# 12 Approaches to Modeling SSF Bioreactors

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## 12.1 What Are Models and Why Model SSF Bioreactors?

The key message of this book is that mathematical modeling is a powerful tool that can help in the design of SSF bioreactors and in the optimization of their performance. It is not necessary for all workers in the area of SSF to know how to construct and solve models, because modeling can be done in collaboration with colleagues with the appropriate expertise. However, even if you have no intention of undertaking the modeling work yourself, it is useful to know what models are and what they can do, because this facilitates interactions with these colleagues. The aim of Chaps. 12 to 20 is to give you an understanding of how models of SSF bioreactors are developed. These chapters do not attempt to provide the necessary background in all the mathematical and computing skills required. Rather they attempt to convey the "modeling way of thinking". This will provide the basis for understanding the uses and limitations of the various models presented in the modeling case study chapters (Chaps. 22 to 25).

What is a mathematical model? The type of mathematical model that we are talking about in this book is a set of differential and algebraic equations that summarizes our knowledge of how a process operates. In other words, a model is a set of equations that describes how the various phenomena that occur within the system combine to control its overall performance, which, in the case of SSF bioreactors, will be evaluated in terms of growth and product formation. A model is a simplification of reality, and the equations therefore only describe the phenomena that are thought to be the most important in influencing the performance of the system. It is the modeler who, on the basis of experience with the system being modeled, decides which phenomena will be included and which will not be. As a simple example of this, amongst other factors, growth within an SSF bioreactor depends on both the $O_2$ concentration and the temperature experienced by the microorganism. However, in many models of SSF bioreactors the problem of controlling temperature is considered to be more difficult than the problem of supplying $O_2$, and therefore frequently equations describing energy generation and water transfer are written in order to predict temperatures, but equations to describe $O_2$ supply and consumption are not included within the model.

Of course, it is possible to make wrong decisions about which of the phenomena are most important, or to simply neglect to consider some phenomena that are important. If a model fails to describe the bioreactor performance well, it is essential to find out why it fails, and to then work to improve it.

The models of SSF processes that will be introduced in Chaps. 22 to 25 consist of differential equations that describe how key variables, such as biomass concentration or temperature, vary with over time and across space within a bioreactor during an SSF process. For example, a simple model of the operation of an SSF bioreactor might include equations to describe the rate of growth and heat production and the heat removal processes occurring. These equations would predict how the temperature of the substrate bed changes during the process, and the temperature would be taken into account in the calculation of the growth rate.

Models are a powerful way of summarizing our knowledge about how a system operates. When a system is as complex as an SSF process, we have a better chance of summarizing the complexity of the interactions with a model than if we simply looked at a large number of graphs of experimental results. However, models are more than simply a means of summarizing experimental data that describe system behavior. Models can be used to predict performance, and therefore can be used to identify optimal design parameters and operating conditions (Fig. 12.1). Consider the situation in which you are doing laboratory-scale work on an SSF process that is showing such promise that you intend to go to production scale. Models developed on the basis of this laboratory-scale work, combined with heat and mass transfer principles, can be used to forecast the performance of a large-scale bioreactor, before it is built. Even if the predictions are not fully accurate, this initial

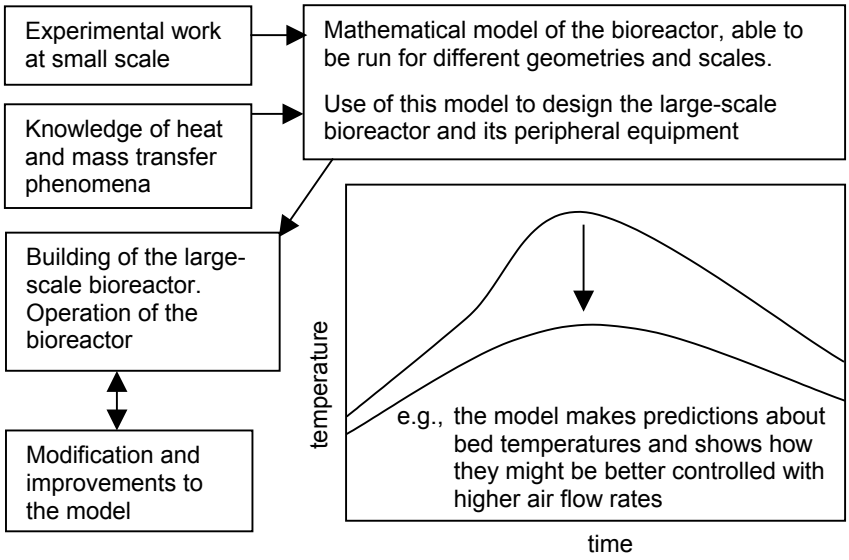


**Fig. 12.1.** An overview of how models can be used in the development of large-scale SSF bioreactors

modeling work has a better chance of leading to a large-scale bioreactor that operates successfully than do "best-guess" or "trial-and-error" approaches. Once the large-scale bioreactor is built and tested, the model can be modified with the new data generated at large scale, and the modified model can be used as a tool in optimizing bioreactor operation.

If powerful "off-the-shelf" bioreactor models were available, then you might never have to think about the "modeling process". However, the current SSF bioreactor models are simply not sufficiently sophisticated. Each research and development group will need to do its own modeling work, although of course this can be done by building on previous work. The point is that you will need to become involved in the modeling process, even if you do not undertake the mathematical and computing work yourself. The remainder of this chapter covers the very basic information that you need in order to understand what models are and how the modeling process operates.

## 12.2 Using Models to Design and Optimize an SSF Bioreactor

Figure 12.2 gives a more detailed view than Fig. 12.1 of how the design process should be carried out for production-scale SSF bioreactors, starting with the necessary laboratory-scale studies and ending with final optimization at large scale. It highlights the fact that it is ideally a process in which experimental and modeling work is undertaken simultaneously, with the mathematical model being refined constantly in the light of experimental evidence. The current section gives a broad overview of this bioreactor design process. It assumes that, after optimizing product formation by a particular organism on a particular solid substrate at laboratory scale, you have decided to develop a large-scale process.

