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REVIEWS

Opinion

Mechanistic Fermentation Models for Process Design, Monitoring, and Control

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Mechanistic models require a significant investment of time and resources, but their application to multiple stages of fermentation process development and operation can make this investment highly valuable. This Opinion article discusses how an established fermentation model may be adapted for application to different stages of fermentation process development: planning, process design, monitoring, and control. Although a longer development time is required for such modeling methods in comparison to purely data-based model techniques, the wide range of applications makes them a highly valuable tool for fermentation research and development. In addition, in a research environment, where collaboration is important, developing mechanistic models provides a platform for knowledge sharing and consolidation of existing process understanding.

Trends

The Quality by Design (QbD) and process analytical technology (PAT) initiatives have encouraged the development of more advanced monitoring and control methods.

Modeling is one method of ensuring that there is an understanding of how the critical process parameters affect the critical quality attributes, therefore ensuring the quality of the product.

Mechanistic modeling is proposed as a very flexible modeling tool that may be applied at multiple stages of the process development pathway without significant adaptation of the model.

Mechanistic Fermentation Models Add Value to a Range of Process Development Activities

Mechanistic models (see Glossary) are mathematical descriptions of the current understanding of a dynamic system. For this reason, developing such models requires time, resources, and significant process insight. This model development process can, however, be a very valuable exercise to consolidate existing understanding of the **fermentation** process [1,2] (Box 1). This process understanding may, for example, be in the form of key process parameters such as biomass growth rates, or equations describing mathematically the mass transfer in the system. Owing to the complex nature of the biological systems, some phenomena are not understood to a level of detail that can be modeled accurately using deterministic models, and in these cases empirical relations are often applied (Table 1). The mechanistic fermentation models are therefore often a combination of fundamental first-principles models of the physical processes, combined with empirical models for metabolic rates and growth kinetics. Documenting equations and process parameters in the form of a model is an effective method of knowledge transfer in an industrial or research setting, and also highlights the limitations of process understanding in the areas where empirical relations are applied. Ideally, a mechanistic model will be extended and developed over time as a deeper process understanding is gained, and this procedure ensures that new knowledge is recorded and documented in a practical form which may be shared with others and applied. For an introduction to a simple mechanistic fermentation model, refer to Box 2.

There is increased interest in mechanistic model development for bioprocesses in view of the **quality by design** (QbD) and **process analytical technology** (PAT) guidelines [2–4]. Important trends defined by the QbD framework are the continuous development of process

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Box 1. An Introduction to Fermentation Processes

The term 'fermentation' is used to describe a biological process in which a substrate is converted into a product of interest by a microbial **strain**. The product of interest may, for example, be an alcohol, acid, enzyme, therapeutic protein, or the cell itself. Fermentation processes are advantageous for the production of such molecules, in comparison to chemical processes, because they are generally considered to be more sustainable due to lower temperature processing, lower pressure, and no requirements for harsh chemicals.

The microbial strain used for production may be a bacterial, fungal, or mammalian cell. The strains are often highly optimized, genetically engineered strains, achieving much greater concentrations of product than are achieved in nature. For bacterial and fungal processes, it is most common to operate the process as a fed-batch, as described graphically in Figure I. The process begins with a batch phase with a bulk of substrate and other essential nutrients for the growth of the strain of interest. Key design parameters at this stage are the initial mass and the initial substrate concentrations. When the strain is inoculated into the tank, it will consume the available substrate until there is a limitation, and the biomass concentration will greatly increase. The process can be prolonged by feeding additional substrate into the system. During this fed-batch phase, the mass in the system will increase due to the feed addition. The rate of feed addition may be fixed as shown graphically in Figure I. It is often desirable, however, to design a control system to regulate feed addition to avoid significant over- or underfeeding, both of which are detrimental to the productivity of the process.

