Scale-Up in Chemical and Bioprocess Engineering

10[2]

Scientists dream about doing great things. Engineers do them.

James A. Michener

Engineering is a great profession. There is the satisfaction of watching a figment of the imagination emerge through the aid of science to a plan on paper. Then it moves to realization in stone or metal or energy. Then it brings homes to men or women. Then it elevates the standard of living and adds to the comforts of life. This is the engineer's high privilege.

Herbert Hoover

10.1 Introduction

Scale-up in the chemical and bioprocessing industries is the process of applying knowledge acquired at the laboratory scale, e.g., in test tubes, Petri dishes, flasks, small reactors, and laboratory-scale fermenters, to a large scale, e.g., in pipes, filters, reactors, and fermenters, in an efficient and economical way. Scale-up is an economic, engineering, and scientific discipline (Heitmann and Rhees 1984). Although the practical application of scaling up emerged only after the First World War, in 1912, a prominent chemical engineer, J. Whiting, defined the scaling-up process as follows: (1) laboratory stage, (2) small-scale model, (3) large-scale or development unit, (4) semicommercial plant, and (5) commercial plant (Heitmann and Rhees 1984). Since Whiting's definition first came out, the field has seen many advances, and the scaling-up process has been systematized. Even the field of chemical engineering has evolved and today includes bioprocess engineering. Advances in scale-up transformed the chemical industry of the twentieth century and, in addition, led to the creation and development of the bioprocess industry of our era.

Penicillin production

Perhaps the history of the development of penicillin symbolizes a big change in the chemical engineering profession in many ways, including the scaling-up process. It is a gripping story and marks the birth of biochemical engineering, perhaps better called bioprocess engineering. According to the historical background, the person who first noticed the presence of penicillin was not Alexander Fleming but the French medical student Ernest Duchesne, in 1896. Alexander Fleming rediscovered penicillin in St. Mary's Hospital in London in 1928. Fleming noted that a culture of *Staphylococcus aureus* in a Petri dish was contaminated with a blue-green mold (*Penicillium notatum*), and

R. Simpson and S.K. Sastry, *Chemical and Bioprocess Engineering: Fundamental Concepts for First-Year Students*, DOI 10.1007/978-1-4614-9126-2_10,

staphylococcus stopped growing in the vicinity of the fungus. Alexander Fleming published his findings in 1929 and called the substance *penicillin*. Although Fleming was the first to observe and speculate on the pharmaceutical potential of penicillin, it would take 14 years to finally translate into a product on an industrial scale. Why did it take so much time? Partly because it was a biochemical process, and, although Fleming understood clearly how to produce small amounts of penicillin on a laboratory scale, it was unclear how to achieve industrial-scale production and, in addition, make it economically profitable. Another situation that complicated scaling up was that it took years to be absolutely certain that penicillin was an effective drug. Its effectiveness began to be clarified mainly by the work of Howard W. Florey and his research group in 1939. In these studies, Florey and his group were able to produce sufficient amounts of penicillin to be tested in mice. Then Florey and a colleague, Norman G. Heatley, traveled to the USA to raise funds and pursue industrial-scale production. Although it took years, a number of companies with strong government support began producing penicillin in 1943 and on a larger-scale in 1945. In fact, penicillin was used as a medicine on soldiers who participated in D-Day (Heitmann and Rhees 1984).

Among other achievements, the extremely successful history of the scaling up of the production of penicillin resulted in a big scaling down of its price from $20 per dose in 1943 to just $0.55 per dose in 1946, an almost 40-fold reduction. Today, the price of a pill is in the range of US$0.10–$0.20. In addition, in the early 1940s, the term *biochemical engineering* was coined. Since then, bioprocess engineering has emerged as a potent field.

In 1945, Sir Alexander Fleming, Ernst B. Chain, and Sir Howard W. Florey were awarded the Nobel Prize in Physiology or Medicine *"for the discovery of penicillin and its curative effect in various infectious diseases."*

10.2 Understanding Size Change

We are used to watching, in movies, superheroes, giants that seem like us (in terms of their physical proportions), and enormous animals (e.g., King Kong, Godzilla), which often are extremely large—many times their real size in nature. To take a concrete example, most of us are probably familiar with *Gulliver's Travels* of Jonathan Swift (1667–1745). In the first part of the novel, the narrator describes the life of Lemuel Gulliver and how he enjoys traveling. Lemuel Gulliver takes his first trip to the island of Lilliput (1699–1702), where the inhabitants, the Lilliputians, measure just 6 [in.] tall, approximately 12 times smaller than us. Initially, Gulliver is welcome on the island, but with the passage of time, he is accused of treason for not obeying the orders of the King and is sentenced to be blinded. Fortunately, with the help of a friend he manages to escape the island in a boat, is later rescued by a ship that sails these waters, and, finally, returns home safely. After returning home, he embarks on a new trip, now on the *Adventure* ship. Later, the ship is caught in a terrible storm and runs aground, where his companions abandon him in Brobdingnag. There he is rescued by a peasant. In Brobdingnag, the people are 12 times bigger than us. By Gulliver's estimates, the inhabitants are about 18.1 m. The farmer takes him home and leaves him in the care of his daughter. Of course, the peasant put him on exhibit as a curiosity and charges viewers for it. Although the novel continues and is enjoyable and full of irony, we will stop here and analyze mathematically the short paragraph that we just read and also ask ourselves some questions.

