Process Simulation and Modeling for Industrial Bioprocessing:

Tools and Techniques

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Maximizing profits by operating the most efficient process is the primary goal of all industrial bioprocessing operations. To help create efficient operations companies use process simulation, which is the application of a range of software tools to analyze complete processes, not just single unit operations. Process engineers and scientists use simulation models to investigate complex and integrated biochemical operations, without the need for extensive experimentation.

Simulation tools can be used at any stage of process development, from initial concept, through design, to final plant operation. These tools tackle a range of tasks, including creating process flow diagrams, generating material and energy balances, determining equipment sizing, and estimating capital and operating costs. Although the application of bioprocess simulation is not yet widespread, large-scale bioprocesses have been studied for many years and their viability and usefulness is well established in some areas. For example, NREL (National Renewable Energy Laboratories, Denver, CO) has been developing comprehensive process models to study different processes for conversion of biomass to ethanol for over 15 years (Wooley et. al., 1999).

A recent development in bioprocess modeling is the use of computational fluid dynamics (CFD). Commercial software packages, such as FLUENT (Fluent Inc.; Lebanon, New Hampshire), and Star-CD (CD-Adapco; New York, NewYork) can model mixing effects by incorporating physical properties of fluids and aeration patterns, together with detailed information of vessel internals, such as impeller geometry and baffle location. CFD programs compute the velocity profiles within the fluid to model gas dispersion, calculate residence time distributions, and visualize the mixing process. Results from these models highlight such phenomena as areas of poor mixing or areas of high fluid shear.

The recent interest in CFD can be attributed to two reasons. First, computationally intensive CFD models are more readily accessible as they now run on inexpensive workstations and even laptops. Secondly, companies are operating at larger scales where flow phenomena such as degree of mixing are more important.

Modeling Individual Unit Operations

Performance of a process is sometimes highly dependent on the operation of a few key unit operations. If the design and performance characteristics of these units can be described by a mathematical representation then potential problems can be investigated in silico, reducing the need for expensive experimentation. Popular tools for writing such models include Excel (Microsoft); MATLAB, (Mathworks, Natick, Massachusetts) and MathCAD (Mathsoft, Cambridge, Massachusetts). Mathematical models can also be written in native software languages (Fortran, C++, etc) , but there is the issue of maintaining and documenting these approaches, which makes it more convenient to use a commercial software package.

In addition to the generic mathematical packages mentioned above, MATLAB, and MathCAD, there are more targeted process simulation tools. Simulation packages usually contain a library of common unit operation models but also support development of customized models. Examples of commercial software that support this development are Aspen Engineering Suite (Aspen Technology; Cambridge, Massachusetts) and gPROMS (PSE; London, UK). Both packages have the ability to solve complex systems of differential and algebraic equations and can be used for complete flowsheet simulations or for rigorous modeling single unit operations.

The level of detail in any model depends on the questions posed. Typically you start from a simple model and add layers of complexity until the model meets its requirements. Models start from simple mass balances and progress to very detailed models (*Table 1*).

Table 1. Commercial software packages for modeling single unit operations.

	Excel	MATLAB MathCAD	Aspen	gPROMS	FLUENT (CFD)
Mass balance	✔				
Mass and heat balance	✔				
Detailed description	✔	✔	✔	✔	
Rate-based models		✔	✔	✔	
CFD plus rate-based models.			✔	✔	✔

The increased complexity of modeling approaches is described here by using an example of modeling a crystallizer.

<u>Simple mass balance</u>
The question posed is: In the simplest case, describe the crystallization process as a mass conversion or reaction;

Product - > Crystal Product

The ‘reaction’ is mass based, with a percentage reaction extent used to determine the formation of crystals. If the reaction extent were 40%, then every 100kg product would produce 40kg crystals. This approach ensures that a consistent material balance is generated. Any stream entering and leaving the operation is identified, with a list of all the components in the process. This level of detail is insufficient when considering a single unit operation but is perfectly acceptable when describing a flowsheet, as described below, and is a starting point for any model.