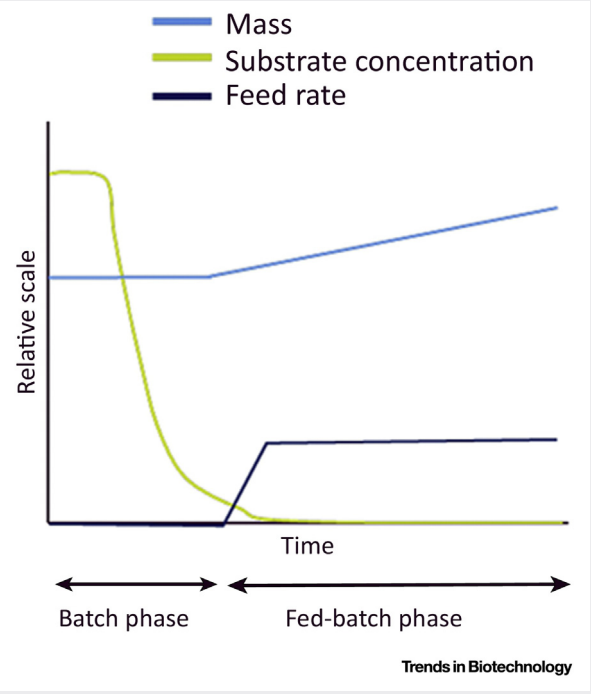

Figure I. Graphical Summary of a Fed-Batch Fermentation Process.

understanding and a better understanding of how process changes affect the **critical process parameters** (CPPs) and therefore the **critical quality attributes** (CQAs) and the product. Modeling methods provide a basis for describing these input–output relations, which may then be consolidated by experimentation. In addition, the PAT guidelines aim for improved monitoring and control capabilities than are traditionally applied in bioprocesses [3,5]. Again, models may improve monitoring capabilities and aid control strategy development.

This Opinion article describes how a mechanistic model may add value across many stages of the fermentation process development pathway, and also provide additional insights when applied to a process online in real time. Applications may be offline, for example, using model simulations to test and define suitable process operating conditions, initial conditions, and

Glossary

Computational fluid dynamics (CFD): the use of fluid mechanics to model fluid flows in complex systems.
Critical process parameters (CPPs): process parameters that are highly influential to the process operation and may affect the critical quality attributes for a given product.
Critical quality attributes (CQAs): measurable process parameters or product characteristics that are used to define that the product is within quality specifications.
Fed-batch process: a process operated as an initial batch, followed by feed addition consisting of substrate and/or nutrients.
Fermentation: a biological process where a substrate is converted into a valuable product by a microbial organism.
Good manufacturing practice (GMP): a regulatory standard to ensure consistent product quality in manufacturing sites by appropriate control, quality measures, and documentation.
Mechanistic model: a model described by first-principles model equations and by defined model parameters that have physical meaning.
Non-linear process: a process that exhibits non-linear process dynamics over time.
Process analytical technology (PAT): methods of utilizing process technology to describe CPPs, and therefore gain understanding and control of the CQAs for a product.
PID controller: a Proportional-Integral-Derivative controller, a type of controller algorithm that is typically used in feedback control systems for set point tracking.
Quality by Design (QbD): FDA guidelines for process development where there is an emphasis on process understanding and the relationships between key process parameters and the final product quality.
Strain: the specific genetic variant of an organism.

Table 1. Summary of the Physical and Biological Model Terms and Their Typical Model Type