### 12.2.1 Initial Studies in the Laboratory

Early studies will be needed in the laboratory to understand how the organism grows and how this depends on the environmental conditions that it experiences. On the basis of these studies, a growth kinetic model will be proposed (See Boxes 1 and 2 in Fig. 12.2). However, several questions must be asked before the experimental studies are planned. For example, what type of model will be used to model the growth kinetics? With what depth will it model the growth process? Will it simply describe biomass growth as a global value, such as g-biomass g-dry-solids$^{-1}$, or g-biomass m$^{-3}$? Or will it describe the spatial distribution of biomass at the particle level, for example, describing the biomass concentration as a function of height and depth above and below the particle surface? In answering these questions, it is important to consider that any decision that increases the complexity of the model may bring subsequent difficulties not only in solving it, but also in measuring all the necessary model parameters. These difficulties

must be balanced against an evaluation of the potential advantages of improved predictive power that can be gained by describing the phenomena in greater detail. The appropriate level of detail for modeling growth kinetics within SSF bioreactors is discussed in greater depth in Chap. 13. It is only after these decisions have been made that the experimental program is planned. The experiments are planned

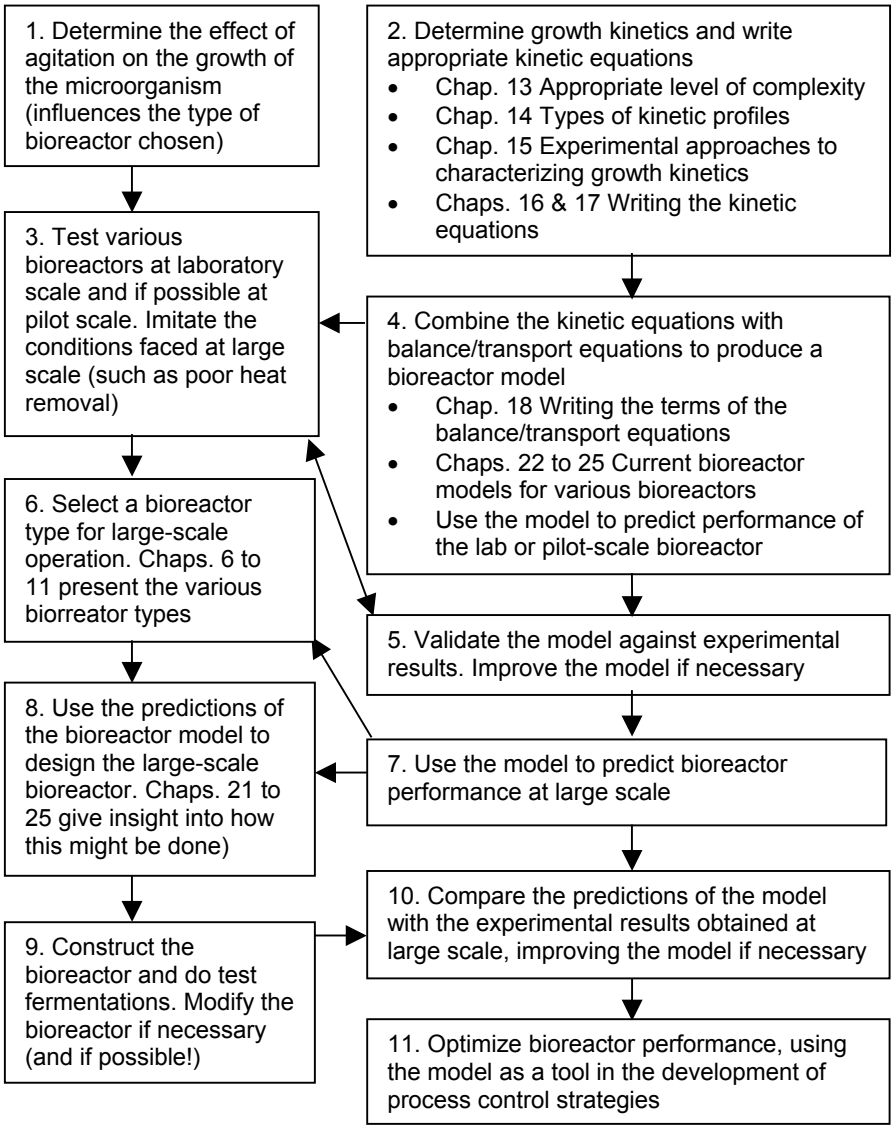


**Fig. 12.2.** Details of the strategy for using models as tools in the design and optimization of operation of SSF bioreactors

in such a way as to enable the development of mathematical expressions relating the growth rate to the various environmental variables. The way in which these experiments might be done and the types of mathematical expressions that might be used are described in Chaps. 14 to 17.

Ideally, various bioreactor types should be tested experimentally at laboratory scale, and, in fact, preferably at pilot scale, although few laboratories have sufficient resources to build laboratory-scale prototypes of all the possible bioreactor types, let alone pilot-scale prototypes (Fig. 12.2, Box 3). At the very least, experiments should be done in which some cultures are left static and others are submitted to various agitation regimes of different frequency, duration, and intensity. The results will be very useful in guiding bioreactor selection and determining the agitation regime to be used in the fermentation.

### 12.2.2 Current Bioreactor Models as Tools in Scale-up

Mathematical models have already been proposed for the various bioreactor types that are used in SSF. It makes sense to take advantage of these models, imperfect as they are (Fig. 12.2, Box 4). At this stage, it is quite likely that many of the parameters, such as transfer coefficients and substrate bed properties, will simply be based on literature values for similar systems. It may be appropriate to improve one or more of the models (Fig. 12.2, Box 5). Ideally laboratory-scale bioreactors should be operated in such a way as to mimic any limitations that will prevail at large scale, and the model predictions carefully validated against performance of these bioreactors. Disagreements between predicted and real performance should stimulate an investigation into the cause, which might be the mathematical form of the equations, but could also be the values used for some of the model parameters.

Simulations with the models will point to which bioreactor has the best potential to provide appropriate control of bed temperature and water content at large scale (Fig. 12.2, Box 6). Once a bioreactor has been selected, the appropriate model then represents a very useful tool for making decisions about design (e.g., geometric aspect) and operating conditions (e.g., air flow rate) (Fig. 12.2, Boxes 7 and 8). Careful attention must be given to the question as to whether the operating conditions necessary for good performance in the simulations are practical to achieve at large scale.