Does size matter?

Galileo Galilei (1564–1642) was an Italian astronomer, mathematician, philosopher, and physicist. In 1638, he wrote a book entitled *Dialogues Concerning Two New Sciences,* wherein he explains and analyzes why objects cannot be of just any arbitrary size and clarifies why there are no giants like in

Gulliver's Travels. Evidently, there is no gorilla like King Kong towering 18.5 m tall (like the inhabitants of Brobdingnag). Galileo might have been the first person to analyze the topic of scaling in a scientific way. Nowadays, scaling is utilized in many branches of science and engineering, from anatomy to process and bioprocess engineering.

But why are there no giants like King Kong or Godzilla?
For simplicity, if some animal were shaped like a regular cylinder with a height of H meters and a diameter of D meters, then its volume would be

$$V = \frac{\pi D^2}{4} H. \tag{10.1}$$

If we increase the size of our animal ten times, from H to $10H$ and from D to $10D$, then the volume of this little giant (V_G) would be

$$V_G = \frac{\pi (10D)^2}{4} 10H = 1,000 \frac{\pi D^2}{4} H = 1,000V. \tag{10.2}$$

That is, the linear dimensions, height and diameter, increased ten times (the animal is ten times bigger) but the volume (weight) increased 1,000 times. Before doing any anatomical analysis, we can speculate that the bones of this little giant would break under the weight of the body because the new animal would not be 10 times heavier, as it is 10 times bigger, but 1,000 times heavier. Doing some simple calculations and assuming that the bone resistance (strength) is approximately proportional to the area of the bone's cross section, and choosing a diameter d for the bone, we have

$$\text{Original cross section } (A) : A = \frac{\pi d^2}{4}, \tag{10.3}$$

$$\text{Final cross section } (A_G) : A_G = \frac{\pi (10d)^2}{4} = 100 \frac{\pi d^2}{4} = 100A. \tag{10.4}$$

As mentioned, the little giant is 10 times bigger than the original one, but its volume increased 1,000 times and the bone strength increased just 100 times. This little giant would almost surely collapse. The volume increased very rapidly (by L^3)—ten times more than the area (which increased by L^2).

Gazelles are antelopes of the genus *Gazella*, and they are graceful and beautiful animals. One of their main characteristics is their speed; they attain maximum speeds of almost 100 [km/h]. But, as was mentioned and explained earlier, they could not be much bigger than they already are unless (a) they had thicker legs like those of a rhinoceros or (b) they had a compressed body with oblique legs to gain stability like giraffes. The interesting thing is that rhinoceroses and giraffes are of the same order as gazelles. In addition, rhinoceroses and giraffes also attain high running speeds (50–70 [km/h]), much quicker than the world's fastest human, Usain Bolt (approximately 37.6 [km/h]).

Why can a wet fly not fly?
In summer, many people like to go swimming in a pool and go off the diving board. Once out of the water, you might shake some of the excess water off your body before using your towel. All this comes naturally to us but can be a nightmare for a fly. As you may know, flies cannot fly when they are wet; they have to crawl. Why?

An interesting concept in scaling (comparing different sizes) is to take into account the surface-area-to-volume ratio (A/V). As we will show later in this chapter, this concept is very important when, for example, scaling heat transfer processes, reactors, and fermenters. In the specific case of a fly, we will estimate the amount of water that a human being and a fly carry with them out of a pool as a proportion of body weight. Again, we will use a regular cylinder as the reference shape, in this case for both fly and human. For the human being we will use a regular cylinder of 0.250 [m] diameter and a height of 1.60 [m] (approximately 80.0 [L]) and the fly will be 0.0200 [m] (2.00 [cm]) long with a diameter of 0.00500 [m] (5.00 [mm]). Now we are ready to calculate the volume of the human being and of the fly before going to the pool, but to calculate the water they carry, we need to define the thickness of the layer of water for both human and fly. Let us assume a value of the thickness layer, as a rough calculation, and then estimate what percentage of the body weight is carried out when both human and fly get out of the pool. Let us assume that the thickness of the layer is d.

Human being

$$\text{Before} : V = \frac{\pi(0.25)^2}{4} 1.6 = 0.0785 \left[\text{m}^3\right] = 78.5 \text{ [L]}; \tag{10.5}$$

$$\text{After} : V_{\text{W}} = \frac{\pi(0.25 + 2d)^2}{4} (1.6 + 2d). \tag{10.6}$$

If $d = 1$ [mm] $= 0.001$ [m], then the amount water that the human being will carry with him as a percentage of his volume is

$$100 \frac{V_{\text{W}} - V}{V} = 100 \frac{79.9 - 78.54}{78.54} \cong 1.73 \text{ \%}. \tag{10.7}$$

Clearly, the human being can easily shake off all the water. He just carries a small amount of water in relation to his volume (proportional to weight).

Fly

$$\text{Before} : V = \frac{\pi(0.005)^2}{4} 0.02 = 0.000393 \text{ [L]}; \tag{10.8}$$

$$\text{After} : V_{\text{W}} = \frac{\pi(0.005 + 2(0.001))^2}{4} (0.02 + 2(0.001)) = 0.000847 \text{ [L]}. \tag{10.9}$$

Thus, the amount water the fly will carry as a percentage of its volume is

$$100 \frac{V_{\text{W}} - V}{V} = 100 \frac{0.000847 - 0.000393}{0.000393} \cong 115.5 \text{ \%}. \tag{10.10}$$

Obviously, the human being will have a much easier time getting out of the pool. The fly, on the other hand, will have a very hard time getting out. Can you imagine carrying 80–90 [kg] of water?

