Classical enzymology ignores the role which cellular membranes may play in regulating reaction kinetics in vivo. The correct description of cellular metabolic processes must derive from a mass balance equation for each reacting species. An elementary mathematical model, called the "continuous flow stirred tank reactor" in the chemical engineering literature, has been applied to Michaelis-Menten kinetics, substrate inhibition kinetics, and kinetics involving hydrogen ion as a byproduct. A number of remarkable phenomena, including multiple stationary states, threshold effects, temporal patterns, homeostatic regulation, amplification, and irreversible differentiation can result. Predictions of the model are in qualitative accord with experimental and theoretical studies of insolubilized enzymes, which are conventionally modeled by a more difficult mathematical formalism.

The classical theory of steady state enzyme kinetics (Dixon and Webb, 1964) deals with the kinetics of enzymes in stirred solution. This theory has been abundantly confirmed by experiments on purified enzymes removed from their cellular milieu and placed in well-stirred solution. In cells and tissues, however, enzymes are compartmentalized by the cell surface membrane as well as by intracellular organelles. It is likely, therefore, that diffusion modulates the movement of substrates and products within and between cells, leading to the development of concentration gradients. To deal with this situation the theory of enzyme kinetics must be extended to incorporate the role of diffusion.


† Present address: Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Mass. 02139.
While this topic has been studied extensively in the chemical engineering literature (Satterfield, 1970), relatively little application has been made to biochemical kinetics (Moo Young and Kobayashi, 1972; Atkinson and Daoud, 1968; O'Neill et al., 1971).

In this paper we will examine the consequences of incorporating diffusion into enzyme kinetics. Commonly accepted rate laws, such as Michaelis-Menten and substrate inhibition kinetics, as well as kinetics involving hydrogen ion as a reaction byproduct, will be considered. Diffusional effects enter kinetics through the continuity equations which express the law of conservation of atomic identities in chemical reactions in open systems. The usual formulation of these equations (Bird et al., 1960) leads to a mathematical representation in terms of coupled, nonlinear second order boundary value problems. These problems are difficult to treat, either analytically or computationally, although certain systems have been analyzed (Thomas et al., 1972; Goldman et al., 1968).

In cells and tissues, it may be reasonable to suppose that the principal diffusional resistances occur in thin membranes, while reactions take place in a more nearly homogeneous cytoplasm, although this is clearly a simplification of the actual situation. A model of this situation, shown in Figure 1, is called a continuous flow stirred tank reactor (CFSTR) in the chemical engineering literature (Denbigh and Turner, 1971; Perlmutter, 1972). Mass balance for the $i$th species in the reactor is given by (1).

$$\frac{dC_i}{dt} = P_i(C_i^{0} - C_i) - \sum_{j} R_{ij}(C_1, \ldots, C_n), \quad i = 1, \ldots, n. \quad (1)$$