It is advisable to proceed to a scale that is intermediate between the laboratory scale and the final production scale, although this has not always been done. In any case, once a larger scale version of the selected bioreactor has been built, it is essential to validate the model again, since it is quite possible for the relative importance of the various heat and mass transfer phenomena to change with increase in scale (Fig. 12.2, Boxes 9 and 10). Phenomena that were not important at small scale and which were therefore not included in the model might suddenly become quite important at large scale. In this case the model will probably fail to describe large-scale performance with reasonable accuracy. If necessary, the model must be improved. Parameter values also must be determined with care. For example, it may be necessary to determine the bed-to-air mass transfer coefficient that is actu-

ally achieved within the production-scale bioreactor rather than to rely on estimates based on correlations given in the literature.

### 12.2.3 Use of the Model in Control Schemes

Once the bioreactor has been built with the help of the model, the model, improved in the light of data obtained at large scale, is still useful. It is highly likely that bioreactor performance will be significantly improved by implementing control strategies and the model can also play a useful role in the development of the control scheme (Fig. 12.2, Box 11). For example, the proposed control scheme can initially be tested and tuned with the model, which is obviously much cheaper than doing this initial testing and tuning with the bioreactor itself. The model may be embedded into the control system that is used to control the bioreactor.

## 12.3 The Anatomy of a Model

So models can and should play a central role in the development of large-scale SSF bioreactors. The remainder of this chapter gives an overview of the structure of mathematical models and the manner in which they are developed. The aim is not to teach those readers who do not have a background in modeling how to construct and solve models, but rather to increase their ability to interact with a modeling expert in the modeling process.

The structure of a model is presented in terms of a case study of a simple model of a well-mixed SSF bioreactor. Figure 12.3 shows the bioreactor, highlighting the various phenomena described by the model. Figure 12.4 shows the equations of this model, highlighting the fact that mathematical models of bioreactors contain two parts: the kinetic sub-model describes microbial growth kinetics, while the balance/transport sub-model describes transport phenomena and overall mass and energy balances. Work must be undertaken to generate data for both parts of the model.

Various symbols appear in these equations, representing different quantities. These quantities are of fundamentally different types, or, in other words, the various symbols represent a range of state variables, independent variables, operating variables and parameters. These are defined below.

**State variables.** These represent variable properties of the bioreactor, or the various phases within the bioreactor. For example, the state variables within the well-mixed SSF bioreactor model are the temperature of the substrate bed ($T$) and the amount of biomass in the bioreactor ($X$). They are called state variables because, together, the values for all these variables at a particular instant describe the state of the system at that instant. They are variables because their values vary as the independent variables change.

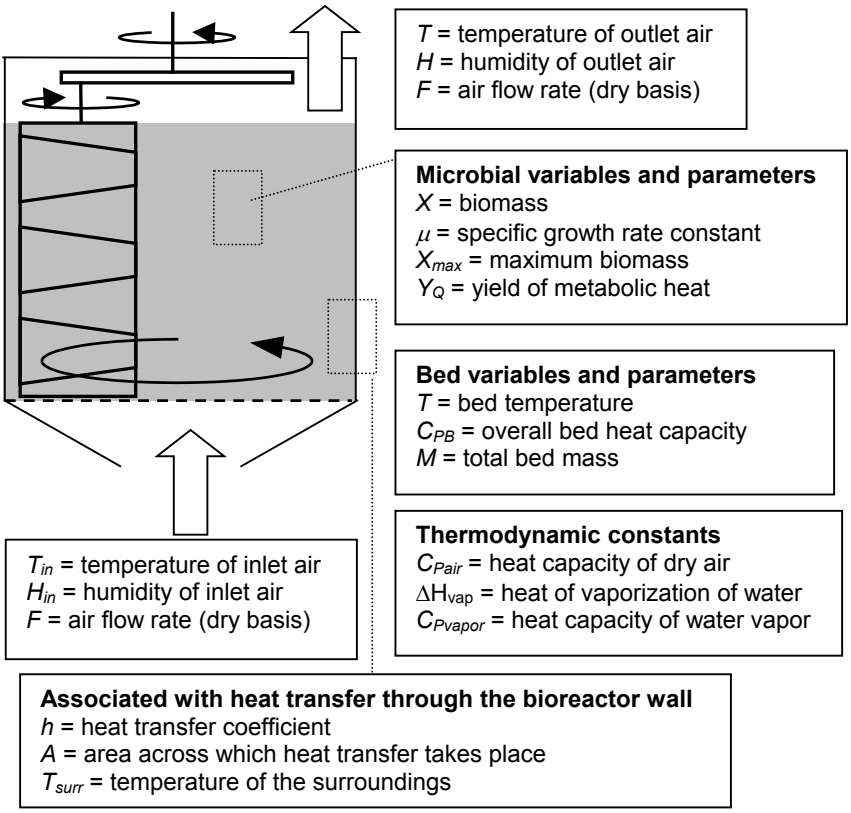


**Fig. 12.3.** A simple mathematical model for predicting the temperature within a well-mixed SSF bioreactor: The system modeled and the various variables and parameters involved in the model. Note that due to assumption of perfect mixing, the conditions within the bioreactor are equal to the outlet conditions

**Independent variables.** These represent variables that do not depend on the system and how it is operated. Rather the system depends on these variables. The independent variables that appear in models for SSF bioreactors are either time or space or both. In the current example it is assumed that the bioreactor is well mixed and therefore time is the only independent variable. In some cases the variations across space are significant while the variations in time occur only slowly. In this case, it might be appropriate to write the equations with space as the only independent variable, and the equation is referred to as a "pseudo-steadystate" equation. There are also bioreactors in which both the temporal and spatial variations are significant: the temperature at a specific position changes over time, and if the temperature is measured simultaneously at different locations within the substrate bed, the measured temperature varies with position. In this case both time and position appear as independent variables.

