5 The Scale-up Challenge for SSF Bioreactors

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5.1 Introduction

Having now seen the various types of bioreactors used in SSF processes (Chap. 3) and the transport phenomena that occur within them (Chap. 4), we now return to the question of how the limitations on the efficiency of the transport phenomena within the bioreactor make it almost impossible to operate large-scale bioreactors in such a manner that the conditions within the substrate bed are maintained throughout the process at the optimum values for growth and product formation.

Is it really difficult to design an efficiently operating large-scale SSF bioreactor? In the case of SLF, there are examples of successfully operating bioreactors of hundreds of thousands of liters. Why cannot we do the same for SSF processes? Or can we? The answer is that the challenges in operating a bioreactor of several hundreds of thousands of liters are typically more difficult to overcome in SSF than in SLF, and it is no simple matter to develop efficient large-scale SSF bioreactors. This difficulty, often referred to as "the scale-up problem", is discussed in the following sections.

5.2 The Challenges Faced at Large Scale in SLF and SSF

The major challenge in the scale-up of aerobic submerged liquid fermentation processes is the transfer of O_2 into the liquid at a sufficient rate to obtain high cell densities. Scale-up strategies that address this transfer, which is characterized by the parameter k_La, have long been available in the area of SLF (Kossen and Oosterhuis 1985). Although heat transfer calculations must be done, in order to provide sufficient cooling capacity, heat removal is typically not an overly challenging task. If the outer surface of the bioreactor does not provide a sufficiently large surface area to give the necessary rate of heat removal to the cooling water in a water jacket, then a cooling coil can be incorporated into the design without causing much complication in construction or operation.

On the other hand, in the case of SSF, heat removal is typically the major concern. It is more difficult to remove the waste metabolic heat from a bed of solids

in which the inter-particle phase is occupied by air than it is to remove this heat from a continuous aqueous phase. There are two reasons for this:

- the thermal properties of a continuous aqueous phase, namely the thermal conductivity and heat capacity of liquid water, are superior to those of a bed of moist solids with inter-particle air;
- mixing greatly promotes heat removal by bringing the medium into contact with the cooling surfaces within the bioreactor. However, typically mixing must be minimized in SSF bioreactors, for several reasons: Firstly, it requires higher energy inputs to mix the bed of solid particles within an SSF bioreactor than to mix the liquid medium in an SLF bioreactor. Secondly, the presence of internal heat transfer surfaces such as plates or coils within the bioreactor will interfere much more with the mixing of a solid bed than it will with the mixing of a liquid medium. Finally, a liquid medium can be mixed reasonably well without causing undue shear forces, whereas in a bed of solids in an SSF process involving a fungus, even the slightest mixing action will cause significant physical damage to the mycelium growing at the particle surface.

The difficulty of heat removal from large-scale SSF bioreactors has two consequences for bioreactor design:

- evaporation may occur as a result of temperature rises in the bed (see Fig. 4.3.(c)), and in some cases it may in fact be promoted deliberately, given that it is one of the most effective heat removal mechanisms. However, continued evaporation can dry the bed out to water activities low enough to restrict growth. Therefore the maintenance of the water activity of the bed becomes a consideration that guides design and operation.
- given that in many SSF bioreactors the air phase plays a central role in heat removal and that the aeration rates needed in order to remove heat at a reasonable rate are more than sufficient to ensure a reasonable O_2 supply to the surface of the particles, O_2 supply is typically a minor consideration (except for Group I bioreactors, i.e., static beds without forced aeration).

The following discussion about the general scale-up problem therefore focuses on heat removal as the key scale-up criterion and maintenance of water activity as a related consideration. O_2 supply will not be covered in this general discussion, although something will be said about it in Chap. 6, which talks about Group I bioreactors.