Modeled term	Model types	Discussion
Physical model		
Volume or mass balance	Mechanistic	A volume or mass balance can be described mechanistically based on knowledge of the system inputs and outputs, such as substrate addition, acid and base addition, antifoam addition, evaporation, and sample volume removal. It is most common to describe biological systems on a volume basis rather than a mass basis because it is most common to describe states in volume terms (g/L). As discussed by Mears and colleagues, there are benefits to modeling mass, especially in high-density industrial fermentations, because the mass is independent of both the fermentation broth density and the gas holdup [11]. The gas holdup describes the volume of gas in the liquid volume.
Viscosity	Empirical	Empirical models have been developed to describe the viscosity, and this is often proportional to the biomass concentration and power input. Because the fermentation broth is a non-Newtonian fluid, the viscosity of the fermentation broth is dependent on the shear rate in the system, and is therefore termed the apparent viscosity at a given shear rate. Owing to the complexity of modeling the viscosity, it is generally an empirical description which is fitted to observed data, as shown by both Albaek and colleagues and Goldrick and colleagues [7,8,13].
Oxygen mass transfer coefficient (k_La)	Empirical **Computational fluid dynamics** (CFD)	Simple empirical correlations are typically used to describe the oxygen mass transfer coefficient in fermentation processes, assuming a constant k_La across the full volume. The rate of oxygen transfer may, for example, be described in terms of the power input per unit volume, and the viscosity of the broth. The state of the art for modeling the k_La is to apply CFD. With the application of CFD to fermentation systems it is possible to solve for the k_La at different locations in the vessel, as shown by Bach and colleagues [41]. This allows a much more detailed understanding of the physical properties of the fermentation system.
Mixing/fluid flow	Empirical Mechanistic CFD	The mixing may be described simply in terms of the power input into the liquid volume (P/V). This assumes a homogenous fluid and an equal power input to the whole liquid volume. Although this is a simplification, it may be a suitable level of complexity for most model applications. The most advanced approach is to apply CFD to describe the fluid flow in the system in terms of velocity profiles, and show flow patterns for a specific system with a specific impeller type and size. This allows a detailed description of the fluid flow and mixing [41].
Temperature	Mechanistic	Heat generation due to metabolic activity and mixing may be modeled, in addition to the rate of heat loss due to a cooling jacket or coil. Based on this and the fluid properties, a thermal energy balance may be applied to the system.
Biological model		
Biomass growth	Empirical Mechanistic	A commonly applied, simple empirical model to describe growth kinetics is the Monod equation, which is used to describe the growth rate of the organism as a function of the maximum growth rate and substrate concentration. Extended models are also applied to include product or substrate inhibition. One alternative is to use reaction stoichiometry to solve the biomass formation rates [4]. Such models describe the biomass as a single homogeneous entity. Another alternative is to describe the biomass as an inhomogeneous entity, for example, consisting of growing, non-growing, and degenerated cells [7]. This requires a more advanced description of the growth of the cells and differentiation between populations of cells. The level of detail may even increase to describe intracellular metabolism of the cell, and therefore describe the cell also in terms of the intracellular components, such as ATP, NADH, metabolites, etc. This requires a detailed understanding of the metabolic pathways, for example, using metabolic flux analysis models. Gernaey and colleagues give a summary of biological modeling methods [2]. The appropriate level of complexity depends on the model application.
Biomass concentration/ product concentration	Empirical Mechanistic	The solving of the biomass and product concentration is mechanistic; however, it relies on empirically derived fermentation parameters for growth rate and yield coefficients, for example. The solving of the concentration is a mass balance based on rates of formation and volume dynamics.
Oxygen uptake rate (OUR)	Empirical Mechanistic	The OUR is often modeled as the rate of oxygen uptake required for growth and production in addition to a constant term for maintenance, which is proportional to the biomass concentration. The result is a kinetic/empirical model description of the OUR.
Dissolved oxygen concentration (DO)	Empirical Mechanistic	The DO is described mechanistically as the balance between the OUR due to metabolism and the oxygen transfer rate (OTR) from the gas phase. The OTR is dependent on the k_La and the driving force, namely the difference in oxygen concentration between the gas and liquid phases. This description is mechanistic, although some terms involved are defined empirically, for example, the oxygen mass transfer coefficient as previously described. It is therefore considered to be a combination of empirical and mechanistic model terms.

Box 2. A Simple Textbook Example of a Mechanistic Fermentation Process Model

A textbook fermentation model will describe the volume, V, biomass concentration, X, product concentration, P, substrate concentration, S, and dissolved oxygen concentration, DO, in the system. The model comprises differential equations and model parameters.

The basis for a fed-batch fermentation model is a volume balance to account for the changing volume in the system due to feed addition, F. This is the equation in its simplest form, and may also be extended to account for water loss due to evaporation or additional inputs to the system such as antifoam, acid, or base.

$$dV/dt = F \text{ [L/h]} \quad \text{[I]}$$

Biomass formation is described by a specific growth rate, μ. Simple empirical equations are generally applied to describe the growth rate, such as the well-known Monod equation, but a range of descriptions are available [1]. The product formation is often growth-associated, and therefore may be described by a yield of product formation relative to the growth rate of the biomass, y_{PX} [1]. Based on the growth rate of the organism and the yield of substrate consumption on biomass production, y_{XS}, the substrate mass balance may be described, including also a maintenance term, ms, to describe substrate consumption due to maintenance. The concentration of the substrate feed is defined as C_S. All concentrations in the system are balanced by accounting for the changing volume in the fed-batch system, as shown in equations II–IV.