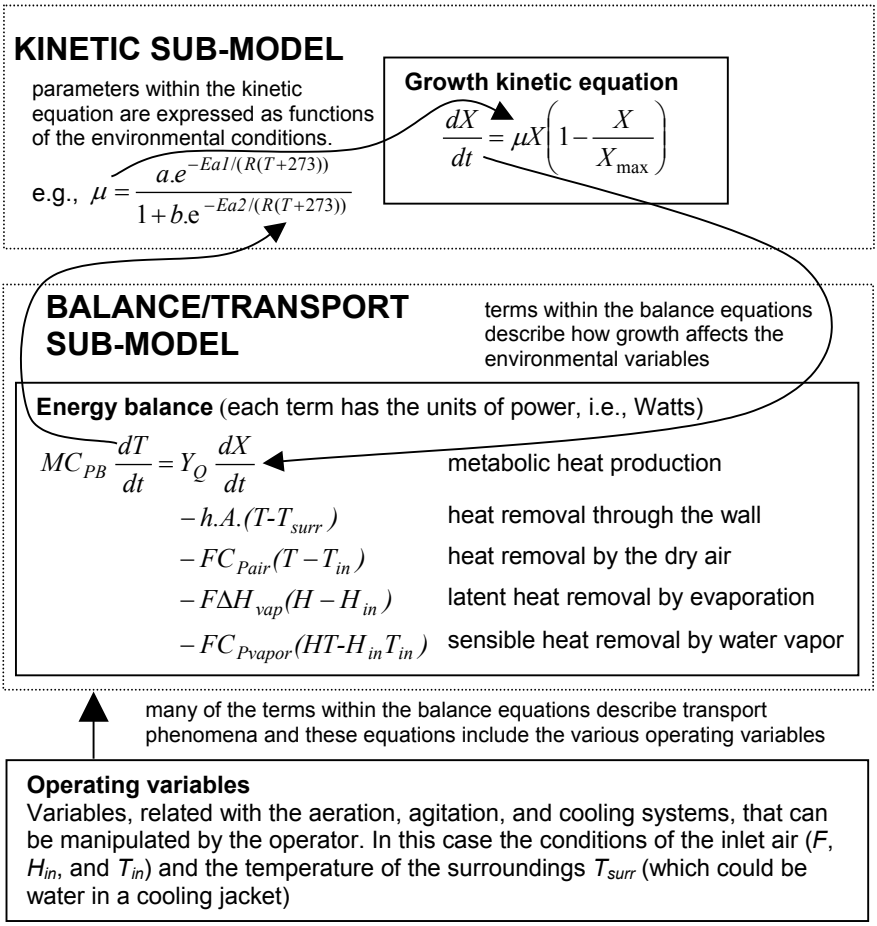


**Fig. 12.4.** A simple mathematical model for predicting the temperature within a well-mixed SSF bioreactor: The model equations, showing the kinetic and balance/transport sub-models and their interrelations

**Operating variables.** These are variables that we can control the value of and which affect the performance of the bioreactor. We can use these in an attempt to control the state variables at their optimum values for the fermentation. In the current example, the operating variables are the conditions of the inlet air ($F$, $H_{in}$, and $T_{in}$) and the temperature of the surroundings $T_{surr}$.

**Parameters.** These represent various physical and biological properties of the system. They may be constants or their value at a certain time and position might depend on the state of the system (e.g., its temperature). In SSF systems there are various different types of parameters:

- design parameters, related to how the bioreactor was built. For example, in the current example, the area for heat transfer ($A$) is a design parameter.
- transport parameters, related to the transport of material and energy within and between phases. For example, in the current example, the coefficient for heat transfer between the bioreactor wall and the cooling water ($h$, J $m^{-2}$ $s^{-1}$ °$C^{-1}$) is a transport parameter.
- thermodynamic parameters, related to quantities of energy and the equilibrium state of materials. The enthalpy of vaporization of water ($\Delta H_{vap}$) is one of the thermodynamic parameters in the current example.
- biological parameters, related to the behavior of the microorganism. In the current example, the maximum possible biomass content ($X_{max}$) and the yield of waste metabolic heat from growth ($Y_Q$) are biological parameters.

Figure 12.5 shows various variables and parameters that might be included within bioreactor models that are more complex than the simple model shown in Fig. 12.4. The biological parameters are addressed in detail in Chaps. 14 to 17 while the transport and thermodynamic parameters are addressed in Chaps. 19 and 20.

## 12.4 The Seven Steps of Developing a Bioreactor Model

In order to develop a mathematical model for your bioreactor from scratch, you would need to undertake 7 steps (Fig. 12.6). These steps were followed in the development of the various mathematical models presented in Chaps. 22 to 25. Of course, with the availability of these models, it is currently possible to start in the middle of the process. For example, you could use model equations from the literature for the same type of bioreactor and start at Step 4, with the determination of the parameter values for your particular system. However, even it this is done, it is necessary to check the original development of steps 1 to 3 in the literature model, to make sure that you agree with the decisions made by the authors during these steps.

You should also note that even though the steps are presented as a linear sequence here, the modeling process does not necessarily occur in a simple linear fashion. Frequently it is necessary to return and revise earlier decisions as the model is refined.

This section covers the 7 steps of modeling an SSF bioreactor, highlighting the tasks and questions that arise at each of the steps. It does not offer answers to these questions. Chapter 13 discusses how several of the key questions have been answered in the past, for example, in the development of the various bioreactor models that are presented in Chaps. 22 to 25.

