known proteases. Multimerization can be reduced by choosing a host with a defective recombination system. However, host cells with a defective recombination system tend to grow poorly. Many other possible host cell modifications enter into considerations of how to best construct a vector for a commercial operation.

These qualitative ideas allow us to anticipate to some extent what problems may arise in the maintenance of genetic stability and net protein expression. However, a good deal of research has been done on predicting genetic instability.

14.6. PREDICTING HOST–VECTOR INTERACTIONS AND GENETIC INSTABILITY

Many of the structured mathematical models we discussed previously can be extended to include component models for plasmid replication. Such models can then predict how plasmid-encoded functions interact with the host cell. The quantitative prediction of the growth-rate ratio and the development of plasmid-free cells due to segregational losses can be readily made. The most sophisticated models will predict the distribution of plasmids within a population and even the effects of multimerization on genetic stability. These models are too complex to warrant discussion in an introductory course.

We will consider some simple models that mimic many of the characteristics we discussed with models of mixed cultures. A number of simple models for plasmid-bearing cells have been proposed. The key parameters in such models are the relative growth rates of plasmid-free and plasmid-containing cells and the rate of generation of plasmid-free cells (i.e., segregational loss). These parameters can be determined experimentally or even predicted for more sophisticated models of host–vector interactions.

Let's consider how a simple model may be constructed and how the parameters of interest may be determined experimentally.[†]

The simplest model considers only two cell types: plasmid free (n_-) and plasmid containing (n_+), where n_- and n_+ are the number concentrations of plasmid-free and plasmid-containing cells, respectively. The model assumes that all plasmid-containing cells are identical in growth rate and in the probability of plasmid loss. This assumption is the same as assuming that all cells have exactly the same copy number. As we showed in Example 14.1, the actual distribution of copy numbers can make a significant difference on plasmid loss. Also, plasmid-encoded protein production is not a linear function of copy number, so assuming that all cells have the same copy number may lead to incorrect estimates of the growth rate of plasmid-bearing cells. The assumption of a single type of plasmid-bearing cell is a weak assumption, but other assumptions result in a level of complexity inconsistent with this book's purpose. However, models that recognize the segregated nature of the plasmid population are available in the research literature.

Let us further restrict our initial considerations to a single-stage chemostat. Then

$$dn_+/dt = \mu_+ n_+ - Dn_+ - Rn_+ \tag{14.7}$$

$$dn_-/dt = \mu_- n_- - Dn_- + Rn_+ \tag{14.8}$$

[†]This analysis is adapted from the paper of N. S. Cooper, M. E. Brown, and C. A. Cauleott, *J. Gen. Microbiol. 133:*1871 (1987).