

“BEST”: Biochemical Engineering Simulation Technology



National Renewable Energy Laboratory
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Golden, Colorado 80401-3393
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Table of Contents

	Page
Abstract	1
Introduction	2
Origins of BEST	3
Description of the BEST Simulator	4
Kinetics	4
Reactors	4
Details of the BEST Models and Methods	5
Biochemical Kinetics	5
Other Factors Associated with Growth Rate	7
Product Formation Rate Expression	8
Substrate Consumption Rate Expressions	8
Batch and Fed-Batch Fermentation Reactor Model	9
Continuous Stirred Tank Reactor Model	10
Reactor Geometry and Aeration and Heat Transfer Calculations	10
Oxygen Transfer and Agitator Power	11
Reactor Heat Transfer	12
For the Jacket	12
ASPEN/SP-BEST Examples	14
Summary	16
AspenTech's Bioprocess Simulator (BPS)	16
ASPEN PLUS BPS Overview	16
CSTERILE—Continuous Sterilizer	17
BFERM—Batch and Fed-Batch Fermentor	17
CFERM—Continuous Fermentor	17
Comparison of ASPEN/SP-BEST and the ASPEN PLUS BPS Systems	17
Other Models	19
Summary of ASPEN/SP-BEST and ASPEN PLUS BPS Comparison	20
References	20

BEST

Biochemical Engineering Simulation Technology

Abstract

The idea of developing a process simulator that can describe biochemical engineering (a relatively new technology area) was formulated at the National Renewable Energy Laboratory (NREL) during the late 1980s. The initial plan was to build a consortium of industrial and U.S. Department of Energy (DOE) partners to enhance a commercial simulator with biochemical unit operations. DOE supported this effort; however, before the consortium was established, the process simulator industry changed considerably.

Work on the first phase of implementing various fermentation reactors into the chemical process simulator, ASPEN/SP-BEST, is complete. This report will focus on those developments. Simulation Sciences, Inc. (SimSci) no longer supports ASPEN/SP, and Aspen Technology, Inc. (AspenTech) has developed an add-on to its ASPEN PLUS (also called BioProcess Simulator [BPS]). This report will also explain the similarities and differences between BEST and BPS.

ASPEN, developed by the Massachusetts Institute of Technology for DOE in the late 1970s, is still the state-of-the-art chemical process simulator. It was selected as the only simulator with the potential to be easily expanded into the biochemical area. ASPEN/SP, commercially sold by SimSci, was selected for the BEST work. SimSci completed work on batch, fed-batch, and continuous fermentation reactors in 1993, just as it announced it would no longer commercially support the complete ASPEN/SP product. BEST was left without a basic support program. Luckily, during this same time frame, AspenTech was developing a biochemical simulator with its version of ASPEN (ASPEN PLUS), which incorporates most BEST concepts.

The future of BEST will involve developing physical property data and models appropriate to biochemical systems that are necessary for good biochemical process design.

Introduction

Chemical unit operations have long been simulated to design and optimize process operations. They started as simple models of unit operations (using many assumptions and simplifications to ease the calculation) that could be solved by hand or with mechanical calculators, and evolved into very sophisticated and rigorous models that could only be solved by modern computers. The importance of computers in this scheme is that simplifying assumptions are no longer needed to ease the computations. Also, computers solve the unit operations, so connecting many operations together (complete with recycles), and having the computer repeat the calculations until the recycles are balanced, is easy. Thus was born the modern sequential modular process simulator for whole flowsheets.

The modern process simulators were first developed commercially for oil and gas processing by companies such as Simulation Sciences, Inc. (SimSci), and ChemShare. There were also some early developments, such as PACER at the University of Pennsylvania and FlowTran at the University of Missouri and Monsanto, that were available noncommercially. The problem with these early simulators was that they were not flexible enough in their thermodynamic property calculations or in their ability to add new unit operations. In addition, none handled solids in process streams—an important requirement in the chemicals industry, but less important in the oil and gas industries.

To address the need for a process simulator that would allow the new alternative energy developments (primarily gas and oil from coal and oil shale) to be developed and optimized, the U.S. Department of Energy (DOE) invested in the development of a new generation of process simulator. This development, managed by the Massachusetts Institute of Technology (MIT) was named Advanced Simulator for Process Engineering, or ASPEN. This project was cost shared by many important chemical companies and resulted in a publicly available simulator. The cost of the project, about \$6 million, was primarily paid by DOE and was completed in 1981.

The ASPEN process simulator met many of the chemical industry's needs. It could model solids, both conventional (with a known chemical formula) and nonconventional (e.g., coal, which is not definable by a chemical formula, but which can be described by various attributes). ASPEN was built with a flexible structure that allowed the user to easily add new unit operations or physical property models. This flexibility was in addition to a very solid foundation of state-of-the-art unit operation models (e.g., a new concept, the inside-out calculation, was used to efficiently solve diverse distillation problems, a multiphase Gibbs Free Energy minimization reactor model was included), and a comprehensive set of thermodynamic and transport property models. In addition, to be able to add new physical property models, an easy method to select various models to be used for various properties was included, as was the ability to use different property models in different areas of the flowsheet. As an example, Peng-Robinson equation of state could be used for the chemical portions of the flowsheet, and the ASTM steam tables for a boiler in the process. There was also an extensive database of chemical properties and the ability to easily regress new data to the models used by ASPEN. This regression system was a modern, generalized, least-squares method that could simultaneously regress multiple properties with individually specified errors.