$$dX/dt = \mu X - X/V\ dV/dt \text{ [g/L.h]} \quad \text{[II]}$$

$$dP/dt = \mu.y_{PX}X - P/V\ dV/dt \text{ [g/L.h]} \quad \text{[III]}$$

$$dS/dt = C_S.F/V - (\mu.y_{XS} + ms)X - S/V\ dV/dt \text{ [g/L.h]} \quad \text{[IV]}$$

Biomass formation changes the apparent viscosity, μ_{app}, of the fermentation broth, which is an important consideration for the process dynamics, and should therefore be modeled. This is especially relevant for fungal processes with a high-viscosity broth. Empirical relations are used to relate the viscosity to the biomass concentration:

$$\mu_{app} \propto X^a \quad \text{[V]}$$

The DO is a balance between the oxygen transfer rate (OTR) into the liquid phase and the rate of oxygen consumption (oxygen uptake rate, OUR) by the biomass:

$$dDO/dt = (OTR - OUR)/V - DO/V\ dV/dt \text{ [mol/L.h]} \quad \text{[VI]}$$

This equation is extended to describe the OTR and OUR in the system. The OTR is a function of many system properties, including the temperature, viscosity, oxygen concentration, power input, and media composition. Similarly, the OUR is modeled accounting for the biomass concentration and the rate of feed consumption. Extensive modeling is necessary to describe this physical process successfully.

control strategies. Models may also be applied online for use as monitoring tools or as part of a control algorithm. The model structure may be adapted to suit these different applications, as shown graphically in Figure 1 (Key Figure).

Mechanistic Models for Offline Fermentation Process Development

Offline Process Development

A primary task during fermentation process development is to define the operating conditions (e.g., temperature, pH, headspace pressure, stirrer speed, and aeration rate) leading to the most profitable fermentation process, subject to equipment limitations and safety constraints. This task is often initiated based on a series of laboratory-scale studies, and then scaled-up to a production process that achieves the desired process yields, and is also applicable to the production scale equipment. This scale-up procedure is employed because it is prohibitively expensive to conduct the optimization studies at the final production scale, which can be on the order of 100 m^3 [6,7]. To achieve this scale-up procedure successfully it is important to understand equipment limitations at different scales of operation [6]. Mechanistic fermentation models are applicable at this stage to assess process sensitivity to changes in the process conditions, for example, to assess changes in heat and mass transfer rates at different scales. It is also interesting to assess the effect of different reactor dimensions or technologies, such as impeller types [8]. These studies can be made using mechanistic model simulations because they may be extrapolated outside the conditions used to develop the model. Although many

Key Figure

Suitable Model Structures for Applying Mechanistic Process Models for Process Development and Optimization Activities, Both Offline and Online