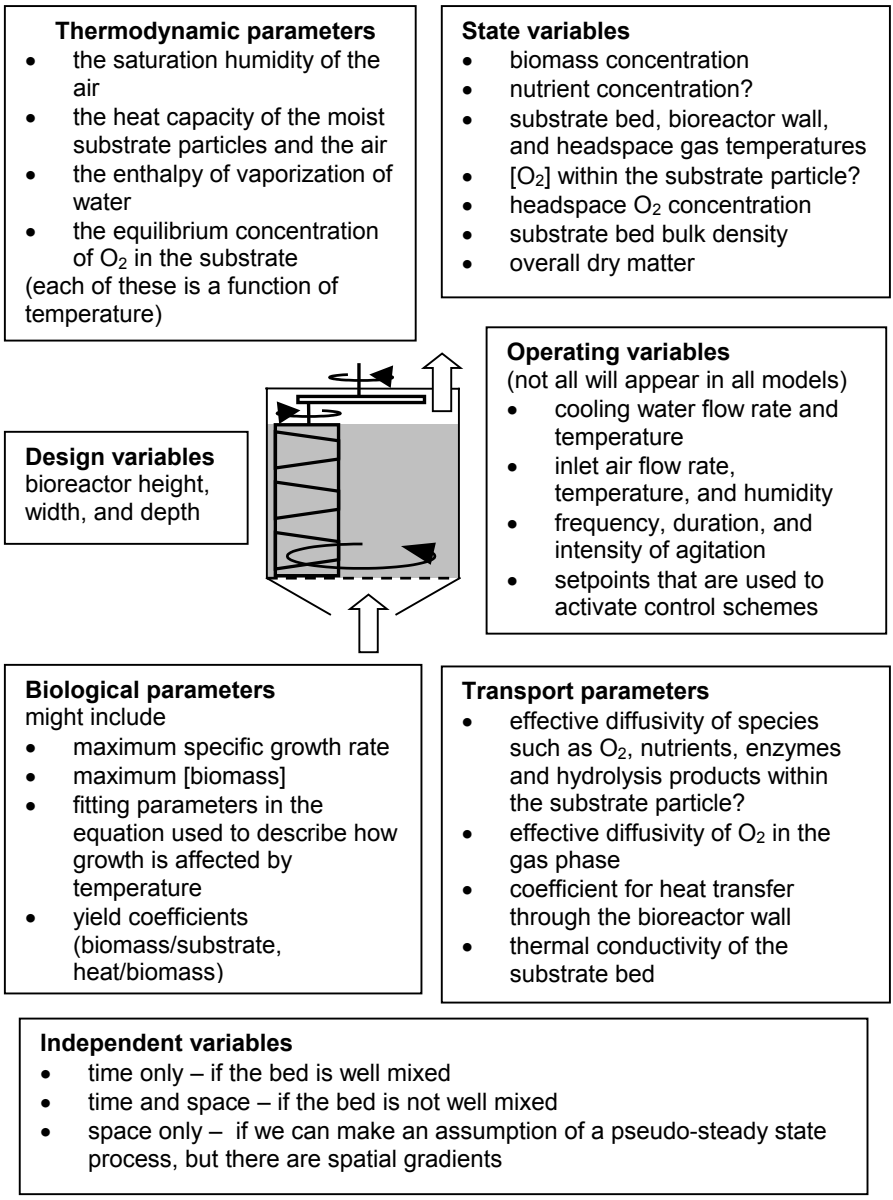


**Fig. 12.5.** Various parameters and variables that might be included in SSF bioreactor models. Not all these parameters and variables will appear within a particular model. Items marked with a question mark are typically not included within bioreactor models due to the complexity they would bring

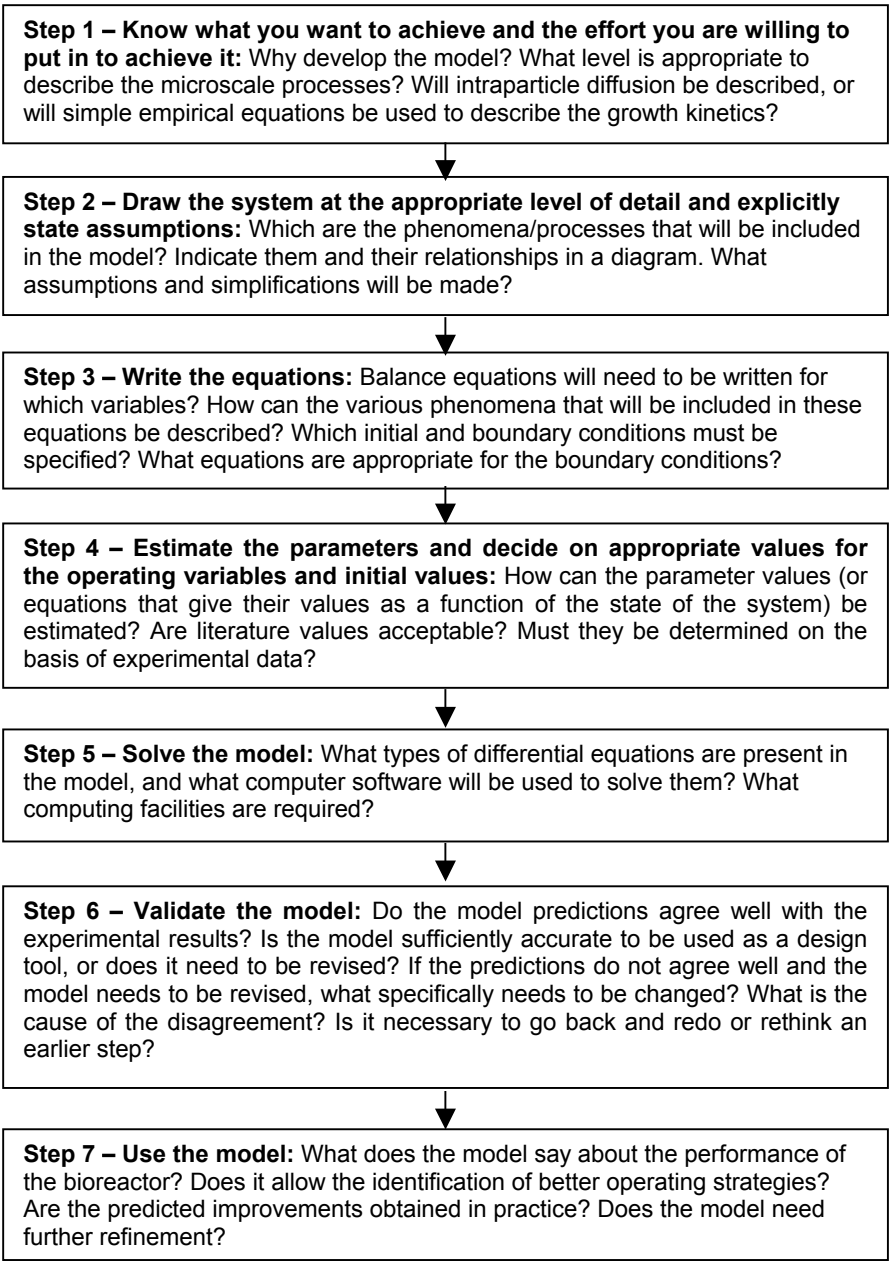


**Fig. 12.6.** The seven steps of the modeling process

### 12.4.1 Step 1: Know What You Want to Achieve and the Effort You Are Willing to Put into Achieving It

You will typically want to construct a model that can be used as a tool in the bioreactor design process or in the optimization of operation of a bioreactor that has already been built. Models that have already been constructed with this motivation are described in Chaps. 22 to 25.

