unsuccessful examples (described in several of the references at the end of the chapter). Results are more favorable with Newtonian broths than with non-Newtonian systems.

The failure of any of these rules is related to changes in the controlling regime upon scale-up. No empirical rule can satisfactorily address such situations. Advances are being made in models that predict flow distribution, mixing times, and gas dispersion in fermenters, as well as models to predict explicitly cellular responses to changes in the local environment. If these models can be integrated, they may provide a much more fundamentally sound basis for scale-up. With the advent of improved supercomputers, the computational demands of such sophisticated models can be met. An approach to estimating mixing times in a stirred fermenter is given in Example 10.4.

It has been shown empirically for fermenter volumes of 0.1 to 100 m^3 that mixing time can be correlated to reactor volume according to an expression like[†]:

$$t_m = T_k \cdot V^{0.3} \tag{10.11}$$

where t_m is mixing time and V is vessel volume. The constant, T_k, is a function of impeller type, placement, and vessel design. Equation 10.11 assumes multiple Rushton-type impellers and is based on data from vessels of different sizes at practical operating conditions.

In summary, scale-up as currently practiced is an empirical, imprecise art. As long as geometric similarity is demanded at various scales, microenvironmental conditions cannot be made scale independent. Models and the use of scale-down procedures are potential approaches to improving scale-up, but these approaches are not yet fully developed.

The nature of the practical operating boundaries for an aerated, agitated fermenter can be summarized as in Fig. 10.7. The exact placement of such boundaries depends on the fermentation and change as the system is scaled up or scaled down. The boundaries are fuzzy rather than sharp. Nonetheless, the bioprocess engineer must appreciate the existence of such constraints.

10.2.5. Scale-down

Although scale-up models and the use of characteristic time analysis are potentially attractive, a more immediate approach to the rational scaling of reactors is *scale-down*. The basic concept is to provide at a smaller scale an experimental system that duplicates exactly the

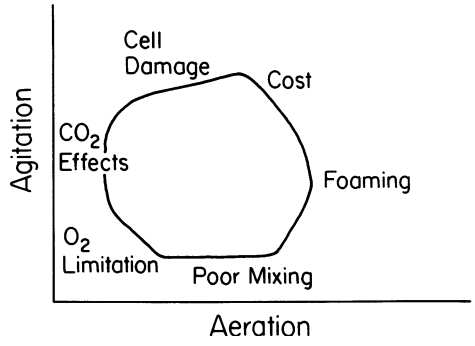

Fig. 10.7. Practical operating boundaries for aerated, agitated fermenters. (After Lilly, M. D., (1983) in *Bioactive Microbial Products 2;* D. J. Winstanley and L. J. Nisbet, eds., Academic Press, London, pp. 79–89.)

[†]B. C. Buckland and M. D. Lilly. In *Biotechnology* 2d ed., H.-J. Rehm and G. Reed. Vol, 3. G. Stephanopoulos, VCH, New York, 1983, pp. 12–13.