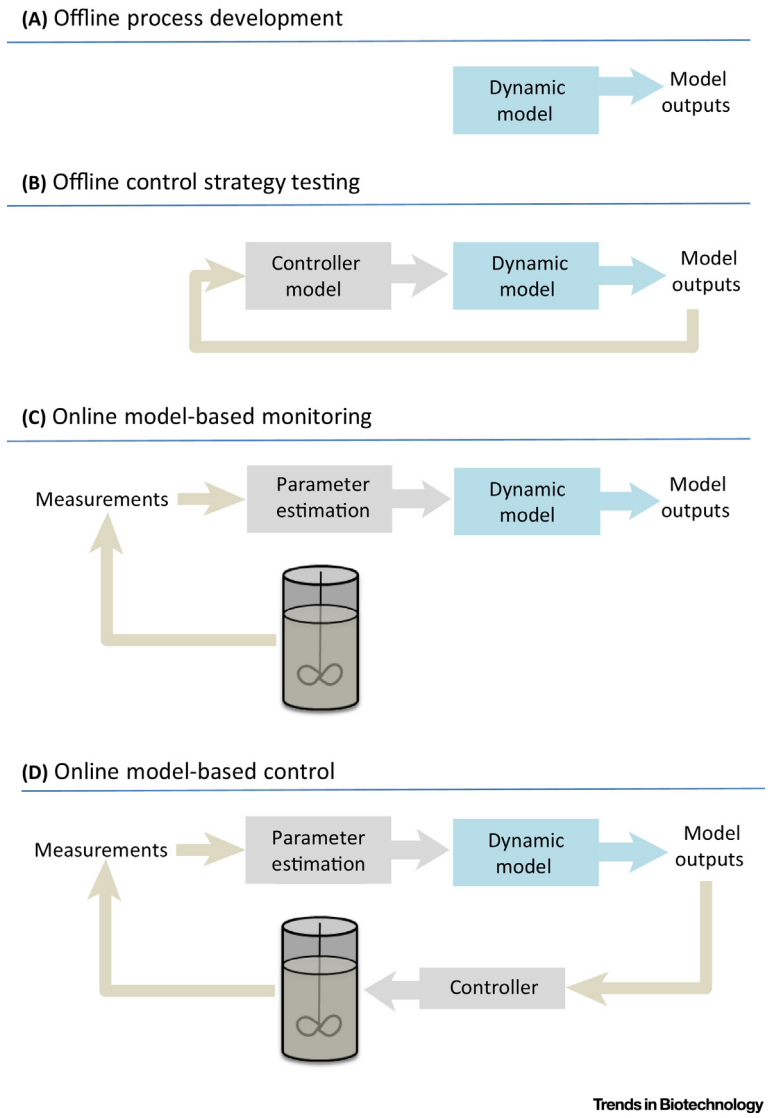

Figure 1. Mechanistic model structures for (A) offline process development, (B) offline control strategy testing, (C) online model-based monitoring, and (D) online model-based control.

model types are suitable for describing the input–output relations of a system, it is only with a mechanistic model that it can be appropriate to test new conditions or new equipment types for which there are no data. It is for this reason that mechanistic models are considered most suitable for this task during process development.

In addition to the process operating conditions, the initial conditions should also be defined for the operation. These initial conditions include the starting mass, the starting substrate concentrations, and the biomass concentration. Industrial fermentation systems are often operated as a **fed-batch process**, which poses specific challenges for planning the start mass and scheduling the process duration. For a given process operation, the starting volume (tank fill) should be defined such that the maximum tank fill is reached in the desired process time to maximize capacity from the production facilities. The batch phase of the process may vary considerably in length because of variations in the lag time, as well as other inherent batch-to-batch variation in initial conditions [9]. It is desirable to always achieve full vessel capacity [10] to maximize the productive volume of each tank in every fermentation run within a given process time. However, owing to variation in the batch phase duration, and other uncertainties in the process operation, the final fill is not always the same for a given start fill.

One variation is the evaporation rate, which depends on the air humidity and temperature, as well as on the process aeration rate and process temperature. There is limited discussion of evaporation rates in relation to fermentation process development. Despite this, the highly aerated industrial vessels are often operated for periods on the order of a week, and may therefore experience large deviations in volume due to water stripping with aeration, and the climate also has an effect on this evaporation rate [11,12]. This potentially results in different volume dynamics for processes operated at different times of the year or at different geographical locations. This is an important consideration for maximizing tank capacity. Models that account for this changing rate can therefore aid process planning [11]. Although other model types may be suitable for describing this evaporation effect, the benefit of using a mechanistic model is that this is then integrated as a part of the full mass balance in the system, and the effect on the process may be investigated because the volume change has an effect on all other process parameters, such as biomass concentration and product concentration.

Another possible application of process models during the process planning stage is to assess process efficiency. As described by Albaek and colleagues, it is possible to utilize a model to investigate the energy efficiency of the process [13] and determine the optimal operating conditions, not only from a biological perspective but also including an economic analysis. Increased stirrer speed and aeration rates will increase the oxygen mass transfer rate for a given process; however, if analyzing the model also from a cost perspective this additional operating cost may outweigh the benefit. Mechanistic process models are therefore also useful as an industrial tool to ensure that the process is economical. This may be achieved by solving the mechanistic model as part of a dynamic optimization procedure to optimize the operating cost (OPEX), subject to constraints.