5.3 The Reason Why Scale-up Is not Simple

Bioreactor design would be simple if all you needed to do was to obtain good performance in a laboratory-scale bioreactor and then simply construct a geometrically-identical larger version of this bioreactor. However, this is impossible to achieve. Recalling the argument presented in Sect. 2.3 (also see Fig. 2.3):

- the aim of the bioreactor is to control the conditions within the bed, such as the temperature and water activity, at the optimum values for growth and product formation;
- however, the growth of the organism causes deviations from the optimum conditions in its immediate surroundings, through the release of waste metabolic heat and the consumption of O_2, amongst other processes;
- in operating a bioreactor, we are limited to manipulating external operating variables;
- the effects of the operating variables on the conditions within the bioreactor, such as the bed temperature, are not direct. Between the manipulation that we make in the operating variable (for example, changing the temperature at which the air enters a forcefully aerated bioreactor) and any particular position in the bed, we have various transport phenomena. For example, to arrive at mid-height within a packed-bed bioreactor, the inlet air firstly has to pass through half of the bed, and the temperature of that air will have risen from the inlet value by the time it reaches the middle of the bed, due to the heat transfer that occurred over the intervening distance. This will decrease its ability to cool the middle of the bed (in fact, this phenomenon is the basis of the axial temperature profile shown in Fig. 4.3 for the forced aeration of static beds);
- the importance of these transport phenomena increases as the distance over which transport must occur increases. This distance typically increases as the size of the bioreactor increases.

So transport phenomena are of crucial importance in controlling how the bioreactor operates. Scale-up becomes a challenging task because the underlying physiology of the microorganism is independent of scale. The microorganism will respond in exactly the same way for a given set of conditions that it finds in its local environment, regardless of whether it is located within a bioreactor holding 10 g of substrate or a bioreactor holding many tons of substrate. In other words, in both bioreactors it will give the same rate of growth and heat release for a given combination of O_2 concentration, nutrient concentration, pH, temperature, and water activity.

The key question of the scale-up problem then becomes “Is it possible to keep the local environmental conditions at or very near optimal values as scale is increased?” Note that it is relatively easy to control the local environment within small-scale bioreactors. In fact, it is for this reason that thin columns are used for basic kinetic studies (which will be seen in Chap. 15).

It is important to understand that the conditions in the local environment depend on the balance between the changes caused by the microorganism and the transport phenomena that arise to counteract these changes. For example, the local temperature sensed by the organism (and which will affect its growth) depends on the balance between the rate of waste metabolic heat production and the rate of conduction of energy away to regions in which the temperature is lower (Fig. 5.1(a)). If the rate of waste heat production is higher than the rate of conduction, then the local temperature will rise, which of course occurs during the early periods of the fermentation when the growth rate is accelerating (Fig. 5.1(b)).