Some may argue that the assumption of the thickness of the water layer is not accurate, but before considering this, let us try to understand is happening in this "scaling" situation (fly to human). As mentioned, the critical concept here is the surface-area-to-volume ratio. Let us calculate this parameter for both the human being and the fly:

$$\text{Human being}: \left(\frac{A}{V}\right)_{\text{Human}} = \frac{\pi DH + 2\left(\frac{\pi D^2}{4}\right)}{\frac{\pi D^2}{4}H} = \frac{4}{D} + \frac{2}{H} = \frac{4}{0.25} + \frac{2}{1.6} = 17.3, \tag{10.11}$$

$$\text{Fly}: \left(\frac{A}{V}\right)_{\text{Fly}} = \frac{4}{D} + \frac{2}{H} = \frac{4}{0.005} + \frac{2}{0.02} = 900. \tag{10.12}$$

As suspected, the surface-area-to-volume ratio of the fly is much greater than the surface-area-to-volume ratio of the human being, in this example, approximately 52 times greater. You could argue about whether the data and the shape used as reference are strictly representative, but clearly, the smaller the object, the bigger the surface-area-to-volume ratio. Here are some examples of the surface-area-to-volume ratio of various three-dimensional bodies:

$$\text{Sphere}: \left(\frac{A}{V}\right)_{\text{Esphere}} = \frac{4\pi r^2}{\frac{4}{3}\pi r^3} = \frac{3}{r}; \tag{10.13}$$

$$\text{Cube}: \left(\frac{A}{V}\right)_{\text{Cube}} = \frac{6a^2}{a^3} = \frac{6}{a}; \tag{10.14}$$

$$\text{Tetrahedron}: \left(\frac{A}{V}\right)_{\text{Tetrahedrum}} = \frac{\sqrt{3}a^2}{\frac{\sqrt{2}a^3}{12}} = \frac{6\sqrt{6}}{a}. \tag{10.15}$$

In all cases, as is normal, the smaller the object (a or r), the bigger the surface-area-to-volume ratio. An extreme example is the surface-area-to-volume ratio of a bacterium. Assuming a bacterium with a spherical shape with a diameter of 2.0 [μm], then

$$\text{Bacterium}: \left(\frac{A}{V}\right)_{\text{Bacterium}} = \frac{3}{r} = \frac{3}{2 \times 10^{-6}} = 1.5 \times 10^6. \tag{10.16}$$

It has a surface-area-to-volume ratio that is almost 1,700 times bigger than that of the fly!

The extremely high surface-area-to-volume ratio is one of the main reasons why microorganisms like bacteria are able to reproduce in just 20–30 min. Although two objects can be geometrically similar in terms of linear dimensions L, the area changes by L^2 and volume changes by L^3. A strong message here is that size really does matter. Several aspects of life are strongly affected by size, for example, metabolism rate and temperature regulation. As we will discuss later, in process engineering, you normally start working and doing research studies at the laboratory scale with the aim of having an end product at the industrial level. For example, if you are testing and experimenting with different types of wines, your laboratory-scale fermenter will have a volume of 1–5 [L]. Meanwhile, an industrial fermenter could have a volume of 50,000–100,000 [L], i.e., 10,000–100,000 times bigger than the laboratory-scale fermenter.

Does size confer advantages?
Like us, insects require oxygen to live and produce CO_2 as a waste product. For insects, the oxygen transport mechanism (respiration) is by diffusion through a series of tubes called the tracheal system, and it is clear that if the distances are short, the mechanism is efficient. But, interestingly, this mechanism significantly limits the size of insects, and it is hard to imagine that they could measure more than 2 [cm]. Returning to the subject of giant animals like King Kong but with a different mechanism, giant insects cannot exist, as is commonly portrayed in horror movies around the world.

One of the most obvious advantages of being human is that we can control and regulate temperature efficiently. In fact, the amount of food required is proportional to the transfer area of the body (remember, the bigger the body, the lesser surface-area-to-volume ratio). For example, 5,000 mice weigh around the same as one human (200 [lb]), but their demand for oxygen and food is approximately 70 times our demand. A mouse, for the sole purpose of controlling temperature, needs to consume in food one-fourth its body weight per day (which in our case would be about 15–20 [kg]). This is one reason why most small animals cannot live in icy environments or at low temperatures.

Socialization (management). Of all animals, humans have a capacity to socialize in larger groups, which might be explained by the ability of our brains to handle greater complexity. Dunbar's number (Robin Dunbar 1947–) is a theoretical cognitive limit on the number of people with whom humans can maintain stable social relationships. Although not necessarily an exact number, the number that has received the widest acceptance is 150. According to Dunbar's research, in examining 21 hunter-gatherer societies for which we have reliable historical information, the average size of the communities was 148.4 (approximately 150). This number appears in different settings of human groups—e.g., companies, combat battalions—and it seems that higher numbers require imposing a set of rules intended to manage the administration and organization of the group. Dunbar argues that management and organization in groups with fewer than 150 persons is optimal for the management and maintenance of a certain level of informality and familiarity.

