4.6.2. Metabolic Pathway Control

In Chapter 3, we learned how enzyme activity could be modulated by inhibitors or activators. Here we discuss how the activities of a group of enzymes (a pathway) can be controlled. The cell will attempt to make the most efficient use of its resources; the fermentation specialist tries to disrupt the cell's control strategy so as to cause the cell to overproduce the product of commercial interest. An understanding of how cells control their pathways is vital to the development of many bioprocesses.

First, consider the very simple case of a linear pathway making a product, P_1. Most often the first reaction in the pathway is inhibited by accumulation of the product (*feedback inhibition* or *end-product inhibition*). The enzyme for the entry of substrate into the pathway would be an allosteric enzyme (as described in Chapter 3), where the binding of the end product in a secondary site distorts the enzyme so as to render the primary active site ineffective. Thus, if the cell has a sufficient supply of P_1 (perhaps through an addition to the growth medium), it will deactivate the pathway so that the substrates normally used to make P_1 can be utilized elsewhere.

This simple concept can be extended to more complicated pathways with many branch points (see Fig. 4.12). Assuming that P_1 and P_2 are both essential metabolites, the cell may use one of several strategies to ensure adequate levels of P_1 and P_2 with efficient utilization of substrates.

One strategy is the use of isofunctional enzymes (*isozymes*). Two separate enzymes are made to carry out the same conversion, while each is sensitive to inhibition by a different end product. Thus, if P_1 is added in excess in the growth medium, it inhibits one of the

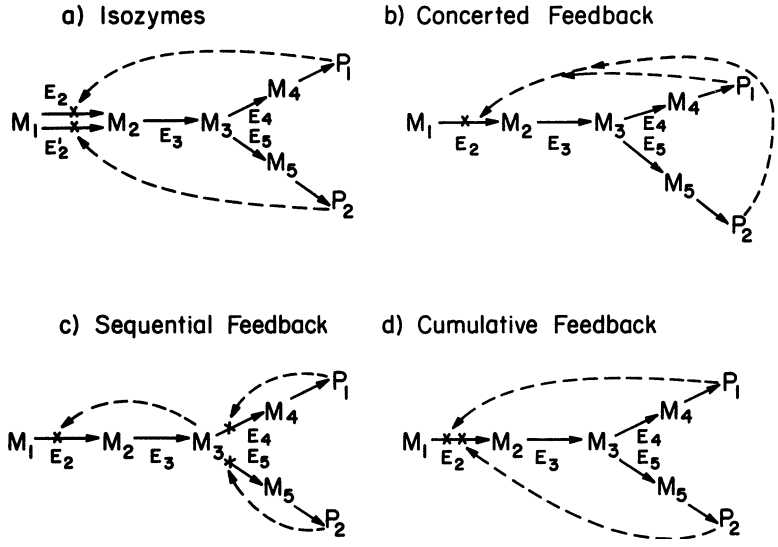

Figure 4.12. Examples of feedback control of branched pathways. P_1 and P_2 are the desired end products. M_1, M_2, . . . , M_j are intermediates, and E_j is the enzyme involved in converting metabolite M_{j-1} to M_j. Possible paths of inhibition are shown by dashed lines.