Mass and heat balance

Typically the crystallizer will be evaporating solvent to produce a supersaturated solution of Product. Assume that 10kg of water is evaporated for every kg of crystal formed.
In addition to the heat of vaporization of the solvent, there is the heat of crystallization. Both these properties are included as heat sinks. In reality, heat is also required to increase the temperature of the liquor to boiling point, and a more comprehensive heat balance would be covered in a detailed model description.

Heat requirement :

10 x 40(kg) x Latent Ht (kcal/kg) + 40(kg) x Heat of Crystalln (kcal/kg)

This level of detail ensures a consistent material balance together with a heat balance sufficient to provide an overall estimate of energy consumption. As with the simple material balance the reason to include a simple heat balance, is to observe the impact of multiple operations in a flowsheet.

Detailed Description

A comprehensive model of a crystallizer includes a complete heat balance, together with a complete mass balance. The model should also include more specific details of the crystallization process; the mode of operation (batch or continuous), the number of units, the method of operation, heat exchange areas, condenser efficiencies, etc. A model of sufficient detail can be used for the design of individual units or for determination of operating performance.

Rate based model

One reason to increase the level of model complexity for a crystallizer model is to study factors affecting the particle size distribution (PSD). Including the amount of seed, the rates of nucleation, crystal growth, and crystal breakage allows for the calculation of the complete PSD as a function of time. Controlling the PSD improves product quality, which directly affects product cost, which further explains the increasing interest in this type of approach.

CFD coupled with rate-based model.

Coupling a rate-based model with a CFD representation of the crystallizer makes it possible to test different impeller designs and different vessel geometries to optimize the process, including controlling the PSD. As a large crystallizer is not completely homogeneous and well mixed, it is possible to divide the crystallizer into regions to better define the actual operation. An example of this approach couples gPROMS together with

FLUENT to create a hybrid multizonal approach. These models provide an accurate method of modeling the effects of non-ideal mixing by representing the volume as a network of well-mixed zones.

Linking Unit Operations: Flowsheet Simulation

Linking unit operations together creates a flowsheet, or process flow diagram (PFD). While it is possible to model flowsheets with Excel, when the flowsheet consists of more than a few operations, using a purpose-built flowsheet simulation package is the only effective solution to represent the flowsheet and solve the resulting equations.

Simulation packages cover a range of complexity and price. Using a high powered, expensive simulator is not a cost effective solution if the only task is to develop a simple material balance. *Table 2* summarizes the conditions to which various commercial simulators are best suited.

Table 2 Commercial software packages for flowsheet simulation

	Excel	Extend	SuperPro	Aspen	gPROMS
Mass balance	✔		✔		
Mass and heat balance	✔		✔	✔	
Batch – discrete event		✔	✔	✔	
Continuous			✔	✔	✔
Dynamic				✔	✔

Batch Processing.
Most bioprocess simulation is targeted at batch processing since most bioprocesses are batch operations. There are generic software packages for solving these procedural or batch process problems, such as Extend (Imagine That; San Jose, California). Extend is a discrete event modeling environment that can be customized for bioprocess applications and is the basis for some proprietary solutions.

SuperProDesigner (Intelligen; Scott's Plain, New Jersey) combines drawing, calculation and scheduling features in a moderately priced package. While this simulator can be used to study both batch and continuous processes it is particularly well suited to batch bioprocesses.

Aspen Technology offers a more expensive range of products. For bioprocessing, the principal product is Batch Plus, a recipe-driven modeling environment for batch processes. PSE offers Model Builder, which is another environment for modeling batch operations.

Continuous Processes

Large volume processes, such as the production of ethanol from corn, require the ability to model both batch and continuous processes. For continuous processes, it is possible to use the conventional Aspen Plus simulator but this requires customization for many bioprocess operations. gPROMS is a moderately expensive package that offers a library of commonly used operations, but this also requires customization for bioprocess applications.

Dynamic Simulation

For batch processes, the productivity focus is the overall throughput and time-averaging the operations is usually adequate. Typically process parameters include the duration of an operation and the mass of the reactants and products. For a continuous operation, the overall process is studied as operating at a steady state condition. However, if more information is needed such as the study of process transients, or upset conditions, then dynamic simulation is used. Dynamic simulation is the study of process variations with time. Dynamic simulations are much more complex to construct and run and require considerable expertise, but can yield insights that are not available by other methods, making the investment worthwhile.

