fed-batch microbial cultivation. The process block in the middle represents the nonlinear plant model using the Differential Equation Editor, with biomass, hydrogen-ion concentration and reactor volume as the major state variables. The other MATLAB Function blocks provide the time-varying specific growth-rate profile, substrate feed flow, and hydrogen-ion production coefficient to the process model.

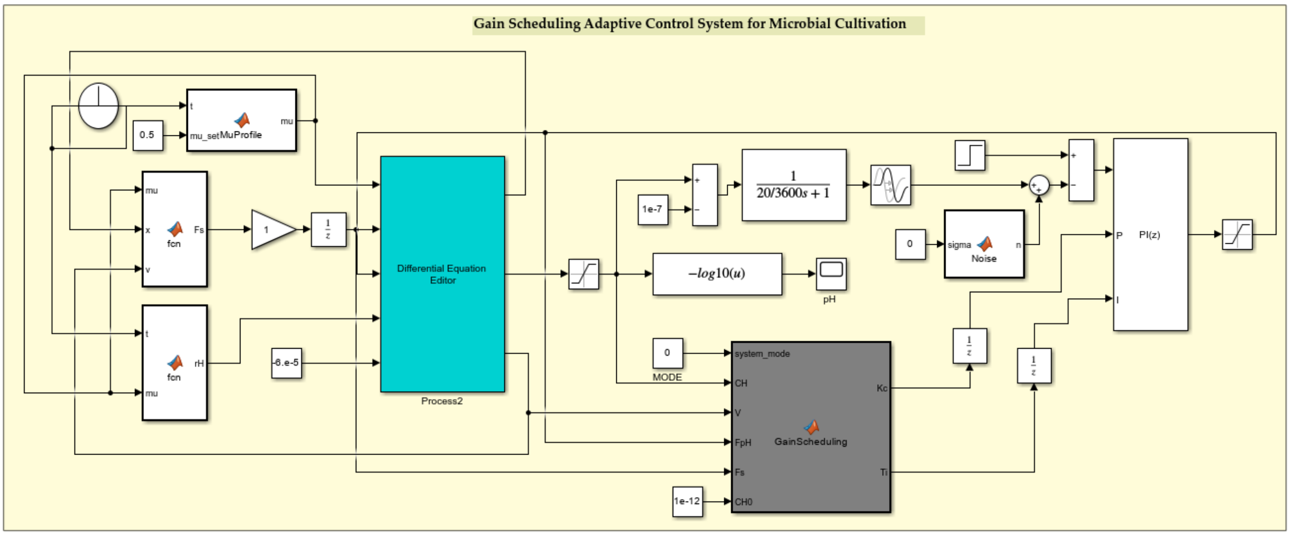

Fig. 19. MATLAB/Simulink model

The plant output is then transformed to pH via the logarithmic definition of pH. In order to model real measurements, the pH signal is filtered through sensor dynamics, delay and Gaussian noise. Then, this noisy signal is used for feedback control.

The controller is a PI block whose proportional gain Kc and integral time Ti are automatically adjusted by the gain-scheduling block. This block adjusts the controller gain and time constant based on the selected process, such as hydrogen-ion concentration, reactor volume, alkali dosing flow, substrate feed flow, and dosing stream hydrogen-ion concentration, and the selected system configuration. This allows the use of the same Simulink model for System A with static PI gains, and Systems B, C and D with different gain-scheduling rules.

3. Investigated Control Systems

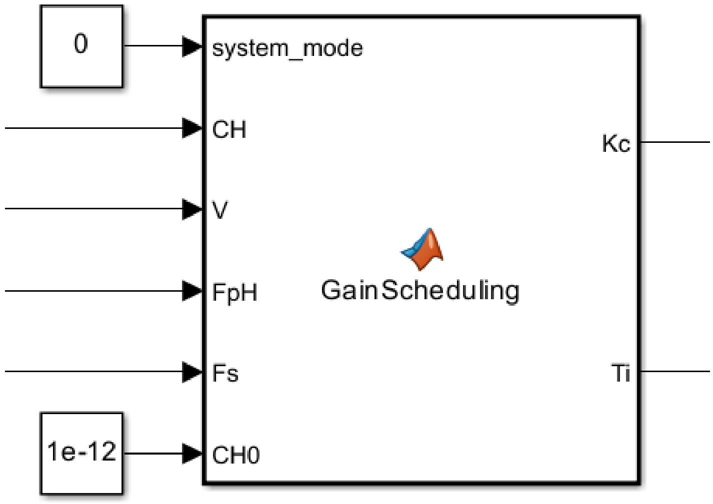

Fig. 20. Simulink Block of gain scheduling

Four control systems were used and compared to determine the impact of various assumptions of instrumentation and schedules structure, Fig.20 shows the Simulink block of gain scheduling. The plant model and PI controller structure are similar in all systems; the only difference is the choice of the controller parameters.

3.1. Control Systems (A–D)

3.1.1. System A: Fixed PI Controller

$$K_c = -2e6\ h/L$$
$$T_i = 10\ h$$

This setup is a reference point of comparison and is a conventional industry PI control. As the plant is time-varying, the performance of System A should vary under different operating conditions, especially when the disturbance occurs or the late part of the batch, when $V(t)$ has grown. Simulink implementation uses System A for system mode 0 and the Gain Scheduling function to produce fixed values of K_c and T_i, result scope of the system shown in Fig.21.