At this stage it is necessary to decide on the appropriate balance between the effort required (i.e., the work involved in writing the model equations, determining the values of the model parameters, and solving the model) and the "power" of the model, where the power of a model is defined by its ability to describe the performance of the system under a range of operating conditions, including conditions outside of the experimental range on which the model development was based. The greater the degree to which a model describes mechanistically the many phenomena presented in Chap. 2, the more likely it is to be more flexible. However, the description of fundamental phenomena can greatly increase the complexity of the model, and can require significant experimental effort to determine the parameters. If, in the particular bioreactor being modeled, there are significant temperature, water, and gas gradients across the bed, then clearly the model needs to describe the heat and mass transfer processes within the bed and to include position as an independent variable. A choice must then be made as to whether to describe the intra-particle gradients that arise. Doing so will lead to a highly complex model, because it will be simultaneously describing heterogeneity at the macroscale and heterogeneity at the microscale. Chapter 13 addresses this question in some detail.

The balance between model power and required effort may be decided from the outset, but it may also be decided later. Once the understanding of how the system functions is outlined in Step 2, the degree of complexity involved in a fully mechanistic approach becomes clearer, as do possible ways in which the mathematical description of the system can be simplified.

### 12.4.2 Step 2: Draw the System at the Appropriate Level of Detail and Explicitly State Assumptions

Once the aim of the modeling project is clear, the next step is to draw a diagram that summarizes the system and the important phenomena occurring within it. It is probably best to do this in two steps. Firstly, a detailed diagram should be drawn to include all the phenomena occurring within the system. Such a diagram might be similar to Fig. 2.6. Secondly, a simplified version should be drawn that includes only those phases and phenomena that have been selected as being sufficiently important to include in the model. For example, Fig. 12.3 shows a simplified diagram for a well-mixed bioreactor. An especially important question is as to whether the solid and air phases within the bed will be treated as separate subsystems, or whether the whole bed will be treated as a single pseudo-homogeneous subsystem that has the average properties of the solid and inter-particle air phases.

It will also need to be decided whether the bioreactor wall will be recognized as a separate subsystem. The diagram should clearly indicate the boundaries of the overall system and the various subsystems within it, the processes occurring within each subsystem, and the processes of exchange between different subsystems and between these subsystems and the surroundings of the bioreactor. It should be clearly annotated with the following information

- the state variables. In Fig. 12.3, these are the bed temperature and the biomass. Each of these should be given a symbol, which will be used in the equations;
- the interaction between the parameters and the state variables. For example, it should be noted that the growth rate of the organism will be modeled as depending on the bed temperature;

At the time of drawing these diagrams, the process of organizing the related information of assumptions, symbol definitions, and units should be started. All the symbols used to label the variables and parameters in the diagram should be listed and described, with their units. Also, all the assumptions and simplifications made should be carefully written down. As an example, for the well-mixed bioreactor in Fig. 12.3, it is assumed that:

- the substrate bed is well-mixed such that the whole bed can be represented by a single temperature, and the heat generation is uniform throughout the bed;
- the gas and solid phases are at temperature and moisture equilibrium, such that the air is saturated at the air outlet at the temperature of the bed;
- saturated air is used to aerate the bed;
- the loss of bed mass as $CO_2$ during the process is not significant, allowing the bed mass to be represented by a constant ($M$, kg);
- the water lost during the fermentation is replaced by a spray, such that the water content of the bed does not change during the fermentation;
- growth follows logistic growth kinetics;
- the specific growth rate constant depends only on the biomass concentration and the temperature and therefore growth is not limited by the supply of $O_2$ or nutrients;
- the thermal properties of the bed remain constant, even as the bed is modified by the growth process.

Of course many other assumptions are possible in order to reduce the complexity of models. Note that final decisions on the necessary variables and parameters and their appropriate units and the necessary assumptions might be made only at the stage of writing the equations.

### 12.4.3 Step 3: Write the Equations

This step builds on the foundation provided by the first two steps. The qualitative description of the system produced in Step 2 shows what equations need to be written and what terms should be included within these equations. The importance

of the diagram drawn in Step 2 cannot be overstated. Lack of clarity in this diagram will lead to great difficulty in writing a coherent set of equations. The basic approach is to write:

- material and energy balance equations, usually in dynamic form (i.e., differential equations), with the state variables each expressed as:

$$\frac{d(variable)}{dt} = \text{system inputs} - \text{system outputs} + / - \text{changes within the system}$$

- These balances must originally be written in terms of quantities that are conserved, although the equations can be rearranged later. For example, a balance on water would originally be written with each term having units of the mass of water per unit volume of bioreactor (i.e., kg-$H_2O$ $m^{-3}$) and not the water content (kg-water kg-dry-substrate$^{-1}$). The differential term would therefore be d($WS$)/dt and not d$W$/dt, where $W$ is the water content and $S$ is the kg of dry substrate per $m^3$ of bioreactor. If it were desired to predict the water content, then the differential terms in $W$ and $S$ would be separated using the product rule, such that in the final equation only d$W$/dt appeared on the left-hand-side;
- relevant thermodynamic relationships for important parameters of the equations (e.g., the saturation water content of the gas phase as a function of temperature, using the Antoine equation);
- relationships for other parameters that are functions of the state of the system (e.g., the specific growth rate may be expressed as depending on the temperature);
- other intrinsic relationships.

In writing the equations, it is necessary to know the mathematical forms appropriate for describing the various phenomena. These mathematical forms are presented in Chaps. 14 to 17 for empirical growth kinetic equations and in Chaps. 18 to 20 for the processes described in balance/transport equations. As an example from Fig. 12.4, convection of heat to the surroundings appears within the energy balance as "$h.a.(T\text{-}T_{surr})$", or, in other words: "the rate of heat removal through the bioreactor wall is equal to a heat transfer coefficient times the area for heat transfer times the difference in temperature between the bed and the surroundings".

Attention to detail is paramount in the writing of equations. All terms of an equation must have the same units. For example, each term in a material balance would have units of kg $h^{-1}$ (or kg $m^{-3}$ $h^{-1}$), while each term in an energy balance would have units of J $h^{-1}$ (or J $m^{-3}$ $h^{-1}$). In fact, the necessity for terms to have certain units can help to give insights into how a particular term is to be constructed. Careful attention must be given as to whether terms are to be added or subtracted within an equation.

The number of dependent state variables selected will depend on the decisions made in Steps 1 and 2. For example, in the simple model in Fig. 12.4, equations are not written to describe the change in either the total mass of dry solids in the bed or the total mass of water in the bed. If the aim were to describe product formation then an extra equation would be written for the product.