10.3 Principle of Similarity

One of the important concepts for scaling up and down a piece of equipment and its operation from the laboratory to industrial scale is *the principle of similarity*. If we can find and optimize a design and operating conditions at the laboratory scale (model), it would be highly desirable to reproduce it on an industrial production scale. According to Johnstone and Thring (1957), "*Process similarity is achieved between two processes when they accomplish the same process objectives by the same mechanisms and produce the same product to the required specifications*." As we have previously mentioned, in the wine-making example, this involves increasing the size of our experiment at the laboratory scale by approximately 10,000–100,000 times or more. On the other hand, we found that when changing scale, it is not possible to retain all the features and characteristics of the object at one time. As an example, in our previous analysis, we discovered that when increasing size, it was not possible to maintain a constant surface-area-to-volume ratio, and the implications were substantial (the wet fly).

The most important stages of similarity in process and bioprocess engineering are (a) geometric similarity, (b) mechanical similarity, (c) thermal similarity, and (d) chemical and biochemical similarity.

Geometric similarity
Figure 10.1 depicts reactors/fermenters at the laboratory (model) and industrial scales.

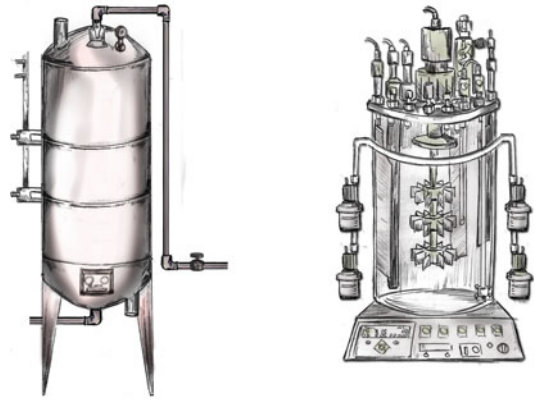

Fig. 10.1 Laboratory and Industrial fermenters

These reactors/fermenters will be geometrically similar if for example:

$$\left(\frac{H}{D}\right)_{\text{Model}} = \left(\frac{H}{D}\right)_{\text{Industrial}}. \tag{10.17}$$

Where H is the height and D the diameter of the reactor/fermenter. As expressed by Johnstone and Thrings (1957), "*two bodies are geometrically similar when to every point in the one body there exists a corresponding point in the other*."

Mechanical similarity

Mechanical similarity includes static, kinematic, and dynamic similarities. In addition, mechanical similarity is an extension of geometric similarity.

(a) **Static similarity.** Two geometrically similar bodies are considered statically similar when, subject to a constant stress, they undergo a deformation in such a way that they remain geometrically similar.

(b) **Kinematic similarity**. Kinematic similarity requires that both the length and time scales be similar. That is, the prototype and the model should have the same speeds at corresponding points. Therefore, the flow patterns between the model and the prototype will be similar. As mentioned with respect to static similarity, kinematic similarity also includes geometric similarity.

(c) **Dynamic similarity**. Dynamic similarity requires that the forces on the model and the prototype be similar at corresponding points. Again, dynamic similarity also includes geometric similarity.

Thermal similarity

Thermal similarity is related to heat flows. Temperature differences between two points at the same instant in time in the model must be equal to the temperature differences at the corresponding points at the same instant in the prototype.

Chemical and biochemical similarity

Chemical and biochemical similarities are associated with transformations due to chemical or biochemical reactions within the system. According to Johnstone and Thrings (1957), "*Geometrically and thermally similar systems are chemically similar when corresponding concentration differences bear a constant ratio to one another and when the systems, if moving, are kinematically similar*."

10.4 A Glimpse of Dimensional Analysis

Dimensional analysis is a method that facilitates the study of systems by reducing the number of independent variables in such a way that it is not affected by changes in scale. According to Bridgman (1969): "*The principal use of dimensional analysis is to deduce from a study of the dimensions of the variables in any physical system certain limitations on the form of any possible relationship between those variables. The method is of great generality and mathematical simplicity*." Dimensional analysis attracted serious attention in the late nineteenth century mainly through the work of Lord Rayleigh, Reynolds, Maxwell, and Froude in England and Carvallo, Vaschy, and other scientists in France (Sonin 2001).

There are two classical methods in dimensional analysis, *Buckingham's pi theorem* and the *method of indices* by Lord Rayleigh. Here we will briefly explain the more common of the two: *Buckingham's theorem*.

Buckingham's theorem. This theorem can be divided into three steps as shown below (Sonin 2001).

Step 1: define the dependent variable and find all the relevant independent variables. This is a critical and, normally, difficult task. A simple example will be to relate the distance covered (dependent variable) by a body in free fall before hitting the ground. Assuming that the air resistance is negligible, the two independent variables are time (t) and acceleration of gravity (g):

$$d = f(t, g), \tag{10.18}$$

where d is distance, t is time, and g is acceleration of gravity.

Step 2: identify the dimensions of the dependent and independent variables. In our example:

d: L,
t: t,
g: Lt^{-2}.

Step 3: "If an equation contains n separate variables and dimensional constants and these are given dimensionless formulas in terms of m fundamental dimensions, then the number of dimensionless groups in a complete set is n − m" (Johnstone and Thrings 1957). In our example, we have three variables, including g, a dimensional constant (d, t, and g), and we have two fundamental dimensions (L and t). Thus, we can form just one dimensionless group.