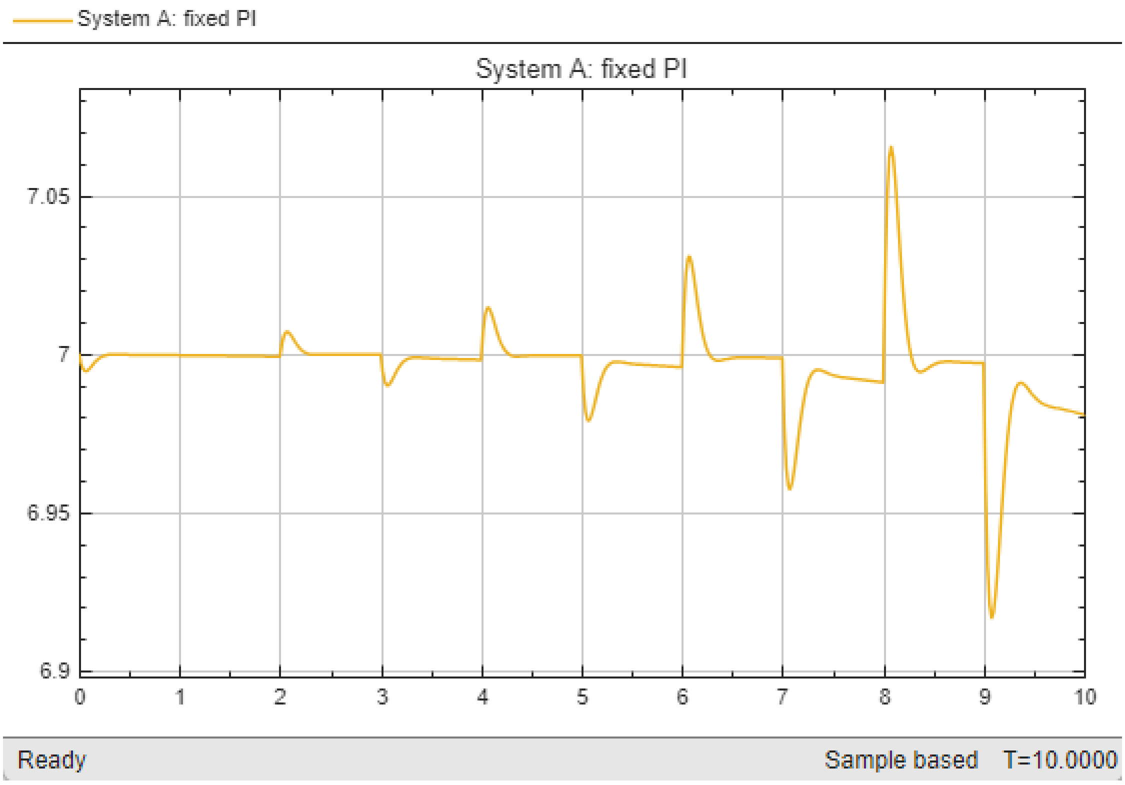

Fig. 21. System A: Fixed PI Controller (X axis - Time(h), Y axis - pH)

3.1.2. System B: Gain Scheduling with Measured V and F_s

System B adopts the full gain scheduling method will suppose that the culture volume V(t) and substrate feeding flow rate $F_s(t)$ can be measured.

$$K_c(t_k) = \frac{K_{Kc}V}{C_{H^+}^0(t_k)+C_{H^+}(t_k)'} \tag{14}$$

$$T_i(t_k) = \frac{K_{Ti}V(t_k)}{F_{pH}(t_k)+F_s(t_k)} \tag{15}$$

This structure is likely to give good performance since it considers the maximum amount of information to adjust parameters to the present process state. System B in the Simulink implementation is associated with system mode 1, and Fig.22. is result of scope gain Scheduling with Measured V and F_s.

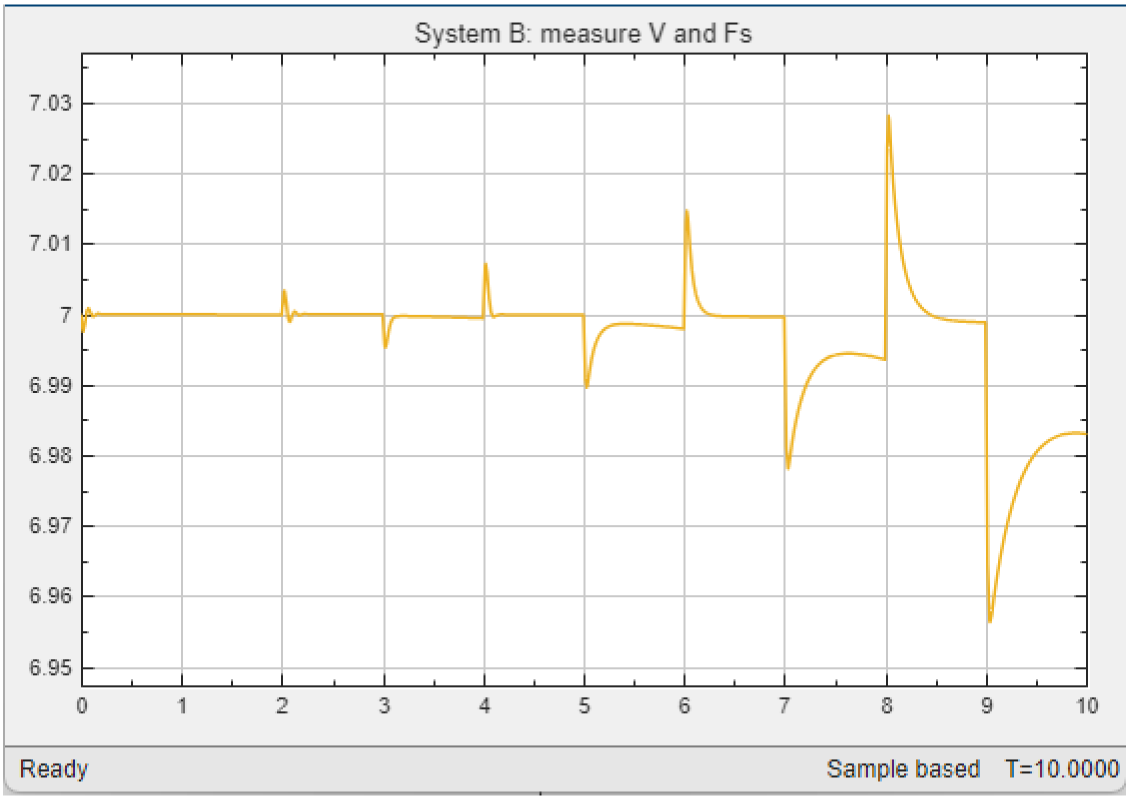

Fig. 22. System B: Gain Scheduling with Measured V and F_s (X axis - Time(h), Y axis - pH)