All in all, the ASPEN process simulator was state-of-the-art and could be expanded to new requirements as chemical engineering modeling knowledge increased. One area not included in the original development was biochemical operations. Biochemical process engineering has evolved from specialty, high-priced, low-volume chemicals to much larger-volume, nearly

commodity chemicals. With this new emphasis on building larger processing plants for biochemicals with lower prices (e.g., ethanol for fuel must compete with very low-priced gasoline) there is a need to design processes with optimized use of resources and utilities and minimized waste. This demands a rigorous process simulator, with the capabilities to simulate this new technology.

Origins of BEST

The National Renewable Energy Laboratory (NREL) was the focal point of a government/industry collaboration to develop, commercialize, and improve bioprocesses for producing fuels, chemicals, and other products, and for such applications as waste treatment and closed life-support systems. The parties to this collaboration recognized a growing need to—

- Screen alternate bioprocess configurations and focus bioprocess R&D
- Evaluate new developments in biotechnology
- Evaluate the progress of bioprocess R&D
- Conduct bioprocess pilot plant work
- Assess the economic feasibility of proposed bioprocess facilities
- Develop quality designs for bioprocess plants
- Optimize bioprocess operations
- Assess and correct operating problems
- Determine the impact of modifications to bioprocess operations and facilities.

They further recognized that process simulation would greatly enhance the efficiency and quality of all the above activities, and that a process simulator that can use biotechnology to produce high-volume, low-value fuels and chemicals was not available.

To meet this need, the parties proposed to collaborate in R&D activities to develop a bioprocess simulator called Biochemical Engineering Simulation Technology (BEST). NREL, on behalf of all parties, managed the overall BEST research effort, including the work of developing BEST at the NREL facilities and controlling (selecting, negotiating, and executing) associated subcontracts, agreements, understandings, and other supplemental arrangements.

The ASPEN process simulation system is the only commercial package that can be easily modified to simulate these new biochemical processes. Of the two commercial companies at the time (SimSci and Aspen Technology, Inc. [AspenTech]), only SimSci was willing to contract for this type of project.

NREL staff formulated the mathematical algorithms and collected the various physical and chemical data necessary to simulate the selected biochemical unit operations and provided this information to SimSci. SimSci then encoded the algorithms and data and integrated them into its version of the original DOE ASPEN simulator, ASPEN/SP.

The project experienced various staff changes at NREL and SimSci, and never expanded the sponsorship beyond DOE's Biological and Chemical Technologies Research (BCTR) program. In addition, SimSci announced in 1993 that it would stop supporting ASPEN/SP as a commercial simulator by the end of that year. This put an abrupt end to the development efforts. However, several reactor unit operation models were completed and integrated into ASPEN/SP. As a result

of the contracts with SimSci, NREL obtained all the completed new models, the source code, and a perpetual license to continue to use ASPEN/SP.

During this time AspenTech developed its own BioProcess Simulator (BPS) as an add-on to ASPEN PLUS (its version of the original DOE ASPEN). When the work with SimSci was complete, the BPS simulator was obtained from AspenTech and this comparison was written.

BPS is an expensive add-on to ASPEN PLUS, which must also be licensed from AspenTech. BPS offers a couple of additional downstream processing models, but the fermentation models are functionally very similar.

Description of the BEST Simulator

Aerobic and anaerobic bioreactors, fed-batch aerobic and anaerobic bioreactors, and continuous stirred tank aerobic and anaerobic bioreactors were incorporated into the ASPEN/SP-BEST simulator. This included incorporating biochemistry reaction specifications apart from the reactors, which allows several reactions to be used for one reactor, or several reactors in the same flowsheet to use the same reactions without having to specify the reaction details in each unit operation. The reactor models allow the user to completely specify reaction kinetics from several built-in models. The specification of reactor geometry is also included so the aeration, agitation, and heat transfer can be accurately modeled.

Kinetics

The built-in kinetics models include:

- Biomass growth. Exponential form, using the generalized Monod, Tessier, Moser, or Contois expressions for the growth rate constant. The logistic growth rate expression is also available, and growth rate can be modified to account for lag phases, cell death, and oxygen transfer rate (OTR) limitations.
- Product formation. This program uses the modified Leudeking-Piret expression to represent product formation. The product rate is a function of the above biomass growth rate.
- Substrate Consumption. The substrate consumption rate is broken into two parts, one that simply corresponds to the substrate used for biomass growth (a function of the biomass growth rate) and another that is necessary to maintain growth.

Reactors

Batch, fed-batch, and continuous stirred tank reactor (CSTR) models are included. In the batch and fed-batch models, various reaction intervals can be specified with different reactions and different kinetics. These intervals can be triggered by a variety of conditions. In all models, the reaction stoichiometry can be specified specifically or through an elemental balance. In the latter case the user specifies only the molecules and their atoms, and the system will determine feasible stoichiometry.

The batch fermentation model operates in the rating mode and calculates—

- Product and by-product yields
- Maximum and average oxygen uptake rates (OURs)
- Maximum and average heat generation rates
- Maximum and average stirring powers
- Maximum and average volumetric air rate requirements
- Maximum and average coolant rates
- Overall steam consumption
- Overall electric power usage
- Total batch cycle time.