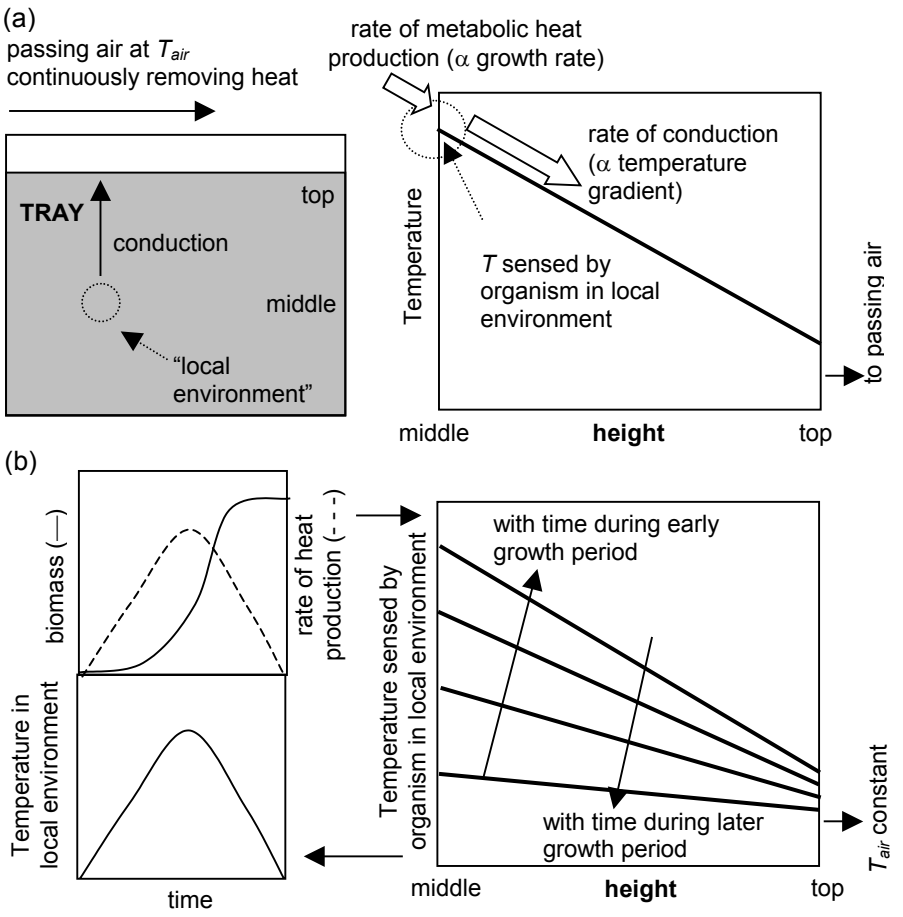

Fig. 5.1. The temperature in the local environment of the organism depends on the balance between heat generation and heat removal. This example is given in the context of a fermentation carried out within a tray, where the main heat removal mechanism in the bed is conduction. The "local environment" of interest is at mid-height in the bed. **(a)** Whether the temperature in the local environment remains constant, increases or decreases depends on the balance between the rate of metabolic heat production (which is proportional to the growth rate) and the rate of heat removal by conduction to the bed surface (which is proportional to the temperature gradient across the substrate bed). **(b)** Due to the change in the rate of production of waste metabolic heat as the growth rate changes, the temperature in the local environment changes over time. During early growth the rate of waste heat production increases. This causes the temperature to increase until the rate of heat removal once again equals the rate of heat production. However, since growth continues to accelerate, the rate of heat production continues to rise, so the local temperature must continue to rise in order to continue to increase heat removal. Later during growth, as the growth rate and therefore the rate of heat production decreases, the local temperature decreases

So the basic question that we need to answer in order to understand the scale-up problem has become: "What is the effect of scale on the ability of the transport processes to remove heat at a rate that is sufficient to prevent local temperatures from reaching values that limit growth?" The effect of scale on the effectiveness of transport phenomena will be discussed here in relation to convective and conductive heat removal in static beds. With respect to solids mixing phenomena, suffice to say that the effectiveness of mixing tends to decrease as scale increases.

Figure 5.2 illustrates the problem, using a packed-bed bioreactor as an example. As explained in Fig. 4.3, the convective flow of air through a static bed in which an exothermic reaction is occurring leads to an increase in the bed temperature between the air inlet and the air outlet. For a given organism, one of the major factors affecting the slope of the temperature gradient in the bed is the air flow rate. A laboratory-scale bioreactor may operate with the temperature exceeding the optimum temperature for growth by only a few degrees. However, as scale increases, the deviations from the optimum temperature will be much greater, especially if the same volumetric flow rate is used. It is possible to try to combat these deviations by changing key operating variables as scale increases. For example, it might appear reasonable to maintain the superficial air velocity constant (the superficial air velocity being the volumetric air flow rate divided by the overall cross-section of the bioreactor). In the simplest case, this will maintain the same temperature gradient in the bioreactor. However, due to the greater height, the temperature in the upper region of the bioreactor will reach much higher values than those that were reached at laboratory scale (Fig. 5.2). One strategy might be to increase the superficial velocity of the air (V_Z, m s^{-1}) in direct proportion to the height (H, m) of the bioreactor (that is, to maintain V_Z/H constant). This might in fact prevent the bed from ever exceeding the maximum temperature observed in the laboratory bioreactor, however, it might also lead to unacceptably high pressure drops, or the required air velocity might fluidize the bed.