3.1.3. System C: Gain Scheduling with Measured F_s and V_{avg}

System C can be used to minimize the level of instrumentation by presuming the absence of online volume measurement. Rather, constant average volume is used in scheduling.

$$K_c(t_k) = \frac{K_{Kc}V}{C^0_{H^+}(t_k)+C_{H^+}(t_k)'} \tag{16}$$

$$T_i(t_k) = \frac{K_{Ti}V(t_k)}{F_{pH}(t_k)+F_s(t_k)} \tag{17}$$

The advantage of this method is that it is easy to implement. Nevertheless, due to the increase of volume in the case of fed batch operation, the V_{avg} method also presents a mismatch, potentially leading to worse performance, particularly towards the latter stages of the process. System C in Simulink is associated with system mode 2, result scope of the system shown in Fig.23.

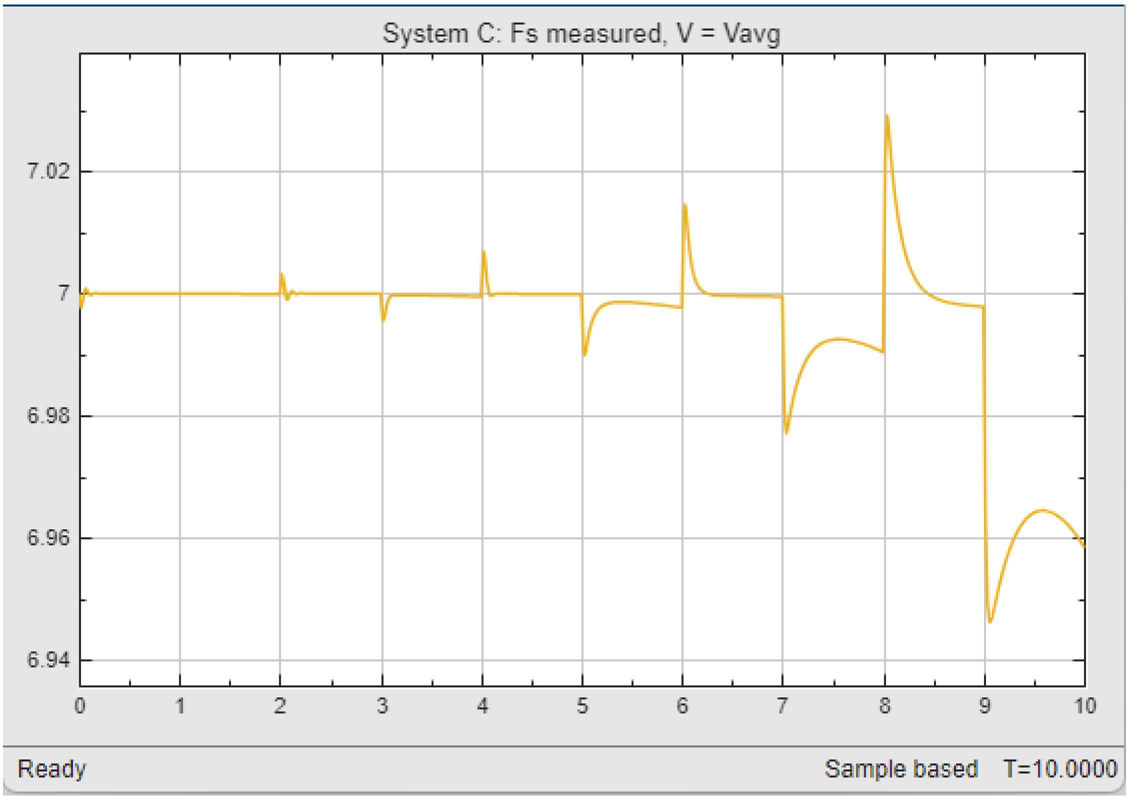

Fig. 23. System C: Gain Scheduling with Measured F_s and V_{avg} (X axis - Time(h), Y axis - pH)

3.1.4. System D: Gain Scheduling with Measured V and Estimated F_s:

System D explores a one in which the feed flow of substrates $F_s(t)$ is not determined online. Rather it is estimated based on a proportional relationship:
Replacement of this estimate into the integral time scheduling law gives

$$F_s = K.F_{pH} \tag{18}$$

$K = 5$, (k is a tuning parameter and is subject to model-based identification), and the attractive system D is the one that is practically used when Fs is inaccessible and F_{pH}, V are measured. But since Ti is directly dependent on F_{pH} System D may be more sensitive in the event of F_{pH} being small or in the case of saturation. Such sensitivity requires numerical protection and flow-sum protection to be used in stable simulation. System D is seen as system mode system mode 3 in Simulink, and Fig.24. shows the result of respective system scope .