For offline batch planning and process design applications such as those described, the appropriate model structure is shown in Figure 1A. The model may be adapted for different operating conditions, equipment, process scales, and environmental conditions; the model outputs provide insight that adds value at the process development stage.

Offline Control Strategy Testing

A major benefit of a mechanistic model over a data-driven model is that it is dynamic and predictive, and can describe the **non-linear process** behavior of fermentation systems. For these reasons, mechanistic models are suitable for benchmarking and testing different control strategies. By adding a control algorithm coupled to the dynamic process model, different control strategies can be simulated and tuned before online implementation [12].

Implementing this control algorithm offline allows tuning to be simulated rather than utilizing considerable resources with online testing and tuning. Although fine-tuning may still be required online, this approach will greatly reduce the cost and time of control strategy tuning.

Typical controlled variables for a fermentation process include the temperature, pH, and dissolved oxygen concentration (DO) [14,15]. These are usually controlled using **proportional–integral–derivative (PID) controllers**. For example, the DO may be controlled using the feed rate as manipulated variable [8,16,17], or the air flowrate as the manipulated variable [18–20]. The control algorithm for offline implementation would then be a simple PID control implementation utilizing the dynamic model output of the DO versus a reference DO set-point trajectory to define the manipulated variable in a closed loop, as shown graphically in Figure 1B.

Fermentation process simulations have proved to be useful for testing advanced control strategies [21–25]. To conduct simulation studies there is a need for open source, validated fermentation models which can serve as a benchmark for developing control strategies [26]. To this end, Goldrick and colleagues have developed an industrially relevant production-scale fermentation model in which the process of interest is a 100 000 L penicillin production process utilizing *Penicillium chrysogenum* as the production host [7]. Such open-source code is important for advancing industrial application of advanced control strategies to biological processes, as has been demonstrated in other fields – for example, chemical engineering and environmental engineering [27,28]. These studies are vitally important to test such novel control strategies and to demonstrate the theory so as to encourage online testing. Only with dynamic mechanistic models is it possible to test control strategies in these complex non-linear processes.

Mechanistic Models for Advanced Online Monitoring and Control

Online Model-Based Monitoring

There is a lack of robust, online sensors for key parameters of interest in the field, such as substrate, product and biomass concentration [5,29], owing to challenges specific to the development of inline sensors that are applicable to industrial fermentation systems. These include the need for the probe to be robust to sterilization and to be stable over long process times [15]. There are also issues of regulation and the need to obtain approval for changes made to the hardware used in a process operating under **good manufacturing practice** (GMP) [26]. A practical issue is also the limited number of ports for additional inline probes on the stainless steel vessels.

There is an interest in state estimators that utilize reliable and available online measured variables to predict the unknown states in real-time [30,31]. The application of soft sensors in the fermentation industry is limited despite the advantages of real-time process understanding, and the lack of required investment in additional hardware [31]. Mechanistic models provide one possible solution to this problem, allowing online monitoring of key process parameters that are not known in real-time. Because the model is applied online, measurement data are available which may also be incorporated for improving the model prediction using online parameter estimation. This method has been successfully applied by Mears and colleagues at pilot scale to an industrially relevant filamentous fungus process [11]. In this case, the model structure shown in Figure 1C incorporates online parameter estimation to utilize the available online measurement data and update model parameters that are known to be changing over time, such as the product formation rate and the biomass formation rate [11]. In this case, the method is applied online for 14 validation batches to predict the product concentration, as shown in Figure 2. Such studies show how model-based methods may be applied to provide valuable insights for industrial processes.