The model also calculates the time-dependent profile information for—

- Substrate, cell mass, product, and by-product concentrations
- OUR
- Heat generation rate
- Stirring power
- Volumetric air rate
- Coolant rate
- Electric power usage.

Details of the Best Models and Methods

The three main elements of the BEST modifications to ASPEN/SP are:

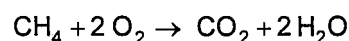
1. The specification of biochemical kinetics,
2. Batch and continuous fermentation reactors and aeration, and
3. Agitation and heat transfer.

The following sections describe the details of what each element can do, which equations are used, and which are included. For more information on the ASPEN/SP BEST input language, consult the BEST User Manual¹. For additional details on the equations used, consult several internal documents that served as the basis for the BEST development^{2,3,4,5}.

Biochemical Kinetics

The biochemical reactions and kinetics are not specified in the reactor blocks, but in separate “BIOCHEMISTRY” paragraphs. The advantage of this methodology is that multiple reactions regimes or reactions can be easily used in one reactor model, or the same kinetics can be used in various reactors without having to painstakingly reenter the kinetic information.

First, the reactions must be specified by one of two methods: known reaction stoichiometry, or specifying only the molecules involved in the reactions and their empirical formulas. An example is knowing the stoichiometry for the reaction of methane and oxygen to form carbon dioxide and water. This can be exactly specified as:



For a more complex reaction in which the stoichiometry is not obvious, the molecules involved and their empirical formulas can be specified. For producing ethanol from glucose, we know that carbon dioxide, ammonia (nutrient), biomass, and water are also involved, but we don't want to figure the stoichiometry, so we can simply specify,

Glucose	$C_6H_{12}O_6$
Ethanol	C_2H_6O
Water	H_2O
Ammonia	NH_3
Carbon Dioxide	CO_2
Biomass	$CH_{1.8}O_{0.5}N_{0.2}$

and the system will determine a feasible reaction set.

Second, the kinetics must be specified. If exact stoichiometry has been specified, a rate expression for one component in each reaction must be specified. If the reaction stoichiometry was not specified, but only the component formulas were specified, a sufficient number of kinetic rate expressions must be entered to satisfy the number of degrees of freedom left. This involves the difference between the total number of unique atoms and the number of components (molecules) involved in the reaction.

$$\text{number of kinetic rate specifications} = \text{number of degrees of freedom} = \text{number of components} - \text{number of unique atoms}$$

The kinetic reaction rate expressions are divided into three types: biomass growth rate, product growth rate, and substrate consumption rate. The last two depend on the biomass growth rate, so for those the biomass growth must also be specified.

The exponential and logistic forms are available for the biomass growth rate. For the exponential, four forms for the growth rate constant—generalized Monod, Tessier, Moser, and Contois expressions—are offered.

The exponential form is given as

$$r_x = \mu c_x \tag{1}$$

where,

- r_x : cell growth rate
- c_x : cell concentration
- μ : growth rate constant.

The generalized Monod expression for the growth rate constant in equation 1 is given as

$$\mu = \mu_m \frac{c_i}{K_{ij} + c_i} \tag{2}$$

where,

- μ_m : maximum specific growth rate
- c_i : concentration of substrate
- K_{ij} : growth of species j on substrate i

The Tessier expression for the growth rate constant in equation 1 is given as

$$\mu = \mu_m \left(1 - e^{-\frac{c_i}{K_{ij}}} \right) \quad (3)$$

The Moser expression for the growth rate constant in equation 1 is given as

$$\mu = \mu_m \left(1 + K_{ji} c_i^{-\lambda_{ji}} \right)^{-1} \quad (4)$$

where,

λ_{ji} : Moser inhibition constant

The Contois expression for growth rate constant in equation 1 is given as

$$\mu = \mu_m \frac{c_i}{B_{ji} c_{x_j} + c_i} \quad (5)$$

where,

B_{ji} : Contois constant for growth of biomass species j on substrate i

The second form available for the growth rate is a logistic equation. This Ricatti equation models the case in which an inhibitor is present and its effect on the rate is proportional to the square of the biomass concentration.

$$r_x = k c_x (1 - \beta c_x) \quad (6)$$

where,

k: Logistic growth rate constant

β : Logistic inhibition constant |

This equation can also be used for activation, in which case β would be negative.

Other Factors Associated with Growth Rate

For any growth rate expression described above, a lag phase can be specified. A lag phase accounts for no reaction for a certain period of time,

$$\text{Lag Phase: } \begin{array}{ll} \mu = 0 & 0 < t < t_{lag} \\ \mu = \mu & t \geq t_{lag} \end{array} \quad (7)$$

For any of the previously described growth rates, a constant cell death rate can be specified,

$$\mu_{net} = \mu - k_d \quad (8)$$

where,

k_d : is a constant cell death rate.

When the system is oxygen limited, the rate can be calculated based on the amount of oxygen available in the system. The equation used for this case is,

$$\begin{aligned} \mu &= \mu & \text{OUR} < \text{OTR} \\ \mu &= \mu_{\text{app}} & \text{OUR} \geq \text{OTR} \end{aligned} \quad (9)$$

$$\mu_{\text{app}} = \frac{Y_{x/o}}{C_x} M_{O_2} \text{OTR}_{\text{max}} \quad (10)$$

where,

OUR: Oxygen uptake rate (determined by the culture)

OTR: Oxygen transfer rate (limited by the mechanical mechanism). See the section on reactor geometry and aeration.