For systems that are both temporally and spatially heterogeneous, and which therefore involve partial differential equations, it is necessary to write equations to describe the "boundary conditions". For example, it may be necessary to write that the temperature at the inlet of the bed is maintained at a particular temperature, and it may be necessary to write an equation that says that the rate at which heat is removed from the side walls of the bioreactor by convection to the cooling water is equal to the rate at which heat reaches the wall by conduction from the bed.

### 12.4.4 Step 4: Estimate the Parameters and Decide on Values for the Operating Variables

In order to solve a set of differential equations, you must have values for all of the parameters of the model, and, in addition to this, initial values must be given for the dependent state variables for which the differential equations are written.

**Parameters.** The types of parameters that appear in the model depend on the particular bioreactor and the phenomena that the model is describing. The values of the parameters may be determined in separate experiments, although at times values from the literature may be used. Note that some parameters might be constants, in which case only a single value is required, or they may vary as the state of the system varies, in which case an equation is needed that relates the parameter value to the state of the system. In the model presented in Fig. 12.4, the parameters were determined as follows:

- The parameters in the equation describing the dependence of the specific growth rate constant on temperature were determined by Saucedo-Castaneda et al. (1990) on the basis of experimental results for the growth of *Aspergillus niger*, obtained by Raimbault and Alazard (1980), by non-linear regression of the equation against these experimental results.
- The heat transfer coefficient ($h$) was obtained from Perry's Chemical Engineer's Handbook (Perry et al. 1984), as a typical value for the transfer of heat across steel. However, it could also be determined experimentally for a particular bioreactor.
- The design parameter $A$ (area for heat transfer to the water jacket) was calculated assuming that the water jacket is in contact with the curved outer surface of the cylindrical bioreactor.
- Thermodynamic parameters were obtained from reference books (e.g., heat capacities of water and water vapor, coefficients of the Antoine equation used in the calculation of humidities, the enthalpy of evaporation of water).
- The heat capacity of the bed ($C_{PB}$) was calculated on the basis of a starchy substrate of 50% moisture content.

Sometimes it is difficult to determine the value of a parameter in independent experiments. Although it is not particularly desirable, it is possible to allow this parameter to vary in the solving of the model, using an optimization routine to find the value of the parameter that allows the model to fit the data most closely.

**Initial values of the state variables.** The state variables that appear in the model depend on the combination of differential equations that make up the model. Their initial values will be determined by the way in which the bioreactor and inoculum were prepared. In the case of the well-mixed SSF bioreactor, it is necessary to give the initial mass of dry biomass and the initial temperature of the bed. Of course it is also possible to choose hypothetical initial values in order to explore the effect of the starting conditions on the predicted performance of the bioreactor.

**Operating variables.** The operating variables appearing in the model depend on the type of bioreactor and what manipulations it allows. The available operating variables for each SSF bioreactor type were presented in Chaps. 6 to 11. The values used for these variables in solving the model will either be experimental values, in the case of model validation, or hypothetical values, in the case where the model is being used to explore the effect of the operating conditions on the predicted performance of the bioreactor.

### 12.4.5 Step 5: Solve the Model

This book does not provide detailed information on how mathematical models are solved. Typically, numerical techniques will be used for solving differential equations. The amount of work that must be done to solve a model depends on the sophistication of the computer software available. In some cases it is necessary to write a program in a computer code such as FORTRAN or MatLab®, using prewritten subroutines as appropriate. With more sophisticated software packages, it may be sufficient simply to enter the equations and initial values in the appropriate fields and ask the computer to solve the equations.

Well-mixed systems will lead to a set of ordinary differential equations (ODEs), that is, equations in which the differential terms are only expressed as functions of time. Such a set of equations can be solved with well-known subroutines, such as the FORTRAN subroutine DRKGS, which is based on the Runge-Kutta algorithm. The solution of such models will be a graph, plotted against time, of the system variables that were described by the differential equations. In the case of the well-mixed SSF bioreactor model, the solution of the model is represented by temporal biomass and bed temperature profiles, such as the predictions presented in Fig. 12.7(a).

Systems with both spatial and temporal heterogeneity will lead to partial differential equations (PDEs), that is, equations that contain a mixture of differential terms that contain time in the denominator and differential terms that contain a spatial coordinate in the denominator. The solution methods involve transforming the PDEs into sets of ODEs, and then using numerical integration to solve these ODEs. Typically the transformation of the PDEs into sets of ODEs must be done by hand, and is not simple to do. The solution of such a model will be a graph against time of each of the state variables, with multiple curves, each curve representing a different position within the bed (Fig. 12.7(b)).

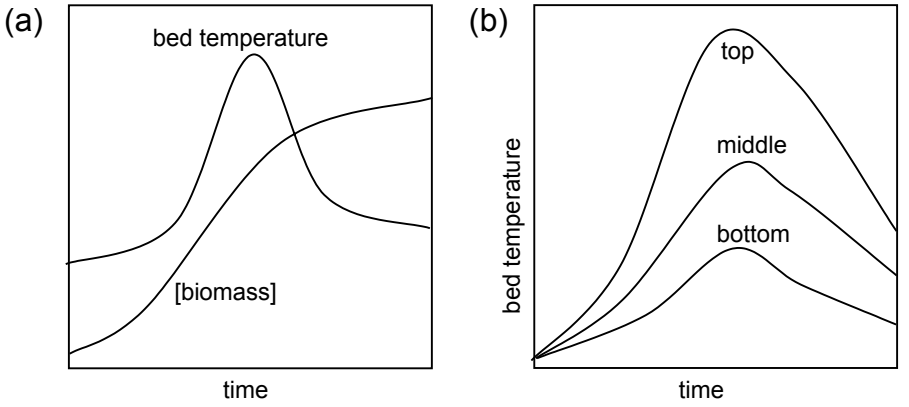


**Fig. 12.7.** What is the result obtained by solving a model? **(a)** For a model containing only ordinary differential equations, it is a predicted fermentation profile, or, in other words, a set of curves against time for each of the system variables. **(b)** For a model containing partial differential equations, fermentation profiles are predicted for various positions in the bed. For example, if the bioreactor shown in Fig. 12.3 were not mixed and the temperatures at various heights within the bed were predicted with an appropriate mathematical model, typical predictions would be as shown

### 12.4.6 Step 6: Validate the Model

If a model has been solved using independent estimates of all of the parameters, then it is of great interest as to whether the model manages to predict reasonably well the behavior of the system that is observed experimentally (Fig. 12.8). If it does, then this can be taken as supporting evidence, but not proof, that the mechanisms and phenomena included in the model are indeed those that are most important in determining the bioreactor behavior. Unfortunately, the validation of bioreactor models has only rarely been done well in the area of SSF to date.