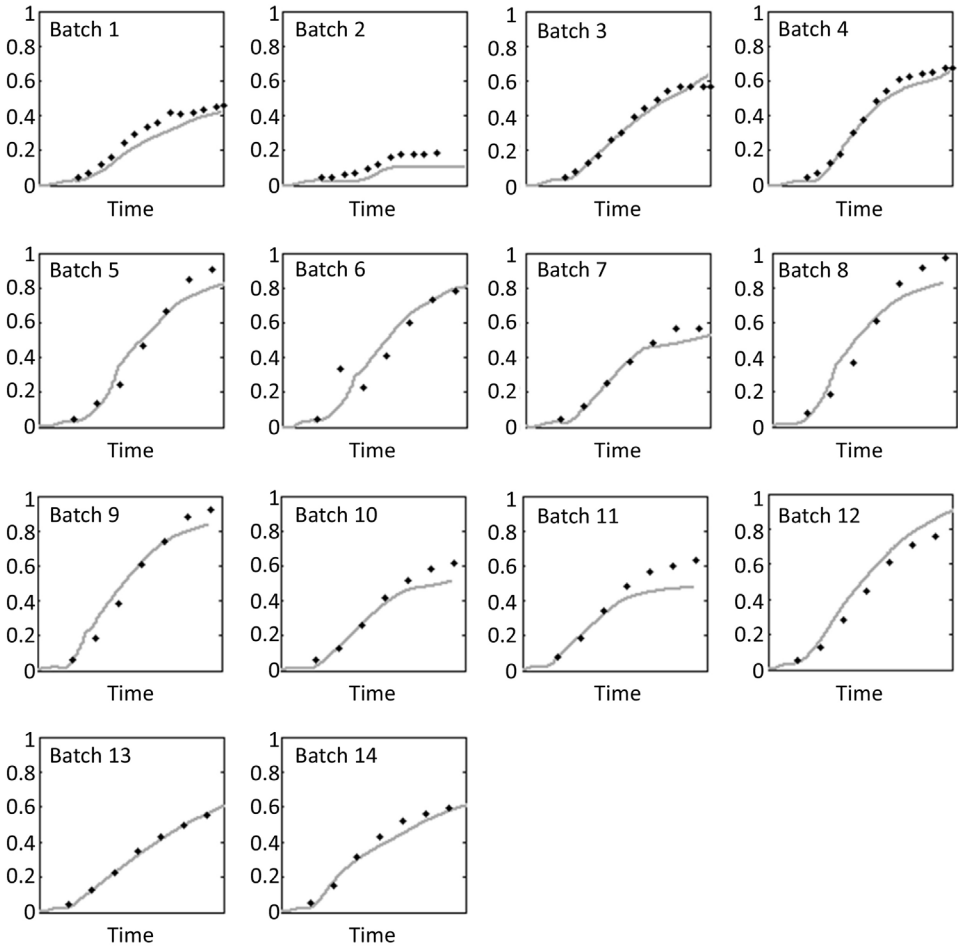

Figure 2. Product Concentration Prediction Using a Mechanistic Model Online at 550 L Scale. Examples of a mechanistic model-based monitoring tool applied to 14 validation batches at the Novozymes A/S fermentation pilot plant at a 550 L scale. The figure shows the product concentration prediction (grey), which is solved online, versus the data obtained from offline sample analysis. Axes are not provided for confidentiality reasons. Image reproduced with permission from [11].

It is often the case that mechanistic fermentation models utilize constant model parameters for yields and formation rates, even though it is widely recognized that these parameters are not constant and instead change over time [32,33]. Parameters in such models may therefore be made adaptive to account for this observed variation in the parameter values. Alternatively the model structure may be adapted to include a more complex description of these terms, for example, describing the biomass in a structured way rather than as a single homogeneous element [26].

Online Model-Based Control

The control problem has been introduced with the perspective of offline control strategy development and testing. These control strategies are not model-based, and the model is applied only for testing the strategy offline. However, it may also be beneficial to apply the model online as part of a control strategy, utilizing the dynamic model output [34].

These model-based control strategies may be beneficial given the multivariate nature of the control problem. Decoupling the control problem into multiple closed loops based on set-point tracking does not consider the full control objective, as can be done with a model-based approach. When applying model-based control, there is complete flexibility in the control objective, for example, glucose concentration control [24], biomass concentration trajectory control [35], avoiding overflow metabolism [25], or maximizing final ethanol concentration [23]. Model-based methods also allow for control based on key process parameters that cannot be measured directly. With the application of mechanistic models, it is possible to use advanced and predictive control strategies which may be used towards a variety of control objectives, and are not limited to set-point tracking only. In addition, model-based solutions are interesting for fermentation systems because these processes are non-linear systems and such dynamics may be accounted for in the model solution.