$Y_{x/o}$: yield coefficient for biomass growth on oxygen (g biomass formed per g O_2 consumed)

M_{O_2} : Molecular weight of oxygen

Product Formation Rate Expression

BEST uses the Leudeking-Piret expression to represent product formation. This expression is a function of the biomass growth rate.

$$r_{p_i} = \alpha_i r_x + \beta_i C_x \quad (11)$$

where,

$\alpha_i r_x$: growth associated

$\beta_i C_x$: non-growth associated

Substrate Consumption Rate Expressions

A simple expression containing one term that accounts for biomass maintenance and a term relating to the product or biomass production is used for the substrate consumption rate.

$$r_{s_i} = -\frac{1}{Y_{x/s_i}} r_x - m_{s_i} C_x \quad (12)$$

where,

Y_{x/s_i} : biomass yield on substrate i (g biomass formed/g substrate i consumed)

m_{s_i} : maintenance requirement for growth on substrate i

Batch and Fed-Batch Fermentation Reactor Model

The batch fermentation reactor model in ASPEN/SP-BEST adds the ability to simulate a time-dependent process into a steady-state simulator. This is accomplished by totaling the flows in and out of the reactor for the complete batch (charge, reaction, and drain) time. The average flows of various streams are then used to interface with the upstream and downstream steady-state units. Essentially, this is simulating large tanks before and after the batch reactor.

The key feature to this batch model is the concept of triggers, which can be set so something is changed in the reactor operation when a criterion is met.

Triggers can be set to go off based on maximums of:

- Time
- Temperature
- Moles, mass, or volume in the reactor
- Concentration of a key component.

They can also be set to go off based on minimums of:

- Moles, mass, or volume in the reactor
- Concentration of a key component

The results of a trigger can be to:

- Start a flow (feed or product) until another trigger stops it
- Stop a flow (feed or product)
- Start a flow (feed or product) for a time or quantity (mass, mole, or volume)
- Switch to a different set of kinetics
- Adjust a flow rate (feed or product) with a maximum and minimum allowable.

To complete the reactor specification, the initial charge and drain time are also specified.

If a small enough time increment is chosen, the differential equation for formation or destruction rate of each component can be solved by differential equation. The differential equation for growth is,

$$r_x = \frac{dc_x}{dt} = f(c_x) \quad (13)$$

If the time increment is small enough, this can be solved as

$$c_{x_{t_k}} = f(c_{x_{t_0}})(t_k - t_0) + c_{x_{t_0}} \quad (14)$$

where,

- t_0 : initial time
- t_k : time after one increment
- $c_{x_{t_k}}$: c_x at time t_k
- $c_{x_{t_0}}$: c_x at time t_0

By stepping off all time increments and performing a heat and material balance at each time step, the complete composition and heat profiles for the reaction are calculated. Further, as triggers are hit, whether they are concentration, time, or something else, other actions can be started or stopped, causing an effect on the next time step. The system also allows a vapor draw from the reactor and a drain time, to calculate the full cycle time properly.

The system will plot all types of temperature and concentration profiles as a function of the reaction time.

The model will calculate dissolved oxygen and heat transfer rate based on the reactor geometry. These calculations can be used to limit the reaction kinetics, in the case of oxygen solubility (see Biochemical Kinetics above), agitator power requirements, and heating or cooling media flow.

Continuous Stirred Tank Reactor Model

This model has the ability to use the same biochemical reaction kinetics specifications outlined above. The model and its calculation are much simpler than the batch reactor, as it is steady state rather than time dependent.

This model simply solves the continuous mass balance equation for a reactor as follows,

$$F(c_{i_0} - c_{i_1}) = Vr_i \quad (15)$$

where,

- F: is the volumetric flow of the feed
- c_{i_0} : is concentration of component I in the effluent stream
- c_{i_1} : is the concentration of component I in the feed stream
- V: volume of the reactor
- r_i : rate of formation of component i

The reactor geometry can be specified and the dissolved oxygen, agitator power requirement, and heating/cooling media flows calculated much as they were for the batch model.

Reactor Geometry and Aeration and Heat Transfer Calculations

The dissolved oxygen caused by air sparging, with or without agitation, can be calculated when the complete reactor geometry is specified. If agitation is used, the power required will also be calculated. In addition, with reactor geometry, the heat transfer coefficient and heating/cooling media flows can be calculated to a reactor jacket or internal coils. The specific reactor model (batch or CSTR) allows the user to select to calculate dissolved oxygen or heat transfer, or both. For heat transfer calculations, inlet and outlet coolant streams need to be identified in the flowsheet. For dissolved oxygen calculations, an inlet air stream is needed.

The reactor geometry is specified in a separate paragraph so multiple reactors could use the same configuration without the user having to specify the details for each reactor.

A detailed description of the calculations performed for dissolved oxygen and heat transfer are given in several NREL internal documents^{3,4,5}. Here the general procedure for calculating the dissolved oxygen or the heat transfer and the required inputs will be given. The method used is the same for batch and continuous fermentors. The only difference is that the batch reactor repeats these calculations for each time step.

Oxygen Transfer and Agitator Power

Procedure for Calculation of Oxygen Transfer Rate (OTR) and the agitation power input is as follows. The user-required inputs, specifying the reactor geometry are in **bold** type.