In our example:

$$d[g]^a[t]^b = 1. \tag{10.19}$$

Thus, $L\left[\frac{L}{t^2}\right]^a[t]^b = 1$; $L^{1+a}[t]^{b-2a} = L^0t^0$.

Therefore:

$$1 + a = 0,$$

$$b - 2a = 0.$$

Therefore, $a = -1$ and $b = -2$.

Finally, there is one dimensionless group:

$$\left[\frac{d}{gt^2}\right],$$

and (10.19) takes the form

$$d = f\left(g, t^2\right) = kgt^2. \tag{10.20}$$

From our basic knowledge of high school physics we know that

$$d = \frac{1}{2}gt^2. \tag{10.21}$$

10.5 Understanding Scale-Up (-Down) in Chemical and Bioprocess Engineering

We will show the relevance of scaling up/down with a vivid example. For this purpose and due to the importance that bioethanol has acquired, we will analyze, in some detail, so-called alcoholic fermentation. In addition, we will try to understand and quantify how the cooking time of a turkey is related to its size.

Alcoholic fermentation.
Ethanol is an oxygen containing organic compound, due to its characteristics as a solvent, germicide, antifreeze, depressant and a fuel (Asli 2009). In addition, since the energy crisis of the 1970s, and now with global warming concerns, alcohol fermentation has been the subject of the most important scientific efforts to obtain a sustainable and renewable energy source (Pramanik 2003, 2005). Alcoholic fermentation is the conversion of sugar into ethanol. Normally, alcoholic fermentation is carried out by yeast, *Saccharomyces cerevisiae,* in controlled operating conditions. As depicted in Fig. 10.2, *S. cerevisiae* reproduces in a similar way to bacteria, but with a significant difference: although from one cell a second cell emerges, they are not two new cells, as in bacteria, but mother and daughter cells. When the newborn cell emerges, it leaves a scar on the mother cell. The number of scars indicates the "age" of the mother cell.

Fermentation is a biochemical reaction in which the substrate (sugar) is converted into alcohol (ethanol), as presented in the following stoichiometry, in this case, the conversion of glucose into ethanol plus carbon dioxide:

$$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2.$$

Strictly speaking, the reaction in a commercial fermenter is better expressed as:

$$\begin{aligned} &\text{Glucose (substrate)} + \text{Nutrients} + \text{Cells (catalyst)} \\ &\quad \rightarrow \text{Ethanol (product)} + CO_2 + \text{Cells} + \text{byproducts}. \end{aligned} \tag{10.22}$$

Alcoholic fermentation is an exothermic reaction (generating heat), and its kinetics (velocity of the reaction) depends strongly on temperature. Several factors affect the course of fermentation (e.g., pH, alcohol concentration, high salt concentration), but temperature has the greatest effect. Several research studies have shown that the optimum temperature for *S. cerevisiae* in alcoholic fermentation is close to 32 °C (Costa et al. 2009).

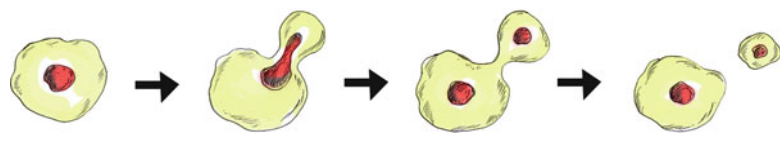

Fig. 10.2 Reproduction of *Saccharomyces cerevisiae*

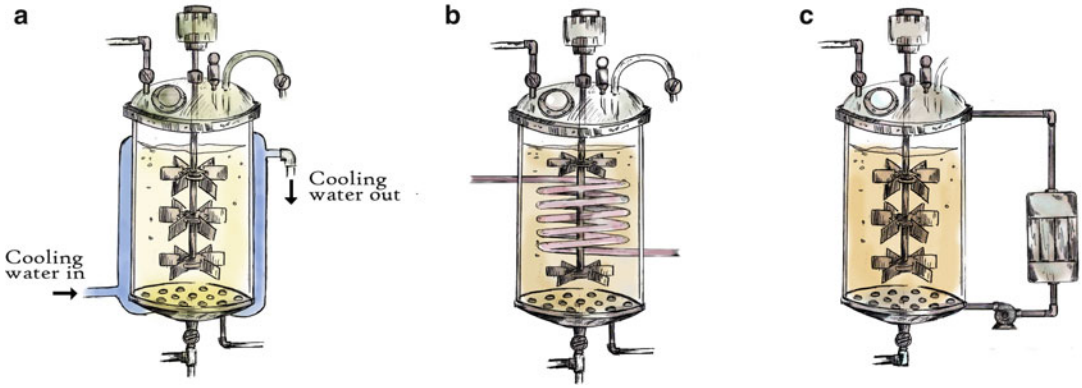

Fig. 10.3 Three different temperature-control systems: Jacket, Serpentine and External Heat Exchanger

Table 10.1 Comparison between a laboratory and industrial scale fermenter: heat transfer

	Laboratory fermenter	Industrial fermenter	Ratio industrial/ laboratory
Heat generation [energy units/h]	Q_F	100,000 Q_F	100,000
Heat transfer area [m^2]	0.016875π	36.5403π	~2,165
Heat generation per m^2 [energy units/h m^2]	~18.9 Q_F	~871.1 Q_F	~46.1

Laboratory and commercial fermenters. In industrial operations (fermenters from 50,000 to 100,000 [L]), to maintain a constant temperature during this exothermic process, heat must be removed. Normally, this can be done using (a) a jacket surrounding the vessel, (b) internal coils, or (c) an external heat exchanger. Figure 10.3 presents the schematic of a fermenter showing all three alternatives to control temperature during fermentation. In addition, to achieve a homogeneous culture—to maximize mass transfer—it is not necessary to implement mechanical agitation due to the strong agitation resulting from CO_2 release during fermentation.