Model predictive control solutions have been developed recently for bioprocesses [23–25], and it is hoped that this trend may continue in future, with online testing for industrially relevant processes. In Figure 1D, the model structure is shown for a model-based control strategy utilizing available measurement data from the process to update model predictions, and utilizing the model output in a control algorithm. There are many possible structures which may be employed, for example, utilizing an optimization procedure in a predictive model control structure, or directly using the model output for control purposes, as depicted in Figure 1D.

Concluding Remarks and Future Perspectives

There is an increasing drive towards applying more advanced monitoring and control methods for biological processes, and mechanistic models provide one method for implementing this. However, there are still many limitations that hamper the more widespread application of such models (see Outstanding Questions). These mainly concern a lack of understanding of these complex dynamic systems and limited model robustness.

To ensure model robustness, appropriate uncertainty and sensitivity analysis methods should be applied to the mechanistic models before wider application [36]. This is especially relevant for complex non-linear fermentation models because parameter identification can be challenging. Despite this, few fermentation models report confidence intervals for the model parameters. With appropriate sensitivity and uncertainty analysis, it is possible to identify the limitations of the model and understand for what applications the model is considered accurate. With more examples of mechanistic models applied to industrially relevant data, in conjunction with uncertainty and sensitivity analysis studies, the field may move towards more advanced applications of such models for monitoring and control purposes.

Hybrid modeling provides an interesting option for bioprocess modeling because it allows specific areas of the model, for which there is detailed and mechanistic understanding, to be modeled using first principles, and areas for which there is a lack of understanding can be modeled using a data-driven method [37]. This approach is highly suitable for biological systems where the physical process environment is well understood but where there is a poor understanding of the changing metabolic rates in the system. There is increasing interest in this method, and hybrid methods are being applied both as monitoring tools [38,39] and for control applications [40].

This article provides an overview of the applications of mechanistic models in an industrial fermentation environment. It is correct that mechanistic models have the disadvantage of long development time; however, it is our opinion that this is far outweighed by the benefits of a flexible model structure that is applicable for many purposes. A key aspect to consider is that black-box models are not applicable outside the conditions used to develop the model, and are

Outstanding Questions

How to encourage more widespread use of modeling tools, especially for industrial applications? What are the challenges to be addressed for implementing mechanistic models to represent available process knowledge as a standard part of a PAT approach in industry?

How should the research community approach the need for benchmark fermentation models, when different strains and processes are so different? Is it possible to create a toolbox of industrially relevant host strain simulation benchmarks with open source code for each as a standard fermentation process simulation model?

How to put more emphasis on process data collection and data management, such that it can be applied for calibration and validation of mechanistic process models? When validating mechanistic process models, what standard requirements should be set for model uncertainty and sensitivity analyses?

How to apply mechanistic models to support scaling of fermentation processes, and which modeling tools will be necessary to aid a smooth transition between scales?

Why is there limited application of advanced control strategies for fermentation processes, and how to address this issue? Does the challenge lie with a lack of user experience with the methods? Cost of implementation? Regulatory issues? Software issues? How to address such concerns to encourage wider acceptance of such methods?

Because industrial data typically are not made available for reasons of confidentiality, how to address in a satisfactory way the need for data for model calibration/validation to fully demonstrate the potential of mathematical models? Is there a need to define a few standard fermentation systems with industrially relevant strains that can be made publicly available?

therefore of limited use for process development compared to mechanistic models. Applying black-box models to multiple processes requires different datasets which are used to develop different models. Mechanistic models may be applied to multiple processes by changing the model parameters. Mechanistic models can be used to explore operational spaces using simulation, that may then be further tested by performing experiments. In addition, for testing control strategies offline, it is important that the non-linear process dynamics are described, and therefore mechanistic models are required. For these reasons, it is considered that mechanistic models are of particular value for process development studies and control strategy testing, which are offline tasks. However, it is likely, with successful application of such models offline, that more advanced online testing will also start to be employed more widely. Given the range of possible applications, mechanistic models provide value, and in a research environment, where collaboration is important, developing mechanistic models provides a platform for knowledge sharing and consolidation of existing understanding.

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