1. Specify the optimum dissolved oxygen concentration for the organism.
2. Specify the mole fraction of oxygen in the inlet gas stream.
3. Specify the reactor back-pressure.
4. Specify the **impeller rotational speed**.
5. Calculate the impeller tip speed, given the **impeller diameter** and speed. Impeller speed should be greater than 2 m/s to ensure adequate gas dispersion.
6. Specify the gas superficial velocity.
7. Calculate the corrected volumetric gas flow rate through the reactor, given **tank diameter** and the gas superficial velocity.
8. Calculate the volumetric flow rate at standard conditions, 273 K, 1 atm.
9. Calculate the molar gas flow rate, given the gas molecular weight.
10. Calculate the oxygen mole fraction in the exhaust gas, using a material balance and knowing OUR. The OUR can be determined by knowing the growth rate of the organism and the oxygen yield coefficient.
11. Calculate the impeller Reynolds number, knowing the impeller diameter and rotational speed, and broth density and viscosity.
12. Calculate the aeration number, knowing the corrected volumetric gas flow and impeller diameter and rotational speed.
13. Calculate the power number using the Brauer equations. The Brauer equations calculate the power number as a complex function of **impeller diameter, turbine blade height, impeller shaft diameter, impeller disk diameter, turbine blade thickness, and turbine disk height**. The user can also specify the power number.
14. Calculate the ungasged power requirement for a single impeller, given the power number, impeller speed, and diameter and broth density.
15. Calculate the ungasged power requirement for all impellers.
16. Calculate the gassed power as a function of ungasged power requirement, impeller diameter and speed, and corrected volumetric gas flow.
17. Calculate the power dissipated by the sparging gas as a function of the standard volumetric gasflow and the pressure at the sparger and in the headspace of the reactor.
18. Calculate the overall **agitation power input** from the gassed power input and the power required to sparge the gas.
19. Calculate the mass-transfer coefficient ($k_L a$) as a function of agitation power, working volume impeller speed, and apparent viscosity. The user can also specify the mass-transfer coefficient.
20. Calculate the dissolved oxygen concentration in equilibrium with the inlet and exhaust gas streams, using the oxygen concentration in the streams and the Henry's law constant for oxygen and the solution (water).

21. Calculate the OTR using the equilibrium dissolved oxygen concentrations and the calculated mass-transfer coefficient.

After this calculation is complete, compare the OTR to the OUR. If the OTR is greater, the reaction can proceed at the kinetically limiting rate. If the OTR is less, it will limit the reactions (see equations 9 and 10).

Reactor Heat Transfer

In general, the heat generated by the biomass reaction increases with its concentration. To maintain a steady temperature, heat must be removed. Again by specifying the reactor geometry, the heat transfer coefficient and outlet cooling medium temperatures are calculated. Two cooling arrangements are allowed: a cooling jacket and coils inside of the reactor. Either or both can be specified.

The procedure for calculating the heat transfer coefficient is given below. The required inputs are in bold type:

1. Specify the coolant (water is the default).
2. Calculate coolant properties at the mean film temperature. A function of the wall and inlet and outlet temperatures of the coolant.
3. Calculate the properties of the broth at the bulk reactor temperature.
4. Specify the **thickness of the fouling layer** on the reactor side of the tubes or jacket.
5. Specify the thermal conductivity of the fouling layer.
6. Specify the **thickness of the jacket wall or coil wall**.
7. Specify the thermal conductivity of the wall.
8. Specify the coolant flow rate (from the flowsheet).
9. Specify the coolant's inlet temperature (from the flowsheet).
10. Calculate the amount of heat that must be removed from the system. This includes the metabolic, agitation, vaporization, and sensible heating of the gas, liquid, and metal.
11. Calculate the amount of heat removed by the coils and by the jacket, if both are present. Assume the outlet temperatures of the jacket and coils are the same.

For the Jacket

- 12j. Calculate the log-mean temperature difference.
- 13j. Calculate the impeller Reynold's number as a function of **impeller speed and diameter** and the broth density and viscosity.
- 14j. Calculate the reactor Prandtl number as a function of the broth density, viscosity, and heat capacity
- 15j. Calculate the reactor Nusselt number as a function of the Reynolds and Prandtl numbers.
- 16j. Calculate the heat transfer coefficient inside the reactor using the Nusselt number, **tank diameter**, and broth thermal conductivity.
- 17j. Calculate the jacket Reynold's number using the average coolant velocity, characteristic length (function of **tank diameter**), and density and viscosity of the coolant.
- 18j. Calculate the jacket Prandtl number using the coolant viscosity, density, and thermal conductivity.
- 19j. Calculate the jacket Nusselt number using the jacket Reynold's and Prandtl numbers.

- 20j. Calculate the heat transfer coefficient inside the jacket using the jacket Nusselt number, the coolant thermal conductivity, and the jacket's characteristic length.
- 21j. Calculate the overall heat transfer using the reactor side and jacket side heat transfer coefficients, thickness of the fouling layer and wall, and the thermal conductivities of the fouling layer and the wall.

The procedure for the coil is essentially the same except the **actual coil diameter** and flow rate through the coil are used to calculate the Reynold's number.

22. Calculate the amount of heat removed by the coils and the jacket using the calculated heat transfer coefficients.
23. Compare the amount of heat removed with that required to keep the reactor isothermal. If that amount of heat cannot be removed, raise the reactor temperature until there is a balance.