On the other hand, at the laboratory scale (1–20 [L]), to maintain a constant temperature, instead of using a cooling device, as is done at the industrial scale, heat must be added. Also, to maintain the required homogeneity of the culture, it is necessary to perform mechanical agitation. The question is why it is necessary at the laboratory scale to add heat and perform mechanical agitation? Since we already know that alcoholic fermentation is exothermic and releases significant amount of CO_2, resulting in a strong agitation of the culture at the industrial level.

Some simple calculations

Heat transfer. To understand what is happening, we will consider for our analysis a laboratory reactor/fermenter with a volume of 1 [L] and an industrial fermenter with a volume of 100,000 [L]; the two fermenters are geometrically similar, i.e., $(H/D)_{\text{Laboratory}} = (H/D)_{\text{Industrial}} = 3$. In addition, the exothermic reaction will liberate Q_F (energy units/hL), where Q_F is independent of fermenter size and depends only on the type of microorganism. To estimate the heat transfer area for calculation purposes, we will consider in both laboratory and industrial scale cases, where the area is given by the mantle of the vessel (πDH). Based on the aforementioned data and our assumptions, we can generate the following table (Table 10.1).

Table 10.2 Comparison of laboratory and industrial scale fermenters: power of agitation

	Laboratory fermenter	Industrial fermenter	Ratio industrial/laboratory
Power of agitation [J/m^{2}s]	0.226 kF_G	10.45 kF_G	~64

As depicted in Table 10.1, while the amount of heat generated increases 100,000 times between the industrial to laboratory scale, the heat transfer area increases just 2,165 times. As mentioned, at the laboratory scale, the heat generated is not enough to maintain or increase the temperature of the culture, meaning that the heat released to the ambient environment is greater than the heat generated by the culture. On the other hand, at the industrial scale, the heat transferred to the ambient environment is lower than that generated during fermentation. The volume increased (proportional to heat generation) 100,000 times and the area just 2,165 times. Returning to the wet fly example at the beginning of this chapter, the key to understanding this unexpected situation is that the smaller the size, the bigger the surface-area-to-volume ratio. Interestingly, based on the aforementioned results, there should be a reactor/fermenter size (volume) where the heat generated is equal to the heat released to the ambient environment. In such a case, it is not necessary to remove or add heat. We encourage students to revisit Chap. 6 and, with the help of heat transfer equations, develop an expression for the volume of a reactor/fermenter that could maintain a constant temperature without cooling or heating the vessel.

Agitation. When a culture of *S. cerevisiae* transforms glucose into ethanol, it also generates CO_2 as a gas in the operating conditions of fermentation (approximately 30 °C and 1 atm). As mentioned, the gas flow generated by *S. cerevisiae* at the industrial scale is sufficient to violently agitate the culture, but, in contrast, at the laboratory scale it is not enough to achieve homogenization of the culture. Again, the question is why? Using the same fermenters as in the previous example, we will estimate the power of agitation due to CO_2 generation in each case: laboratory and industrial scale. We will call F_G [m^3_g/m^3_cs] the amount of gas [m^3] generated per cubic meter of culture per second, where F_G is independent of the size of the fermenter and depends mainly on the type of cells (*S. cerevisiae*) and the operating conditions of the fermentation (e.g., temperature). The power of agitation can be expressed as

$$P_g = k\frac{F_G V_F}{A_C}, \tag{10.23}$$

where P_g is the power of agitation [J/m^{2}s], k is constant [J/m^3_g], F_G is the flow of CO_2 per cubic meter of culture [m^3_g/m^3_cs], V_F is the volume of the fermenter [m^3_c], and A_C is the area of the cross section of the fermenter [m^2].

Therefore, we obtain the following table.

As shown in Table 10.2, the power of agitation at the industrial level is approximately 64 times greater when compared with the laboratory scale. This is why we observe severe agitation at the industrial level, and, on the other hand, if we do not perform mechanical agitation in the laboratory, cells will precipitate and the fermentation process will not progress accordingly.

Cooking a turkey.

Naturally, if we are to prepare a good and tasty turkey, it is logical to turn to the experts, or rather follow the advice and recipe of our charming grandmother. Looking at her old notes, we find the following recipe for stuffed and unstuffed turkey.

Of course, we are not in a position to question our grandmother's recipe, which for years has resulted in excellent turkeys that we have been sharing at family dinners on both Thanksgiving and Christmas. But Table 10.3 has called to our attention that when the turkey's weight doubles from 14

Table 10.3 Cooking times for turkey as reported in the old notes of our grandmother

Turkey mass [lb]	Cooking time (unstuffed) [h]	Cooking time (stuffed) [h]
14	3.2	4
20	3.8	4.8
28	4.8	6

to 28 [lb] the cooking time does not increase in the same way. Let us revisit the principle of similarity and dimensional analysis and make a robust determination about the great recipe of our dearly beloved grandmother.