As mentioned within Step 4, in some cases one or more of the parameters are determined during the solution step, by doing several simulations with different values for these parameters and seeing which solution agrees best with the experimental data (this being done most effectively by using an optimization routine to find the value of the parameter that gives the best statistical fit). The danger of this approach is that it might be possible to adjust the model to the data even if the mechanisms included in the model are inadequate. When this approach is used for parameter estimation, it is not possible to claim that the model has been validated, even if very close agreement is obtained.

A sensitivity analysis might be done at this stage (Fig. 12.9). This involves making changes one at a time to the various parameters in the model and seeing how large the effect is on the model predictions. The objective is to determine which parameters are most important in determining bioreactor performance:

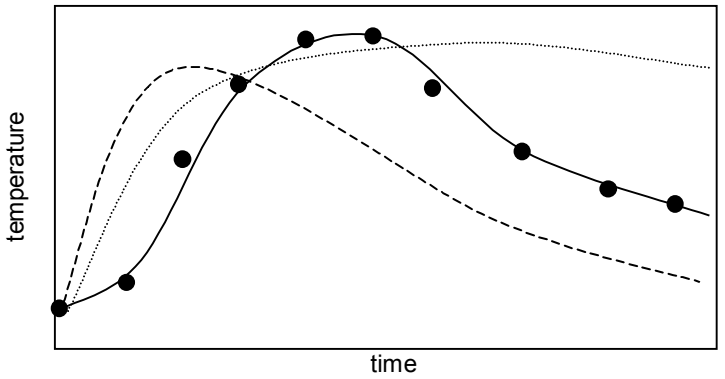


**Fig. 12.8.** Validation of the model. The graph illustrates three possible situations for a comparison between experimentally measured temperatures, represented by the solid circles, and the bed temperatures predicted by the model, represented by one of the curves. (—) Ideally there should be minimal deviation between the model predictions and experimental data; (- - -) At times general features of the experimental curve are described but are offset in magnitude and time. Possibly more accurate determination of one or more parameters is necessary; (·····) At times the predicted results are very different from the experimental results. A key phenomenon may have been omitted in the model

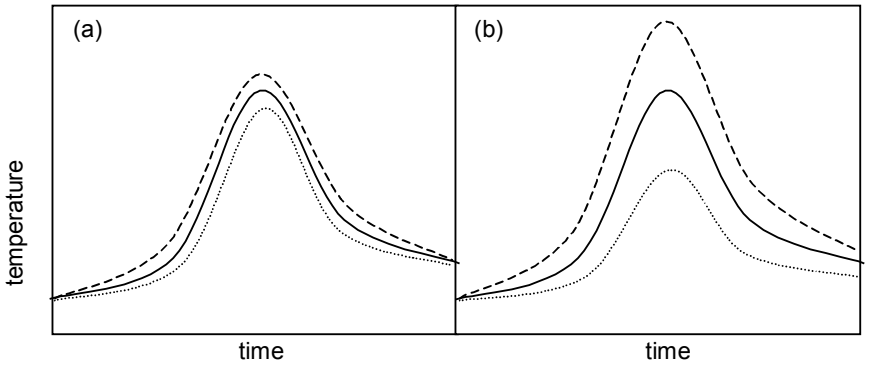


**Fig. 12.9.** Sensitivity analysis. In this example, the model presented in Fig. 12.4 is solved for various values of the heat transfer coefficient, $h$, associated with heat removal through the bioreactor wall. Key: (—) solution using $h$, the best estimate of the heat transfer coefficient; (·····) solution using $2.h$; (- - -) solution using $h/2$. Two possible situations are shown. **(a)** The variations in $h$ have relatively little effect on the model predictions. Probably removal through the bioreactor wall makes only a relatively small contribution to overall heat removal. It might be appropriate to remove this term from the model. (**b**) The variations in $h$ have a significant effect on the model predictions. The term describing heat removal through the bioreactor wall should be maintained in the model, since it is obviously an important contributor to overall heat removal, and it is important to have an accurate value for $h$ if the model is to predict the experimental data well

- If relatively small changes in the value of a parameter significantly affect model predictions, then quite probably the phenomenon with which the parameter is associated is quite important in determining the system behavior and, furthermore, it is quite important to obtain accurate values for the parameter;
- If relatively large changes in the value of a parameter have a relatively small effect on model predictions, then possibly the phenomenon with which the parameter is associated is not very important in determining the system behavior, at least under the particular set of operating conditions used (the phenomenon might become more important under another set of operating conditions). The degree of accuracy needed for estimation of this parameter is not so great and possibly the term describing this parameter can be eliminated in order to simplify the model.

### 12.4.7 Step 7: Use the Model

The use to which the model is put will of course depend largely on the original motivation of the modeling work. For example, the model might be used to explore:

- how the same bioreactor will perform under operational conditions other than those for which experimental results were collected;
- how a different bioreactor geometry affects performance;
- how the size of the bioreactor affects performance.

Chapters 22 to 25 will show examples of such explorations for various different bioreactor types.

Of course there is no guarantee that the model will work well for a situation other than that for which it was validated. Predictions of the model about how performance can be improved must be checked experimentally. However, clearly an experimental program guided by use of a mathematical model has a good chance of optimizing performance more rapidly than a purely experimental program.

Deviations of the performance from predictions will lead to work to improve either or both of the model structure (the equations) and the parameter values. That is, it may be necessary to return to Steps 3 and 4. Such revisions lead to continual refinements of the model and to a greater understanding about how the various phenomena interact to control bioreactor performance.

## Further Reading

*The place of modeling in fermentation processes, argued in the context of submerged liquid fermentation*

Anon (1997) Modelling is an indismissable tool to understand and control bioprocesses. J Biotechnol 52:173

Biwer A, Heinzle E (2004) Process modeling and simulation can guide process development: case study α-cyclodextrin. Enzyme Microb Technol 34:642–650
Schügerl K (2001) Progress in monitoring, modeling and control of bioprocesses during the last 20 years. J Biotechnol 85:149–173