A Flowsheeting Application Example: Water consumption

Flowsheet simulation can be used to tackle a wide range of process problems, but here is an example of some specific issues.

All bioprocessing operations consume significant quantities of water both as part of the process and for cleaning purposes, such as with clean-in-place (CIP) systems. Many operations use several different qualities of water such as USP, WFI, and steam for sterilization, all of which require varying degrees of processing. The general approach today is to reduce, recycle, and reuse as much water as possible.

Scheduling issues

For CIP systems, a single skid is often required to clean multiple pieces of equipment. If the skid can clean only one piece of equipment at a time, then scheduling conflicts will arise. If all the CIP skid activities are modeled in a flowsheet then any conflicts are easily seen, and can be resolved.

Resource consumption

It is important to size the water systems to ensure that multiple uses will not completely drain the system. By modeling all operations the schedule of water use can be calculated. The model can determine if more capacity is required or if modifying the times of certain operations can alleviate spikes in water consumption.

Waste generation/recycling

Any final product will contain little water; therefore most of the water used in the process requires disposal or treatment. If the water streams contain significant amounts of bioburden, then this contributes to a high BOD (biological oxygen demand) value for the stream and is a pollution hazard. Design of on-site treatment plants may be required. Additionally, it may be desirable to segregate water waste streams and recycle the cleaner streams with minimal purification. Simulation models can compare the impact of each scenario to determine the most cost-effective solution.

Summary

Most mathematical modeling involves obtaining data from many sources. To optimize a facility requires inputs from many groups, and experience is needed to find the right data as well as manipulating the software package.

Considerable effort is required for the initial generation and validation of any model. Once built, the model can be used to study process variations, the effect of feedstock variations, the effect of key process parameters, and other what-if scenarios.

For more complex problems, a single software tool may be insufficient. In these instances, it is the interoperability of software that creates a powerful tool. An interface specifically developed for process engineering software, CAPE-OPEN, provides a solution to readily link software packages; for example, a custom unit operation model developed in gPROMS can be inserted into an Aspen Plus flowsheet.

Simulation is best applied to tackle complex problems where solutions are not obvious and where the investment is justifiable. A model of a chromatography skid can help troubleshoot problems ranging from poor separation performance to issues of buffer preparation. From a design standpoint, not needing to add a new major fermentation production line with support systems/facilities can result in huge savings (US$20 to $50 million per line). In operations, reassigning existing CIP skids to avoid purchasing a new skid also results in significant savings. For batch operations it is easy to optimize a single batch, but to maximize productivity for multiple batches usually requires simulation.

Table 3 highlights the areas where different flowsheet simulation approaches are used.

Table 3. Flowsheet simulation – level of detail and applicability

Simple mass balance	**Detailed simulation**	**Dynamic simulation**
Conceptual design	Equipment design	Effect of process upsets
Process economics	Process configurations	Emission profiles
Waste stream management	Heat integration	Start up / shut down
Resource utilization	Debottlenecking	Process control options
Labor requirements	Process optimization	Operator training

Conclusion

Simulation can be used at many levels, from simple mass balances for process audits, to complex descriptions of specific operations. There is now a range of tools available for process simulation. Selecting the appropriate tool depends on the level of detail required for the model and the questions being answered.

Modeling complete flowsheets requires purpose-built software. Simulation can be used to tackle many problems, from initial design and proof-of-concept studies through operation and validation. It is now possible to link powerful software packages together to create unique solutions.

Although a range of software tools exists, customization is usually required for tackling bioprocesses. There is room for improvement here to develop more precise models. Development of these tools is an ongoing process. However, the current tools are sufficient to tackle real-world problems and, as cost pressures increase on biomanufacturers, there will be increased use of these tools to help reduce costs and streamline operations.

References

Wooley, R., Ruth, M.,Glassner, D., Sheehan, J., “Process design and costing of bioethanol technology: A tool for determining the status and direction of research and development:, Biotechnol. Progress Vol 15, 1999, pp794-803