Turkey cooking time analysis. First, we will focus on identifying the relevant variables that have the greatest impact on the cooking time of the turkey. Clearly, the first is its size, but how do we define size here? It could be the mass of the turkey (volume), but clearly more representative is the area exposed by the turkey to the environment in the oven. Why? Remembering our heat transfer equations (Chap. 6), the heat transfer rate (Q) is directly proportional to the area exposed by the body, its thermal properties (in this case thermal diffusivity), and the temperature difference between the oven and the turkey. Thus, we can identify five variables: cooking time (t), heat transfer area (A), thermal diffusivity (α), oven temperature (T_a), and the temperature at the turkey's center (T_T). As the last variable, it seems reasonable to assume that the turkey is cooked properly when the center temperature reaches some desired value (e.g., 70 °C). Following *Buckingham's pi* theorem—or *Rayleigh's method of indices*—we can reduce these five variables to two dimensionless groups:

$$\frac{T_T}{T_a} \text{ and } \frac{\alpha t}{A_T}. \tag{10.24}$$

Why? First, we invite students to confirm that these two groups are dimensionless and, in addition, to do the analysis to find them. As expected, because the dimensions in this system were completed by three primary quantities, L, T, and t, there should be two dimensionless groups (five variables—three primary quantities). It is worth mentioning that the dimensionless number $\alpha t/A_T$ is known as the Fourier number in heat transfer theory.

Therefore,

$$\frac{T_T}{T_a} = f\left(\frac{\alpha t}{A_T}\right). \tag{10.25}$$

Although we do not know what the function is that relates these two dimensionless groups, we know that to achieve the same thermal effect in two different bodies, the dimensionless group $\alpha t/A$ must be the same in two bodies. Therefore,

$$\left(\frac{\alpha t}{A_T}\right)_1 = \left(\frac{\alpha t}{A_T}\right)_2 = k, \tag{10.26}$$

where k is a constant and 1 and 2 denote two different body sizes. Given that the thermal diffusivity does not change with the size of the turkey, we can rewrite (10.26) as follows:

$$\left(\frac{t}{A_T}\right)_1 = \left(\frac{t}{A_T}\right)_2 = k. \tag{10.27}$$

Table 10.4 Comparison of cooking time as calculated by dimensional analysis and grandmother recipe

Turkey mass ([lb]	Cooking time (unstuffed) [h]	Predicted cooking time (unstuffed) [h]	Cooking time (stuffed) [h]	Predicted cooking time (stuffed) [h]
14	3.2	3.0	4.0	3.8
20	**3.8**	**3.8 (reference)**	**4.8**	**4.8 (reference)**
28	4.8	4.8	6.0	6.0

Before passing judgment on our grandmother's recipe, we need to relate the area of the turkey to its mass. Assuming that the turkey is roughly a sphere, then

$$m_T = \rho V = \rho \frac{4\pi r^3}{3} \text{ and } A_T = 4\pi r^2, \tag{10.28}$$

where m_T is the turkey's mass, ρ its density, V its volume, and r its radius.

Therefore,

$$m_T = \rho \frac{4\pi}{3} \left(\frac{A_T}{4\pi}\right)^{3/2}. \tag{10.29}$$

Then

$$A_T = k_0 {m_T}^{2/3}. \tag{10.30}$$

Finally, replacing A_T in (10.27) we obtain

$$\left(\frac{t}{{m_T}^{2/3}}\right)_1 = \left(\frac{t}{{m_T}^{2/3}}\right)_2. \tag{10.31}$$

Although with this equation we are unable to predict the required cooking time for our turkey, we can use (10.31) to extrapolate the cooking time from one size to a larger or a smaller size. Let us use as a reference the cooking time for a 20 [lb] turkey (Table 10.3). Then we can calculate the cooking time for 14 and 28 [lb] and compare with the data reported in our grandmother's table (Table 10.4).

Again, we invite students to verify these results using (10.31). Although not perfect, the extrapolations are a very good estimate, and we can say confidently that grandma's recipe enjoys strong scientific support. Finally, although the results are very close, I prefer to use my grandmother's recipe instead of our scientific calculations. Why?

10.6 Scale-Up in Nature

What do we see? Today, scientists and engineers have better tools: not only powerful computing capabilities but also much better microscopes or, more properly, nanoscopes (e.g., to capture 3D movies of living cells). Initially, we used our eyes, then we constructed lenses, and today, we have passed from electron microscopes (scanning electron microscopes) to nanoscopes [scanning probe microscopes (SPMs)]. Although with an electron microscope we can see, in optimal conditions, at the scale of the diameter of an atom, the problems or limitations lie in the characteristics of the sample. Electron microscopes require a vacuum setting, and the biological material should be dried in a

specific manner to avoid shrinkage. According to Rachel Harrison, "*live objects could not withstand the vacuum, which limited actual observations of the functions of the objects*." In the 1980s, SPMs were developed and until today they provide the highest resolution. Since then, other microscopes have been invented: atomic force microscopy (AFM) and magnetic force microscopy (MFM). In 1989, scientists at IBM Laboratories (Almaden, San Jose, CA) using a scanning tunneling microscope (STM) were able to manipulate and spell "IBM" with 35 xenon atoms. With these kinds of microscopes, we can now manipulate and observe objects at the nanometer and atomic levels. Therefore, it is time to turn our eyes to look and learn from Mother Nature.