The problem is more severe in the cases where significant amounts of heat are removed from the bed at small scale by conduction, such as in a tray bioreactor, or within a packed-bed bioreactor with a cooled surface. If geometric similarity is maintained, then the distance between the center of the bed and the surroundings or heat transfer surface increases with increase in scale. The effectiveness of conduction in removing heat decreases in proportion to the square of the distance over which conduction must occur. Therefore, maintaining geometric similarity will decrease the relative contribution of conductive heat removal. In fact, it is desirable to maintain the "conduction distances" constant as scale increases. For this reason tray bioreactors are scaled-up by increasing the number of trays, and not the thickness of the substrate layer within the tray. Likewise, as will be seen in Chaps. 7 and 23, it may be interesting for large-scale packed beds to have internal heat transfer plates arranged such that the large-scale version has the same "conduction distances" as a laboratory-scale bioreactor.

In general, as a bioreactor is scaled-up from the laboratory to production scale, it is not a simple matter to keep constant either V_Z/H or the distance over which conduction must occur. As a consequence, the local conditions, at least in some

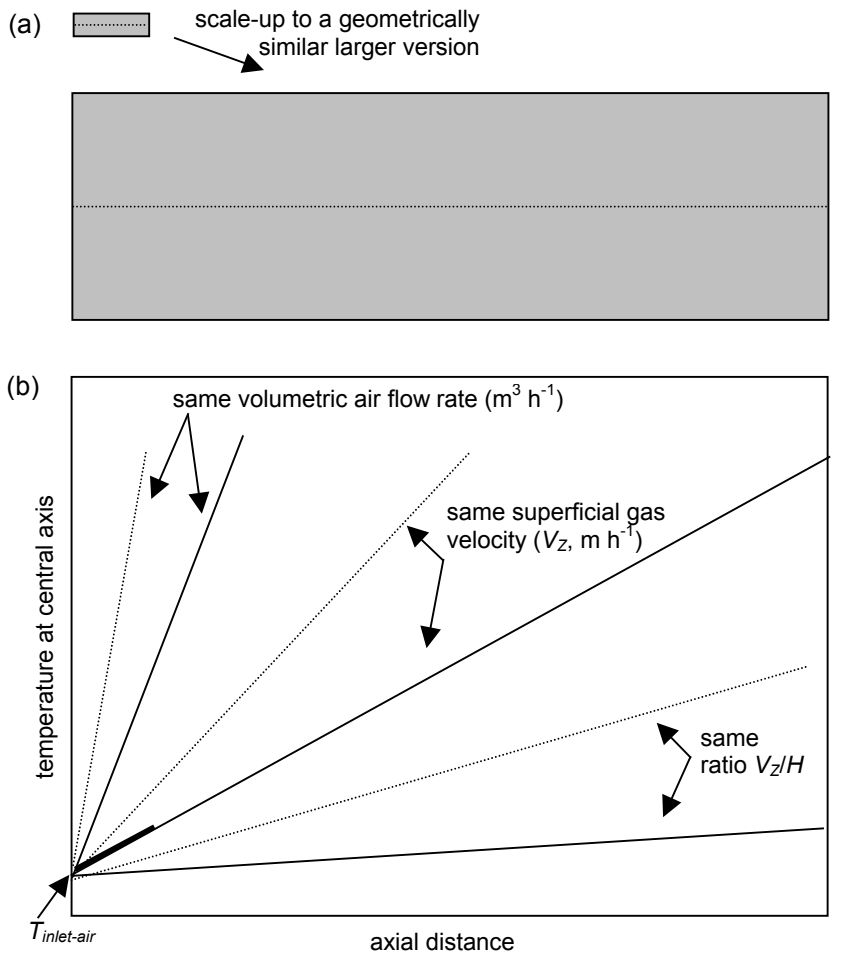

Fig. 5.2. Scale up on the principle of geometric similarity is not a simple matter. **(a)** Scale-up on the basis of geometric similarity. Both the radius and length have increased 10-fold. **(b)** Temperature profiles along the central axis that might be expected at the time of peak heat production. Key (▬) Temperature profile in the small-scale bioreactor; (—) Temperature profiles that might be expected in the large-scale bioreactor for different strategies regarding the aeration rate, if the results with the small-scale bioreactor had been obtained under a condition where the side walls were insulated (i.e., with no heat removal by conduction though the side walls); (• • •) Temperature profiles that might be expected in the large-scale bioreactor for different strategies regarding the aeration rate, if the results with the small-scale bioreactor had been obtained under a condition where the side walls were not insulated and heat was removed by cooling water in a jacket or waterbath. The different strategies regarding the aeration rate are indicated directly on the figure

regions of the bioreactor, will be less favorable for growth than those that the organism experienced at laboratory scale. The average volumetric productivity of the large-scale bioreactor (kg of product produced per cubic meter of bioreactor volume per hour) will then be smaller than the volumetric productivity achieved with the laboratory-scale bioreactor. The scale-up problem becomes more difficult when we realize that this discussion has not explored all the potential problems and complications. Some further considerations are:

- in mixed beds, the efficiency of mixing is likely to decrease with scale;
- in some beds both convection and conduction play important roles in heat removal. The optimum combination of these two mechanisms may change with scale. For example, in some cases conduction plays an important role in removal at small scale, but its contribution decreases as scale increases as the surface area to volume ratio of the bioreactor decreases;
- bioreactor design will affect the ease of substrate handling, and ease of substrate handling may be an important consideration in the economics of the process, especially in relation to the need for manual labor;
- pressure drop and fluidization considerations may put a limit on possible air flow rates;
- the sensitivity of the microorganism to damage by mixing may put a limit on the frequency with which the bed can be mixed;
- increases in bed heights may have side effects, such as the deformation of particles at the bottom of the bed, affecting inter-particle void fractions, or even crushing the particles.

Given this complexity, we are only likely to achieve the maximum possible efficiency in large-scale bioreactors if we understand the phenomena that combine to control bioreactor performance and if we use quantitative approaches to the scale-up problem.

5.4 Approaches to Scale-up of SSF Bioreactors

Various quantitative approaches have been proposed for scale-up of SSF bioreactors, including the use of mathematical models and of various “simplified approaches” that have some similarity with the “rule-of-thumb” approaches to scaling-up SLF bioreactors. Given the complexity of SSF systems, models will be more powerful tools, and should be preferred where possible, especially since various fast-solving models are available in the literature, and can be adapted to new systems without requiring an onerous amount of work. Some of these mathematical models are presented in Chaps. 22 to 25, where their potential uses are demonstrated and discussed.

It is worthwhile remembering, as noted in Chap. 2, that the inter-particle phenomena themselves are independent of scale, since we will typically be using the same sized substrate particles at small scale and large scale. Significant intra-

particle mass transfer limitations, of O_2 and nutrients, may occur even in particles of only 1 to 5 mm diameter. These limitations are intrinsic to SSF. The best that can be done in the manner in which the bioreactor is operated is to control the inter-particle conditions, for example, to maintain the O_2 concentration in the gas phase in contact with the particle surface at as high a concentration as possible.

The knowledge framework concerning scale up of SSF processes can be characterized as follows:

- **in relation to current large-scale bioreactors:** there is no evidence in the literature that anything other than "best-guess" or "trial-and-error" approaches have been used for the development of almost all current large-scale SSF bioreactors. It is likely that some engineering calculations have been done, even if they were not reported. This is most likely in the soy sauce industry, but the knowledge about scale-up, if it has been generated, has not been made widely available because it is important proprietary information;
- **in relation to the strategies themselves:** Since the work of Saucedo-Castaneda et al. (1990), mathematical modeling work has been done with the aim of developing rational scale-up strategies for SSF bioreactors. However, although such models are potentially very useful tools for guiding the selection and design of large-scale bioreactors, there are no reports describing a scale-up study in which this has actually been done. To date the investigations have been limited to the use of models to demonstrate, using simulations, how models might be used to guide scale up.

Finally, it is important to point out that although mathematical models of bioreactor behavior can be used to predict how a bioreactor will perform before it is built, this modeling work does not replace the need to do experimental work, rather, it is a tool for guiding the experimental program. As will be shown later, mathematical modeling can help to raise questions about bioreactor operation that can be answered through experimentation, it can also help to eliminate ideas which appear reasonable but are actually unfruitful, without wasting time and money to test the ideas experimentally.

Further Reading

Scale up in submerged liquid fermentation processes

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Scale-up of SSF bioreactors

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