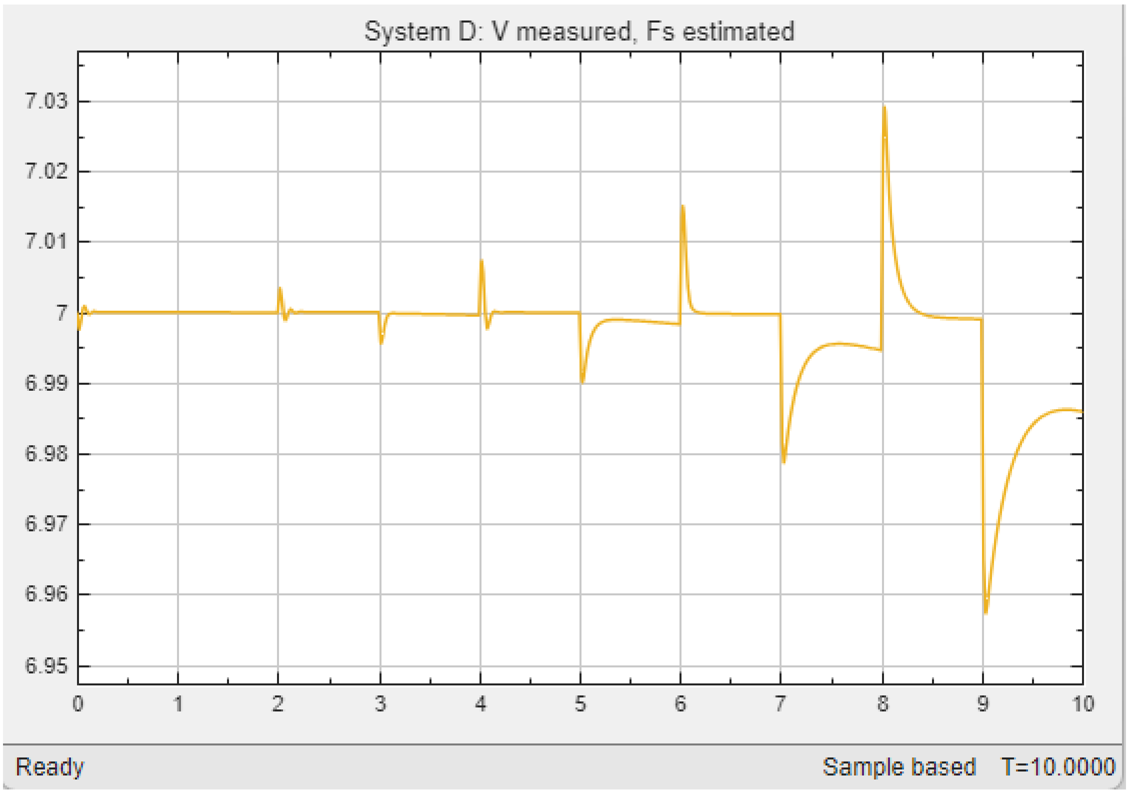

Fig. 24. System D: Gain Scheduling with Measured V and Estimated F_s (X axis - Time(h), Y axis - pH)

3.2. Simulation Results and Performance Comparison

- **System A:** fixed PI controller
- **System B:** gain scheduling with measured V and F_s
- **System C:** gain scheduling with measured Fs and constant V = V_{avg}
- **System D:** gain scheduling with measured V and estimated F_s

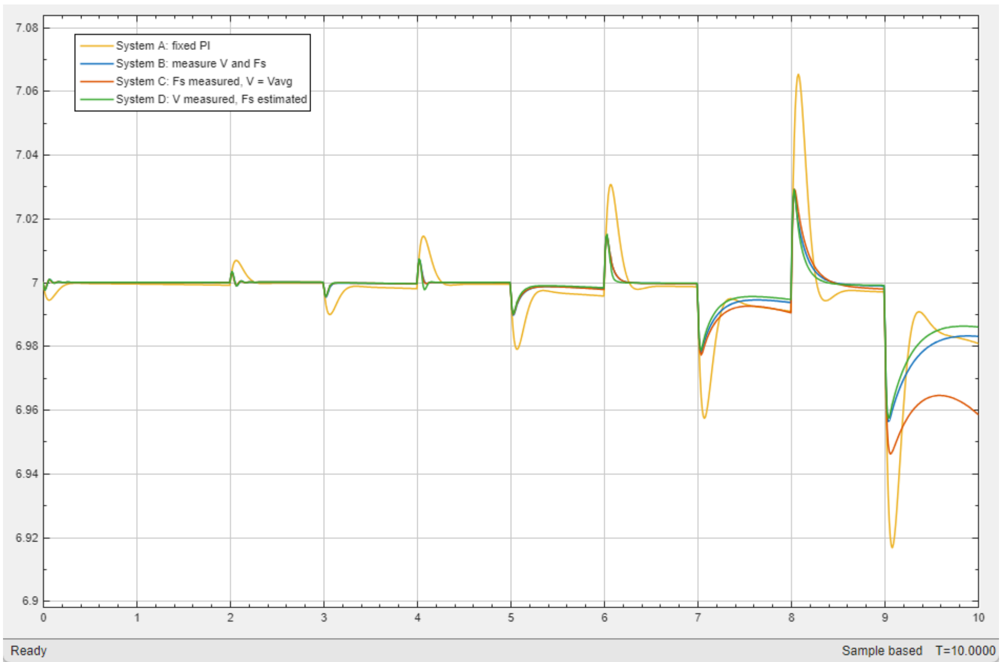

Fig. 25. Comparing all four simulation results (X axis - Time(h), Y axis - pH)

As shown in Fig.25. the simulations were carried out at the same process conditions and disturbance patterns (time-varying growth rate profile), thus, the differences that have been observed can only be ascribed to the control strategy. The plot indicates that adaptive controllers (B - D) keep the pH around the setpoint than the fixed PI (System A), especially in the case of major transients.

An obvious effect of the response is that disturbance creates repeated deviations about the setpoint, both positive and negative. System A tends to have the most deviations and slowest recovery, and the Systems B-D give faster approaches to the setpoint and decreases the size of the deviations.

3.3. The Integral of Absolute Error (IAE)

It was calculated in order to measure the quality of control,
IAE is defined as:

$$IAE = \int_0^T \mid e(t) \mid dt \tag{19}$$

$e(t)$ is the control error,

- IAE total: cumulative error of the entire time of a simulation.
- IAE transients: accumulation of error has been made only within chosen disturbance/transient time windows.
- Overshoot Analysis