Multiscale. As presented in Chap. 4, the lotus plant has inspired the development of materials that are repellent to water, and likewise the structure of honeycombs has inspired structural and mechanical engineers, architects, and artists. As expressed by Coppens (2003), in the chemical and bioprocess engineering fields, there are big differences between engineers' solutions and nature's solutions to similar problems. One aspect of nature that could benefit our field is the way it stretches the gap at large scale, which is a big problem for chemical and bioprocess engineers (Coppens 2005).

Fractals. As described in Chap. 4, fractals are self-similar patterns that constantly repeat from small to large scales. Two interesting examples of fractals in nature that can help process engineers to think and rethink processes in terms of respiration (gas transport) are the structure of lungs and trees. One of the characteristics of fractal objects is that they are almost purely surface. A clear example of this is the lungs. For humans, the area of the lungs is roughly the area of a tennis court (Havlin et al. 1995). Obviously, this feature is critical to increasing the efficiency of the transport of gases in the breathing process. This situation is analogous to trees that, through their thousands of leaves, possess a huge transfer area that facilitates respiration.

10.7 Project Homework

As stated at the beginning of this chapter, an important activity that can serve to familiarize students (in terms of Bloom's taxonomy to reach an adequate level of understanding) with this crucial topic will be to assign team homework because to fully understand and apply scale-up in process engineering requires almost complete mastery of unit operations. We suggest assigning simple and well-defined topics, not necessarily directly related to process engineering, to familiarize students with the concept of scaling up. What we suggest is that the course be subdivided into several groups, with each group being assigned a specific topic, possibly including some modest calculations. The homework could be developed in 2–3 weeks and then shared with the entire class in 10–15-min presentations. Thus, with little effort, the entire class will have a broad perspective on scaling up and discover the importance and difficulties of scaling up in process and bioprocess engineering. To facilitate the work of the professor/instructor, we have included a list of potential topics and several references to guide and lead the effort.

10.7.1 Potential Topics

General questions

1. Why are ants capable of supporting several times their own weight?
2. Why can water striders (family Gerridae) walk across the surface of water?
3. What is the maximum size of birds?

Engineering situations

4. Penicillin production
5. Single-cell proteins
6. Bioethanol
7. Copper bioleaching
8. Wine production
9. Manufacture of yeast
10. Scale-up of chemical reactors

References

Asli, M.S. 2009. A study on some efficient parameters in batch fermentation of ethanol using *Saccharomyces cerevisiae* SC1 extracted from fermented siahe sardasht pomace. African Journal of Biotechnology, 9: 2906-2912.

Bridgman. P. W., 1969, "Dimensional Analysis", in *Encyclopaedia Britannica* (Wm. Haley, Editor-in-Chief), Vol. 7, pp. 439-449: Encyclopaedia Britannica, Chicago.

Coppens, M.O. 2003. *Nature Inspired Chemical Engineering*. Delft University Press.

Coppens, M.O. 2005. Scaling up and down in a nature inspired way. Ind. Eng. Chem. Res. 44: 5011-5019.

Costa, F., Barbosa, J., Deucher, R., Americano, M., Cardemil, J., and Colle, S. 2009. Cooling of ethanol fermentation process using absorption chillers. Proceedings of ECOS 2009. Foz de Iguazu, Parana, Brazil.

http://en.wikipedia.org/wiki/Robin_Dunbar

Havlin, S., Buldyrev, S.V., Goldberger, A.L., Mantegna, R.N., Ossadnik, S.M., Peng, C.-K., Simons, M., and Stanley, H.E. 1995. Fractals in biology and medicine. Chaos, Solitons, & Fractals (6): 171-201.

Heitmann, J., and Rhees D. 1984. *Scaling up*. Science, Engineering, and the American Chemical Industry. Philadelphia. Beckman Center for the History of Chemistry. Chemical Heritage Foundation.

Johnstone, R.E., and Thring, M.W. 1957. *Pilot Plants, Models and Scale-up Methods in Chemical Engineering*. Chemical Engineering Series. McGraw-Hill Education, New York.

Pramanik, K. 2003. Parametric studies on batch alcohol fermentation using *Saccharomyces cerevisiae* yeast from toddy. J. Chin. Inst. Chem Eng. 34(4): 487-492.

Pramanik, K. 2005. Kinetics study on ethanol fermentation of grape waste using *Saccharomyces cerevisiae* yeast isolated from toddy. J. Inst. Eng. India, 85, 53.

Sonin, A.A. 2001. *The Physical Basis of Dimensional Analysis*, 2nd edn. MIT, Cambridge, MA 02139.

Additional Web References

http://www.cas.uio.no/Publications/Seminar/Confluence_Coppens.pdf

Life-Cycle Cost in Process Scale-up http://www.youtube.com/watch?v=q4UQVESH1f4

Alexander Fleming http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html

Scale Up Using Penicillin as an Example http://www.youtube.com/watch?v=n5-TZYZJ51w

Scaling Analysis http://www.youtube.com/watch?v=wOfmvoBNHZU

The Importance of Mixing: Comparing Large Scale and Lab Scale https://mt-emea.adobeconnect.com/_a55714086/p39323957/

Penicillin documentary http://www.nobelprize.org/mediaplayer/index.php?id=343

Dimensional Analysis http://www.youtube.com/watch?v=YFu6pidMbBk

Characterization and scale-up considerations of single-use bioreactors http://www.youtube.com/watch?v=v5DZpFwkHLM