In summary, the specifications required for reactor geometry are:

- Tank diameter
- Tank volume
- Tank working volume
- Impeller rotational speed
- Impeller diameter
- Turbine blade height
- Impeller shaft diameter
- Impeller disk diameter
- Turbine blade thickness
- Turbine disk height
- Number of turbine blades
- Thickness of the fouling layer, reactor wall, and reactor side of tube
- Thickness of the jacket wall or coil wall
- Coil diameter.

The resulting calculation gives:

- Agitator power required
- OTR
- Outlet coolant temperature
- Reactor temperature (if the coolant is not sufficient to maintain isothermal conditions).

Ancillary results:

- Mass transfer coefficient
- Reactor side and jacket (or tube) side heat transfer coefficients
- Overall heat transfer coefficients.

As a result of the heat transfer calculations, three conditions can apply,

$$Q_R = Q_{UA}$$

$$Q_R < Q_{UA}$$

$$Q_R > Q_{UA}$$

where,

Q_R is the amount of heat generated by the reaction.

Q_{UA} is the amount of heat that can be transferred to the cooling medium, given the reactor geometry and coolant flow.

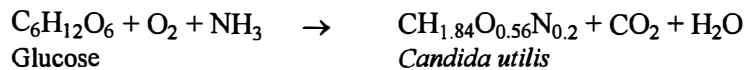
The first two conditions are fine; however, the third case means the reactor temperature cannot be maintained at the condition specified. Several adjustments can be made to increase the heat removal. The simplest is to increase the coolant flow, then lower the inlet coolant temperature, and change the geometry of the reactor by adding more coils or more jacket surface area. The program is not currently set up to make any of these adjustments automatically.

ASPEN/SP-BEST Examples

Two examples are given in the Appendix: batch and continuous aerobic fermentation.

Example 1—Batch aerobic growth of *Candida utilis* with glucose substrate

Reaction



Monod Rate Expression

$$r_x = 0.9722 \times 10^{-4} \frac{c_x}{0.025 + c_x} c_x$$

Biomass 80% water

Reactor Specifications

Total Volume	20 m ³
Agitator Speed	225
Impeller Type	6-blade Rushton

All other tank and impeller specifications are taken as the defaults (see BEST Manual¹).

$$k_L a = 0.003387 (0.3 N_i) \left(\frac{P_{Ag}}{V_w} \right)^{0.4} v_g^{0.6}$$

where,

- N_i Impeller Speed
- P_{ag} Agitator power
- V_w Working volume
- v_g superficial gas velocity in reactor

Reactor Coils and Jacket

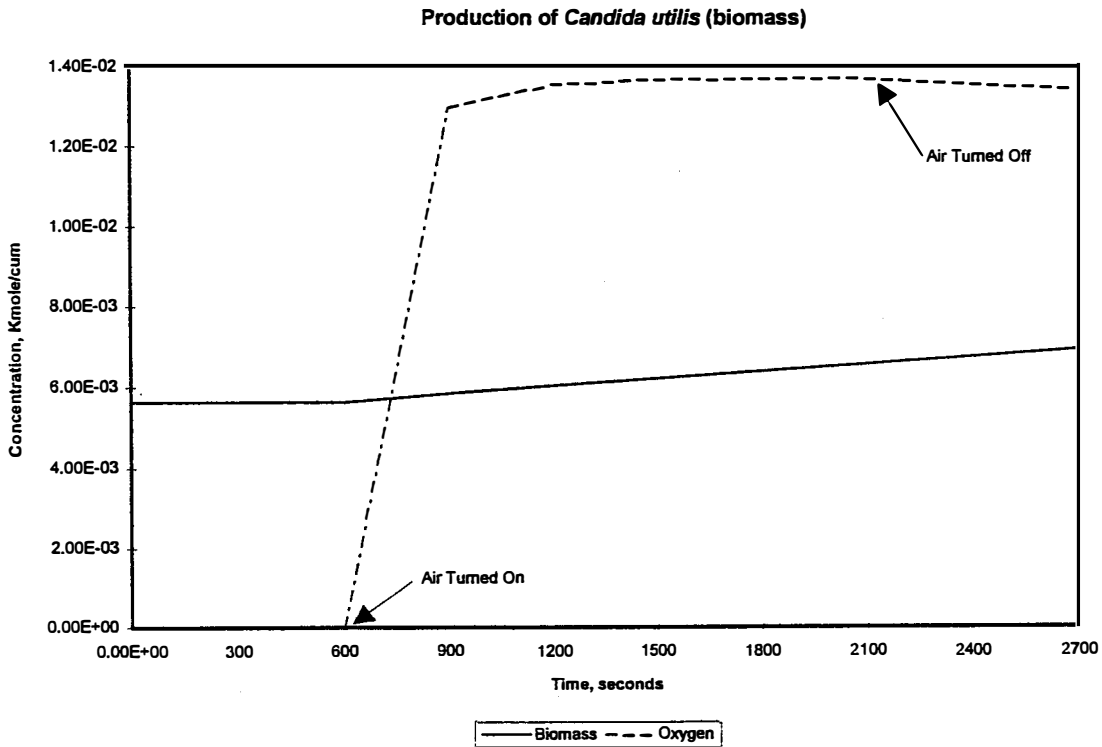
Internal coils and a reactor jacket are specified. All dimensions of these are taken as the defaults (see BEST Manual¹).