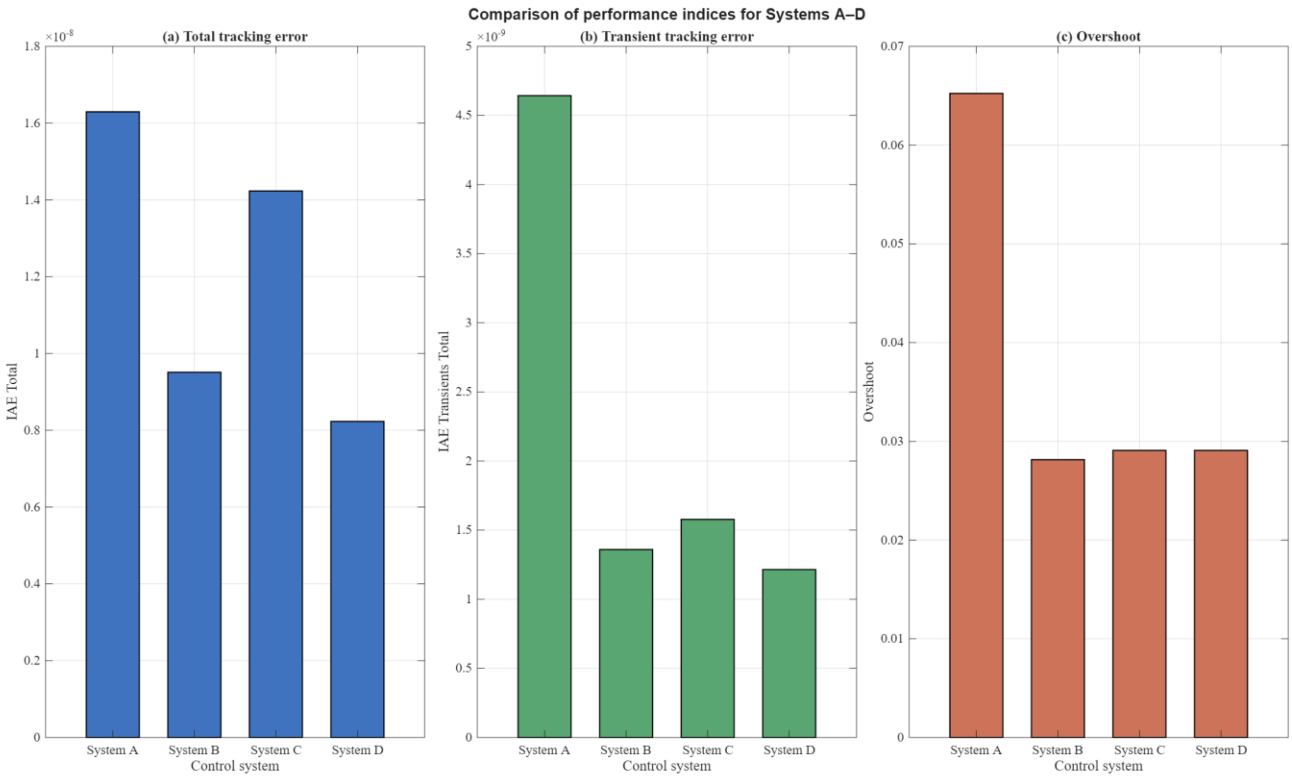

Fig. 26. Simulation Results and Performance Comparison

In the above Fig. 26 shows (a) IAE Total, (b) IAE Transients Total and (c) Overshoot in the nominal case.

Table 7. The Integral of Absolute Error (IAE)

Systems	IAE Total	IAE Transients Total	Overshoot(pH)
A	1.6295×10^{-8}	4.6434×10^{-9}	0.065231
B	9.5111×10^{-9}	1.3596×10^{-9}	0.028137
C	1.4234×10^{-8}	1.5778×10^{-9}	0.029071
D	8.2308×10^{-9}	1.2149×10^{-9}	0.029071

Compared to fixed PI, adaptive control gain scheduling give better result.

- Systems B, C and D minimize the total IAE and transient IAE significantly compared to System A. This proves that the process varies in time significantly enough that scheduling can deliver quantifiable value.

System B gives an optimal over-shoot response

- System B that employs the most complete measurement set (measured V and measured F_s) has the smallest overshoot. This enables better ability to adapt the parameters and prevent over-aggressiveness of the controller in fast dynamics.

In such runs, system D gives the minimum IAE, but is generally sensitive.

- The highest IAE in this dataset is in system D. It can however be sensitive to early times conditions when F_{pH} is small or saturations occur as it estimates F_s using F_{pH}. Thus, although System D may have a high level of performance, stability, and robustness have to be tested during noise and other operating conditions.

In general, according to composite measures, Systems B and D are the most competitive: System B reduces overshoot, whereas System D reduces error area (IAE). System C is better than System A in the conditions that it is tested, although it does not reach B and D because it uses constant Vavg, thereby creating a scheduling problem when the reactor volume is varied.

3.4. Simulation results after adding noise and its performance comparison

The strength of the control systems was also tested by incorporating the Gaussian noise in measurements to the hydrogen-ion concentration signal. Various noise levels were experimented with, and they included low noise, a noise-dominated measurement, and a very noisy measurement.

