Since $1 - f_- = f_+ = \dfrac{n_+}{n_+ + n_-}$, then

$$f_+ = \frac{e^{(1-P)\mu_+ t}}{e^{(1-P)\mu_+ t} + \dfrac{P\mu_+}{(1-P)\mu_+ - \mu_-}\left[e^{(1-P)\mu_+ t} - e^{\mu_- t}\right]} \tag{14.48}$$

Equation 14.48 is usually recast in terms of number of generations of plasmid-containing cells (n_g), a dimensionless growth-rate ratio (α), and the probability of forming a plasmid-free cell upon division of a plasmid-containing cell (P). The mathematical definitions of n_g and α are:

$$n_g = \frac{\mu_+ t}{\ln 2} \tag{14.49}$$

$$\alpha = \frac{\mu_-}{\mu_+} \tag{14.50}$$

With these definitions, eq. 14.48 becomes:

$$f_+ = \frac{1 - \alpha - P}{1 - \alpha - P \cdot 2^{n_g(\alpha + P - 1)}} \tag{14.51}$$

The use of this approach is illustrated in the following example.

Example 14.4.

Estimate the fraction of plasmid-containing cells in a batch culture under the following circumstances. Cells are maintained at constant, maximal growth rate of 0.693 h^{-1} during scale-up from shake flask through seed fermenters into production fermenters. The total time for this process is 25 h. Assume that the inoculum for the shake flask was 100% plasmid-containing cells. It is known that the growth rate for a plasmid-free cell is 0.97 h^{-1}. The value of P is 0.001.

Solution First we calculate α and n_g.

$$\alpha = 0.97/0.693 = 1.4$$

and

$$n_g = \frac{0.693\ \text{h}^{-1} \cdot 25\ \text{h}}{\ln 2} = 25\ \text{gen.}$$

Substituting into eq. 14.51

$$f_+ = \frac{1 - 1.4 - 0.001}{1 - 1.4 - 0.001 \cdot 2^{25(1.4 + .001 - 1)}}$$

$$f_+ = 0.27$$

Consequently, 73% of the cells are plasmid-free, which would result in considerable loss of productivity.