Reactor Conditions

Trigger 1	0.0 sec	Load initial charge
Trigger 2	600 sec	Start Air Flow 1.398 Kg/sec
Trigger 3	2100 sec	Stop Air Flow
Trigger 4	Glucose down to 496.29 Kg/m ³	Start Feed 0.00145 Kg/sec
Trigger 5	Glucose down to 496.09 Kg/m ³	Stop Feed

Maximum reaction time	2700 s
Minimum glucose concentration	0.2 Kg/m ³
Optimum dissolved oxygen, C _L	0.000063 Kmole/m ³
Superficial air velocity in reactor	0.002 m/s

The results of this simulation are given in Figure 1. There is a steady increase of biomass concentration after the air is turned on. There was some biomass in the initial charge to the reactor, and the biomass concentration continued to increase even after the air was turned off because the dissolved oxygen level in the reactor remained sufficient to support the reaction. The reactor oxygen concentration started to decrease after the air was shut off and would have eventually decreased below the level necessary for the reaction. The reaction was ended at the maximum time specified (2700 s).



Example 2—Continuous aerobic growth of *Candida utilis* with glucose substrate

All conditions are the same as for the batch mode. The reactor volume is 17 m³. The results are given in Figure 2 below.

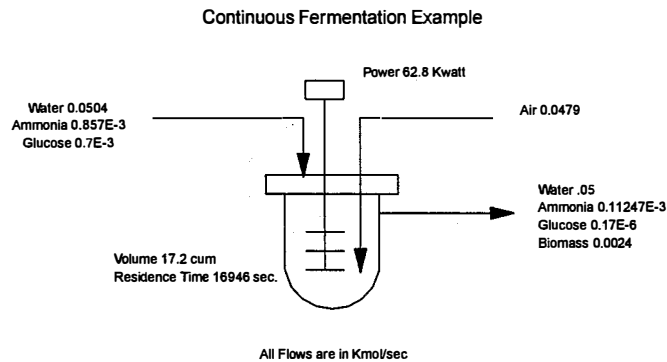


Figure 2

Summary

The ASPEN/SP simulation program has been enhanced with the capabilities to simulate biochemical reactions in batch, fed-batch, and continuous systems. The system has the flexibility to specify multiple reaction schemes for one reactor or use the same reaction scheme for multiple reactors. In addition, the system allows the user to specify the details of the reactor geometry, allowing the simulator to rigorously calculate the oxygen transfer to the broth for aerobic reactions, the agitator power requirements and the heat transfer from internal reactor coils or an external jacket.

The system has several common built-in kinetic rate expressions that can be used. However, the ability to specify unusual or complex kinetics via a FORTRAN subroutine was not included in this system.

AspenTech's Bioprocess Simulator (BPS)

AspenTech has developed an add-on package to its standard ASPEN PLUS simulation package to handle biochemical systems. This package is available for an additional cost of about 150% over the cost of the basic ASPEN PLUS package, which is also required to use BPS, making the ASPEN PLUS BPS a very expensive simulator.

ASPEN PLUS BPS Overview

The BPS system is more extensive than ASPEN/SP-BEST because it includes downstream recovery processes specific to biochemical processing, in addition to the fermentation models. The system includes the following reactor models:

CSTERILE—Continuous Sterilizer

- Plug flow and axial dispersion options
- Logarithmic and non-logarithmic death rate models
- Nutrient and product degradation modeling
- Design and rating options

BFERM—Batch and Fed-Batch Fermentor*

- Aerobic and anaerobic fermentation*
- Atom balance yield*
- Built-in common biochemical kinetic models*
- User kinetics specification
- Multiple reactions*
- Cooling duty/coolant flow calculations*
- Dissolved oxygen*
- Graphical profiles*
- $K_L a$ correlations*
- Agitation power calculations*

CFERM—Continuous Fermentor

- Steady state operation*
- Built-in common biochemical kinetic models*
- User kinetics specification
- Multiple reactions*
- Cooling duty/coolant flow calculations*
- Dissolved oxygen*
- $K_L a$ correlations*
- Agitation power calculations*

*Available in ASPEN/SP-BEST

Comparison of ASPEN/SP-BEST and the ASPEN PLUS BPS Systems

It is only relevant to compare the fermentor systems, as the ASPEN/SP-BEST system does not include downstream processing. The comparison will be done by model feature.

Batch and Fed-Batch Fermentation; Aerobic and Anaerobic Fermentation

Both systems allow for modeling aerobic and anaerobic fermentations equally well.

Atom Balance or Exact Reaction Stoichiometry

Both systems allow the user to specify the particular reactions (exact stoichiometry) or to specify the number of atoms and types in each molecule involved in the reaction. The only difference is that BPS does not require the nitrogen source to be accounted for in the material balances.

Built-In and Common Biochemical Kinetic Models

Both systems include the Monod, Moser, Contois, and Teissier growth models. Both include the Leudeking-Piret model for product formation. The substrate maintenance expression is slightly more complex in the ASPEN/SP-BEST, but can be reduced to the BPS expression.

User Kinetics Specification

This area was originally intended to be in ASPEN/SP-BEST, but was left out because of time and budget constraints. It would need to be added if ASPEN/SP-BEST were to be used extensively. BPS includes this feature, which allows the user to construct very complex kinetic expressions as a FORTRAN subroutine and simply call that subroutine from the model.