$\boldsymbol{\sigma_{CH} = 5e^{-10}\ mmol/L}$

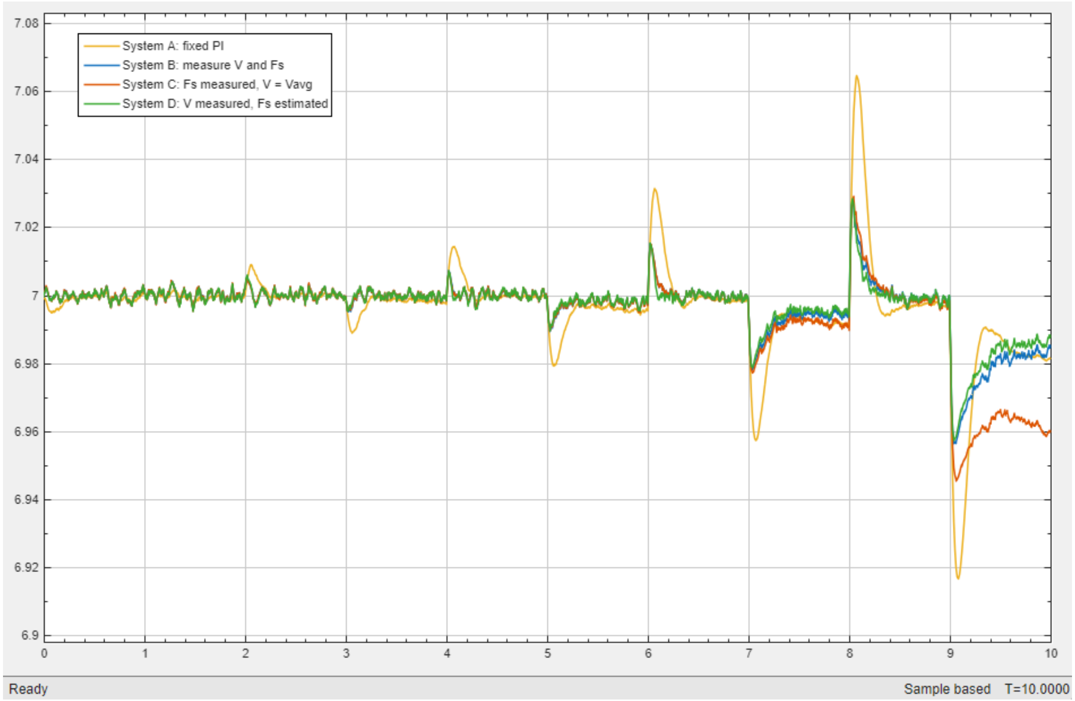

Fig. 27. Added noise at $\sigma_{CH} = 5e^{-10}, mmol/L$ (X axis - Time(h), Y axis - pH)

As shown in Fig.27, $\sigma_{CH} = 5e^{-10}, mmol/L$ at the low noise level, the measured pH signal contains small high-frequency fluctuations. But for System A these fluctuations are not as apparent because the response is dominated by larger transient deviation and overshoot from the setpoint.

At low noise (~0.5% of nominal C_{H^+} ≈10−7mol/L), small high frequency excursions can be observed about the setpoint, but the transient events are still very clear. The gain-scheduled controllers (B -D) provide a closer approach to the desired response compared to the fixed PI (A), suggesting better disturbance rejection and tracking when the sensor noise is light in nature.

$\sigma_{CH} = 1e^{-9}\, mmol/L$

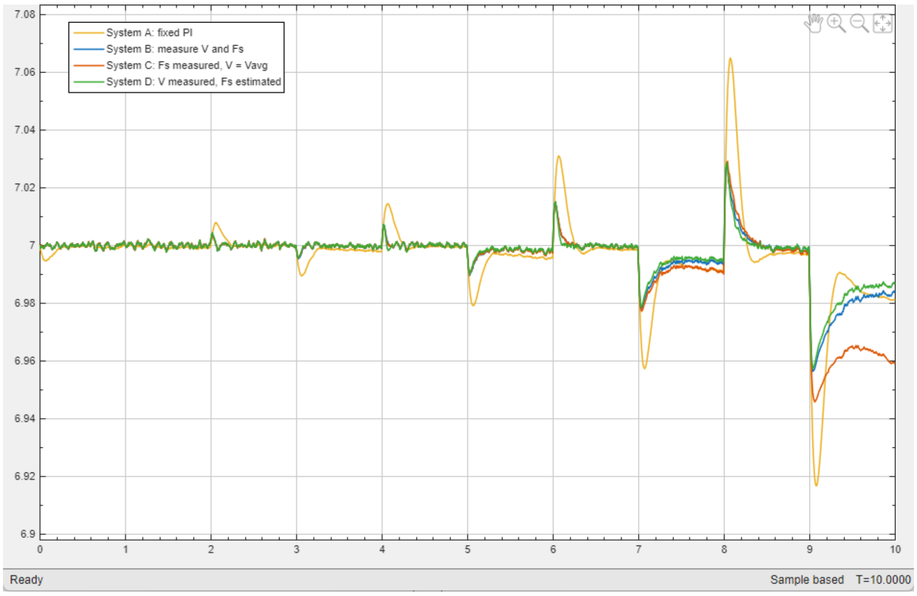

Fig. 28. Added noise at $\sigma_{CH} = 1e^{-9}, mmol/L$ (X axis - Time(h), Y axis - pH)

As shown in the Fig.28. $\sigma CH = 1e^{-9}, mmol/L.$ the noise is added (~1% of nominal C_{H^+}) the signal which is measured becomes visibly erratic, still the closed-loop system is stable. The adaptive strategies remain superior to the fixed PI in the sense that it minimizes the region of deviation and better recoveries following each transient, which is in line with having lower IAE values being reported in Systems B and D.

$\sigma_{CH} = 5e^{-9}\, mmol/L$

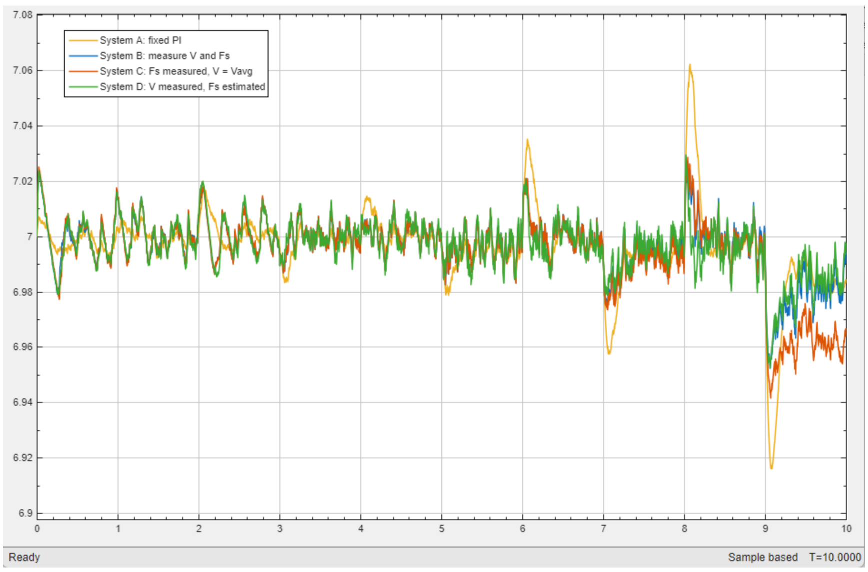

Fig. 29. Added noise at $\sigma_{CH} = 5e^{-9}, mmol/L$ (X axis - Time(h), Y axis - pH)

As shown in the Fig.29. $\sigma_{CH} = 5e^{-9}, mmol/L.$ noise level (~5% of nominal C_{H^+}) generates a highly noisy signal. Consequently, this causes the response to be much-frequency fluctuated and the visual distance between controllers to diminish.

