11.7 Cell Growth Kinetics

The kinetics of cell growth are expressed using equations similar to those presented in Section 11.3. From a mathematical point of view there is little difference between the kinetic equations for enzymes and cells; after all, cell metabolism depends on the integrated action of a multitude of enzymes.

11.7.1 Batch Growth

Several phases of cell growth are observed in batch culture; a typical growth curve is shown in Figure 11.10. The different phases of growth are more readily distinguished when the natural logarithm of viable cell concentration is plotted against time; alternatively, a semi-log plot can be used. Rate of growth varies depending on the growth phase. During the lag phase immediately after inoculation, rate of growth is essentially zero. Cells use the lag phase to adapt to their new environment; new enzymes or structural components may be synthesised. Following the lag period, growth starts in the acceleration phase and continues through the growth and decline phases. If growth is exponential, the growth phase appears as a straight line on a semi-log plot. As nutrients in the culture medium become depleted or inhibitory products accumulate, growth slows down and the cells enter the decline phase. After this transition period, the stationary phase is reached during which no further growth occurs. Some cultures exhibit a death phase as the cells lose viability or are destroyed by lysis. Table 11.6 provides a summary of growth and metabolic activity during the phases of batch culture.

During the growth and decline phases, rate of cell growth is described by the equation:

$$r_X = \mu x \tag{11.52}$$

where r_X is the volumetric rate of biomass production with units of, for example, kg m^{-3} s^{-1}, x is viable cell concentration

Figure 11.10 Typical batch growth curve.

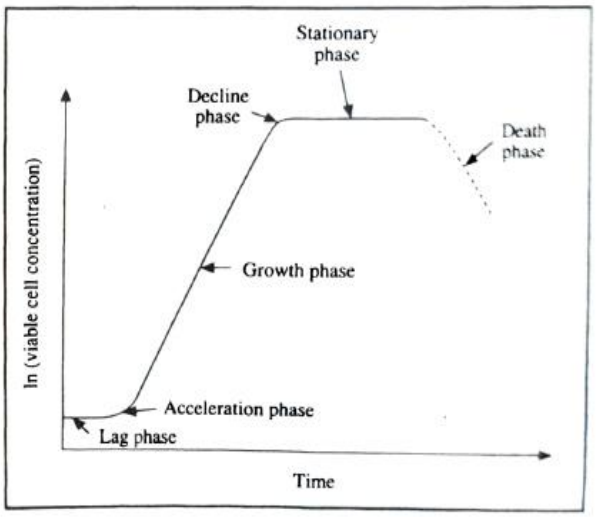

Table 11.6 Summary of batch cell growth

Phase	*Description*	*Specific growth rate*
Lag	Cells adapt to the new environment; no or very little growth	$\mu \approx 0$
Acceleration	Growth starts	$\mu < \mu_{max}$
Growth	Growth achieves its maximum rate	$\mu \approx \mu_{max}$
Decline	Growth slows due to nutrient exhaustion or build-up of inhibitory products	$\mu < \mu_{max}$
Stationary	Growth ceases	$\mu = 0$
Death	Cells lose viability and lyse	$\mu < 0$

with units of, for example, kg m^{-3}, and μ is the *specific growth rate*. Specific growth rate has dimensions T^{-1}. Eq. (11.52) has the same form as (11.27); cell growth is therefore considered a *first-order autocatalytic reaction*. In a closed system where growth is the only process affecting cell concentration, $r_X = {}^{dx}/_{dt}$ and integration of Eq. (11.52) gives an expression for x as a function of time. If μ is constant we can integrate directly with initial condition $x = x_0$ at $t = 0$ to give:

$$x = x_0 e^{\mu t} \tag{11.53}$$

where x_0 is the viable cell concentration at time zero. Eq. (11.53) represents *exponential growth*. Taking natural logarithms:

$$\ln x = \ln x_0 + \mu t. \tag{11.54}$$

According to Eq. (11.54), a plot of ln x versus time gives a straight line with slope μ. Because the relationship of Eq. (11.54) is strictly valid only if μ is unchanging, a plot of ln x versus t is often used to assess whether the specific growth rate is constant. As shown in Figure 11.10, μ is usually constant during the growth phase. It is always advisable to prepare a semi-log plot of cell concentration before identifying phases of growth. As shown in Figure 3.6, if cell concentrations are plotted on linear coordinates, growth often appears slow at the beginning of the culture. We might be tempted to conclude there was a lag phase of 1–2 hours for the culture represented in Figure 3.6(a). However, when the same data are plotted using logarithms as shown in Figure 3.6(b), it is clear that the culture did not experience a lag phase. Growth always appears much slower at the beginning of culture because the number of cells present is small.

Cell growth rates are often expressed in terms of the *doubling time* t_d. An expression for doubling time can be derived from Eq. (11.53). Starting with a cell concentration of x_0, the concentration at $t = t_d$ is $2x_0$. Substituting these values into Eq. (11.53):

$$2x_0 = x_0 e^{\mu t_d} \tag{11.55}$$

and cancelling x_0 gives:

$$2 = e^{\mu t_d}. \tag{11.56}$$

Taking the natural logarithm of both sides:

$$\ln 2 = \mu t_d \tag{11.57}$$

or

$$t_d = \frac{\ln 2}{\mu}. \tag{11.58}$$