Multiple Reactions

Both systems allow for multiple reactions within a reactor and to switch reactions during a batch simulation when various criteria have been reached. The primary difference is that BEST handles the reactions as a separate paragraph that can be used for several reactors. Also, one reactor can use several reaction paragraphs. The BPS system forces the user to specify the reaction in each reactor, through tedious forms.

Cooling Duty/Coolant Flow Calculations

Both systems perform this calculation. The difference is in the level of rigor used in each system. BEST performs a rigorous calculation of the heat transfer coefficients for coils and jackets, then calculates the amount of heat transfer possible from that. BPS, on the other hand, simply calculates the amount of heat generated from the reaction and calculates a coolant flow rate based on a specified allowable coolant temperature rise. This gives no regard to the reactor geometry.

Agitation Power and Oxygen Transfer Rate

Both systems use the same calculation methods to calculate the unaerated power input. BPS includes three additional literature correlations for the calculation of aerated power. For both simulators, details of the agitator and tank size must be specified for this calculation. Calculating the mass transfer coefficient is a function of the agitation power and a few other properties. The BEST system gives one correlation for $k_L a$ and the BPS system allows the user to select from nine literature equations. Both systems also allows the user to specify the $k_L a$ directly. With BPS the user can call a user FORTRAN subroutine for the calculation of $k_L a$. BPS also allows the user to specify correlations to be used for viscosity of the broth, an important physical property in the mass transfer calculations. BEST simply uses an estimation for viscosity.

Once the mass transfer coefficient has been calculated, the OTR is calculated similarly by both systems.

Again, BPS requires that the agitator and tank geometry be specified in the specific reactor, and BEST specifies reactor geometry in a separate paragraph that can be used by any reactor.

Graphical Profiles

Both systems allow for the plotting and tabulation of all types of time profile data for the batch and fed-batch reactors.

Reactor Triggers

Both systems incorporate the concept of triggers in the batch and fed-batch reactor models. They are generally the same in both simulators. They can activate or deactivate feed streams and product draws, set the time duration or mass amount of a feed or product, based on temperature, time, or concentrations. They also allow changing the kinetic rate expressions used in each interval, but again BEST is much simpler. BEST specifies when to change to another reaction paragraph. BPS requires the user to specify the kinetic parameters for each interval, even if they don't change. These parameters must also be repeated if they are used in multiple reactors.

Other Models

As stated earlier, only BEST was able to complete fermentation models before the end of the project. BPS, however, included other, downstream models that allow a bioprocessing plant to be completely simulated. These other models will be briefly described here. For more information regarding these models, refer to the BPS unit operation manual⁶.

MEMBRANE—Membrane Separations

- Microfiltration and ultrafiltration
- Concentration and polarization/gel polarization/particle polarization
- Rejection coefficients for solutes and particles
- Mass transfer coefficient correlation
- Averaging over length of unit
- Death/denaturing features
- Recycle stream, pump and cooling duty are integral part of the module

CENTRI—Stacked Disc Centrifuge

- Stacked disc, empirical model, based on Alfa-Laval experience
- Data regression capability
- Denaturing
- Correlation coefficients/size parameters reported
- Concentration factor/recovery of settling components reported

DISRUPT—Cell Disrupter

- Quantity of cells disrupted
- Quantity of products released/denatured
- New species introduced as a result of disruption
- Pumping work and cooling duty calculated

CHROM—Rigorous chromatography

- Models load, wash, and elution
- Dynamic model
 - Bulk and pore phases
 - Mass transfer between phases
 - Can solve multicomponent nonlinear isotherms with dependence on pH, ionic strength, and solvent concentrations
 - No axial dispersion
- pH, salt, or solvent concentration gradients during elution
- Trigger-based criteria for various stages

Summary of ASPEN/SP-BEST and ASPEN PLUS BPS Comparison

The ASPEN PLUS BPS and ASPEN/SP-BEST simulators are functionally equivalent for modeling fermentation reactions. ASPEN/SP-BEST's one shortcoming is that user kinetic expressions cannot be specified. The shortfalls of ASPEN PLUS BPS are that the reactions must be individually specified for each interval in each reactor and that there is no heat transfer calculations performed.

ASPEN/SP-BEST has no models that address downstream processing; ASPEN PLUS BPS has four, which are mostly applicable to pharmaceutical operations.

References

1. ASPEN/SP BEST. 1993. *BioEngineering Simulation Technology User Manual*, Denver, CO: Simulation Sciences, December.
2. McMillian, J.; G. Philippidis. 1991. "Batch Stirred Tank Fermentor Module Development," Golden, CO: National Renewable Energy Laboratory Internal Document, November.
3. Landucci, R. 1992. "BEST Fermentor Geometry, Part One: Sparged Mechanically Agitated
4. Fermentors," Golden, CO: National Renewable Energy Laboratory Internal Document.
5. Landucci, R., "BEST Peripheral Module Development, Part One: Aeration and Agitation for
6. Aerobic Fermentors," Internal NREL Document, Golden, CO, 1992.
7. Landucci, R., "BEST Peripheral Module Development, Part Two: Heat Transfer for Aerobic
8. and Anaerobic Fermentors," Internal NREL Document, Golden, CO, 1992.
9. *BPS BioProcess Simulator, Release 3.4, User Guide*, Vol. II, AspenTech, Cambridge, MA, 1993.