$\boldsymbol{\sigma_{CH} = 1e^{-8} mmol/L}$

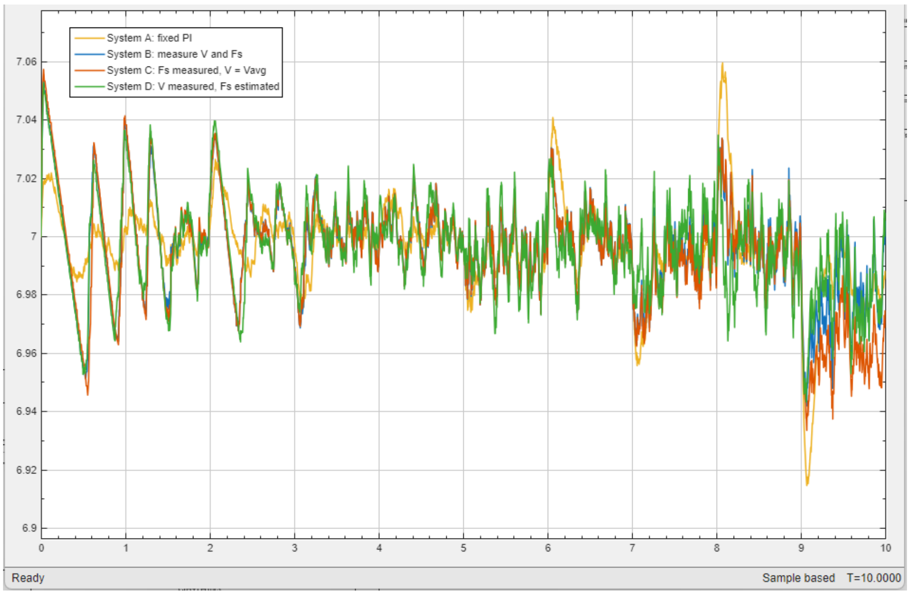

Fig. 30. Added noise at $\sigma_{CH} = 1e^{-8}, mmol/L$ (X axis - Time(h), Y axis - pH)

As shown in the Fig.30.$\sigma_{CH} = 1e^{-8}, mmol/L$. the high noise level (~10% of nominal C_{H^+}), the measured output is noise dominated at this stage. The pH trajectories show significant oscillations around the setpoint and controller variations become hard to discern with the plot only. This is one of the reasons why the IAE values of all systems tend to approach this value.

3.4.1. IAE Total and IAE Transients Total after noise applied

IAE total:

Table 8. IAE Total

σ_{CH}	System A	System B	System C	System D
5×10^{-10}	1.9892e−08	1.4941e−08	1.9550e−08	1.3794e−08
1×10^{-9}	1.7528e−08	1.1895e−08	1.6572e−08	1.0664e−08
5×10^{-9}	4.6373e−08	4.3902e−08	4.7536e−08	4.3419e−08
1×10^{-8}	8.4129e−08	8.4590e−08	8.7216e−08	8.4278e−08

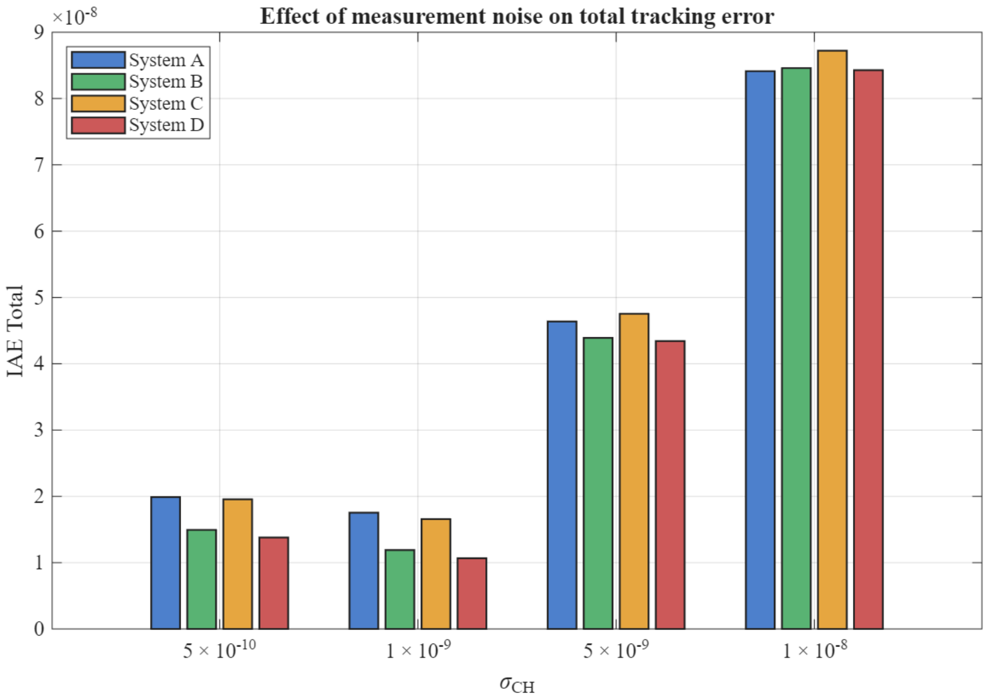

Fig. 31. IAE Total

IAE Transients Total:

Table 9. IAE Transients Total

σ_{CH}	System A	System B	System C	System D
5×10^{-10}	6.3923e−09	4.0135e−09	4.1446e−09	3.8912e−09
1×10^{-9}	5.2649e−09	2.5548e−09	2.7182e−09	2.4058e−09
5×10^{-9}	1.7710e−08	1.6579e−08	1.6619e−08	1.6660e−08
1×10^{-8}	3.3050e−08	3.2664e−08	3.2664e−08	3.2935e−08

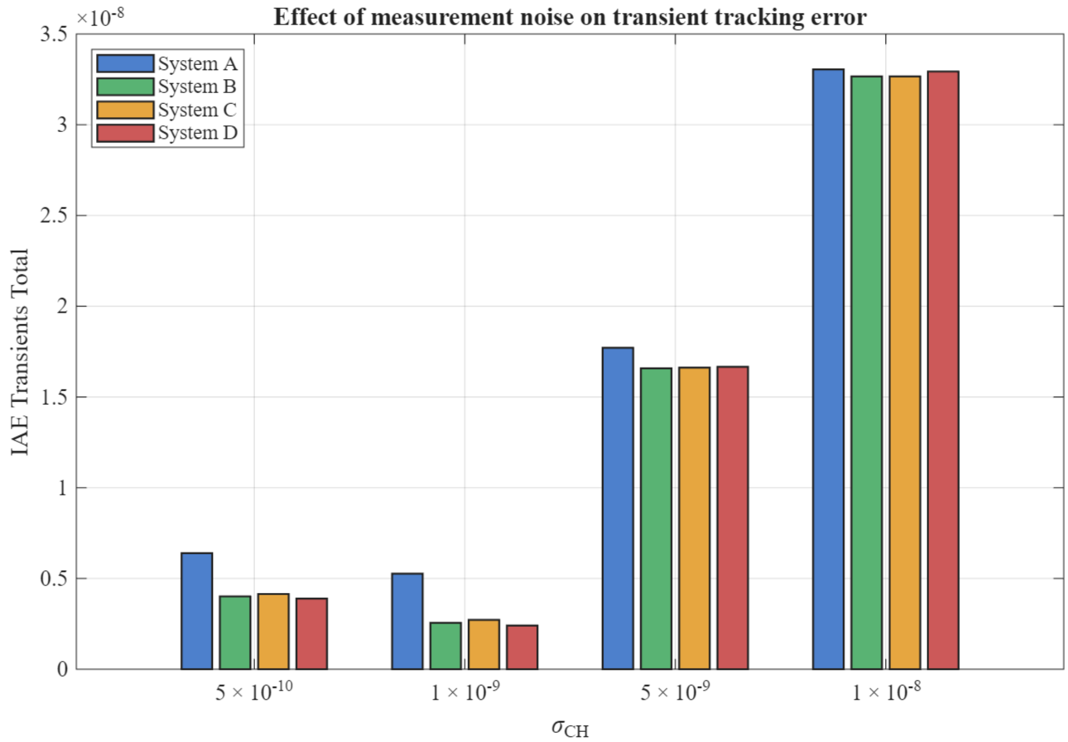

Fig. 32. IAE Transients Total

The Fig. 31-32 and Table 9-10 evidently state that System D performed the lowest overall tracking error (IAE total) with values of $1.3794 \times\ 10^{-8}$, $1.0664 \times\ 10^{-8}$, $4.3419 \times\ 10^{-8}$ respectively over low-to-high noise levels ($\sigma_{CH} = 5 \times\ 10^{-10}$ to $5 \times\ 10^{-9}, mmol/L$.).

System B was always second in the overall of IAE and minimized transient-window error at $\sigma_{CH} = 5 \times\ 10^{-9}$ (IAE transients $=1.6579 \times\ 10^{-8}$,). At $\sigma_{CH} = 1 \times 10^{-8}$, IAE values converged ($8.4 \times\ 10^{-8}$), indicating that the closed-loop response is dominated by noise measurement.

The response plots, which are the visual observations, are confirmed by the IAE results. The gain-scheduled controllers evidently perform much better than the fixed PI controller. Specifically, Systems B and D have the minimum IAE values, indicating that gain scheduling can greatly enhance the quality of control in this time-varying process. System C is also better performing compared to System A, but not as well as the best performing adaptive systems.

Conclusion:

This thesis approached a MATLAB/Simulink model of a fed-batch microbial cultivation process containing pH control using the dynamics of hydrogen-ion concentration, and tested four PI-based control strategies, including System A (fixed PI), System B (gain scheduling of the system with measured V and measured F_s), System C (gain scheduling of the system with measured F_s and constant V_{avg}), and A gain scheduled controller based on the measured reactor volume and estimated substrate feed flow (System D). The performance of the controller was tested by IAE Total, IAE Transients Total and overshoot, and its performance was tested by introducing Gaussian measurement noise to the hydrogen-ion concentration signal.

It is clearly seen that gain scheduled controllers clearly outperform the fixed PI controller in the nominal case, Relative to System A, IAE Total for System B decreased by 41.6% while IAE Total for System D decreased by 49.5%, and IAE Transients Total for System B decreased by 70.7% and IAE Transients Total for System D decreased by 73.8% respectively. Transient response, System B had the least overshoot of 0.028137, corresponding to approximately 56.9% less overshoot than had System A, which had an overshoot of 0.065231.

With measurement noise, the gain scheduled controllers outperformed in tracking at low and moderate noise levels. System D was able to cut down the IAE Total by about 30.7% compared to System A for the case of $\sigma_{CH} = 5\times 10^{-10}, mmol/L$, and by about 39.2% for the case of, $\sigma_{CH} = 1\times 10^{-9}, mmol/L$. Then increase of noise intensity, with the improvement at $\sigma_{CH} = 5\times 10^{-9}, mmol/L$ being approximately 6.4%. At the highest noise level tested $\sigma_{CH} = 1\times 10^{-8}$, the values of the IAE obtained for all controllers are very close, indicating that the closed-loop response at this noise level becomes insensitive to the controller adaptation and is mostly dominated by the measurement noise.

The thesis reveals that gain-scheduled PI control is an appropriate and efficient approach to use during pH regulation of fed-batch microbial culture processes. System D, which offers the best overall tracking performance in terms of IAE both in nominal and low-to-moderate noise conditions, and System B, which offers the best behaviour after following system D.

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