Introduction to Michaelis-Menton Kinetics

Enzymes are simply proteins that behave as catalysts in chemical reactions. In particular, they speed up reactions and reduce the amount of energy needed for the reaction. Enzymes help in the initial phase of the reaction and control the rate of the reaction by binding the *substrate* to the active site (receptor) of the enzyme. The substrate (the particular substance with which the enzyme will bind), S, and the enzyme, E, combine to the form the enzyme-substrate complex, C, which can break down into S and E or proceed to produce the product P and E. The following chemical equation characterizes this process:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} P + E \tag{1}$$

The constants k_1, k_{-1}, and k_2 in (1) are the rates at which the particular components of the reaction occur. The *law of mass action* states that the rate of interaction between two chemicals is proportional to the product of the concentrations of the two molecules. This law allows us to restate the chemical equation (1) as a system of ordinary differential equations. The underlying functions in this system of differential equations will be the concentrations of the four chemicals, which are denoted by corresponding lower-case letters. The variable t will denote the amount of time elapsed since the reaction began. We denote the initial concentrations of the substrate and enzyme by s_0 and e_0, respectively. The initial concentrations c_0 of C and p_0 of P are both zero. We will not specify particular time units.

The system of differential equations can then be written as:

$$\frac{ds}{dt} = k_{-1}c - k_1 se \tag{2}$$
$$\frac{de}{dt} = k_{-1}c + k_2 c - k_1 se \tag{3}$$
$$\frac{dc}{dt} = k_1 se - k_{-1}c - k_2 c \tag{4}$$
$$\frac{dp}{dt} = k_2 c \tag{5}$$

We will now utilize an important observation and an special assumption to reduce this system of equation to the famous *Michaelis-Menton equation* [3]:

$$\frac{dp}{dt} = \frac{v_m s}{K_m + s}, \tag{6}$$

where v_m is the saturation constant, and K_m is the Michaelis constant. The Michaelis-Menton equation relates the concentration of the substrate to the rate of change of the concentration of the product. (The physical meaning of the two constants will be explained later in this introduction.) To derive equation (6), we first observe that the quantity $e(t) + c(t)$ is constant throughout the reaction, and we say that $e(t) + c(t)$ is a *conserved quantity*. Mathematically, this is characterized by noting that the rate of change of $e(t) + c(t)$ with respect to time is zero. To see this, we add equations (3) and (4) and see that

$$\frac{d(e+c)}{dt} = \frac{de}{dt} + \frac{dc}{dt} \tag{7}$$
$$= (k_{-1}c + k_2 c - k_1 se) + (k_1 se - k_{-1}c - k_2 c) \tag{8}$$
$$= 0. \tag{9}$$

Recalling that $c_0 = 0$, we observe that for $t \geq 0$,

$$\begin{aligned} e(t) + c(t) &= e(0) + c(0) && (10)\\ &= e_0 + c_0 && (11)\\ &= e_0. && (12) \end{aligned}$$

In particular $e(t) = e_0 - c(t)$, for $t \geq 0$. It follows from (9) that $dc/dt = -de/dt$, and hence we can eliminate equation (4) from the system. (Substituting $dc/dt = -de/dt$ into equation (4) reveals that equations (3) and (4) are equivalent.) To further simplify the system, we use the *quasi-steady state assumption* due to Briggs and Haldane [1]. Biologically, we explain this assumption in the following manner. Assume that the concentration of small substrate molecules is much greater the concentration of the enzyme. Because of the high concentration of S, as soon as a molecule of the enzyme-substrate complex breaks down, a new substrate molecule will bind to the newly available enzyme-binding site. In this scenario, the enzymes are working at a maximal capacity. Ignoring the beginning and end of the reaction, we can therefore assume that the concentration of the enzyme-substrate complex, c, essentially remains at a nonzero constant level. (The facts that the concentration c is zero at the beginning and end of the reaction and is not necessarily precisely constant throughout the reaction suggests the use of the prefix "quasi-" for this quasi-steady state assumption.) To further simplify the calculations, we invoke the quasi-steady state assumption and set

$$\frac{dc}{dt} = 0. \quad (13)$$

From equation (4), it now follows that

$$k_1 se - k_{-1} c - k_2 c = 0, \quad (14)$$

which we rewrite as

$$\frac{se}{c} = \frac{k_{-1} + k_2}{k_1}. \quad (15)$$

The *Michaelis constant*, K_m, is defined by

$$K_m = \frac{k_{-1} + k_1}{k_1}. \quad (16)$$

Using equation (12) to substitute $e_0 - c$ for e in this last equation and then solving for c, we obtain

$$c = \frac{e_0 s}{K_m + s}. \quad (17)$$

We can now combine equation (17) with equation (5) to obtain

$$\frac{dp}{dt} = \frac{k_2 e_0 s}{K_m + s}. \quad (18)$$

Under the quasi-steady state assumption, all of the enzyme is assumed to be complexed with the substrate so that $e = 0$, and hence $c = e_0$. We can conclude that the production rate of P, dp/dt, is maximal when $c = e_0$. Moreover, equation (18) gives the production rate, dp/dt, as a function of the substrate concentration, s. From equation (18), we can conclude that for large values s (which are in particular much larger than the initial concentration, e_0 of the enzyme E), $dp/dt \approx k_2 e_0$ and that the graph of dp/dt versus s approaches the horizontal asymptote $dp/dt = k_2 e_0$. We can think of the quantity $k_2 e_0$ as the maximal rate of change of the reaction. We set $v_m = k_2 e_0$ and call it the *saturation constant*. (This name is due to the fact that the reaction proceeds at this rate when all of the enzyme is complexed with the substrate.) We then can rewrite the Michaelis-Menton equation in its usual form:

$$\frac{dp}{dt} = \frac{v_m s}{K_m + s}. \quad (19)$$

The Michaelis constant, K_m, has a physical meaning. If $s = K_m$, it follows that $dp/dt = v_m/2$. For this reason, K_m is also called the *half-saturation constant*. We can similarly derive the following expression for ds/dt, which is another formulation of the Michaelis-Menton equation:

$$-\frac{ds}{dt} = \frac{v_m s}{K_m + s}. \tag{20}$$

The advantage of using equation (20) over equation (19) is that rate of the reaction is simply expressed in term of the concentration of the substrate rather than the concentrations of both the product and the substrate.

References

[1] G.E. Briggs and J.B.S. Haldane, "A note on the kinematics of enzyme actions," *Biochemical Journal*, **19**, 338-339, 1925.

[2] L. Edelstein-Keshet, *Mathematical Models in Biology*, Classics in Applied Mathematics **46**, SIAM, 2005.

[3] L. Michaelis and M.I. Menton, "Die Kinetik der Invertinwirkung," *Biochem. Z.*, **49**, 333-369, 1913.

[4] C. Neuhauser, *Calculus for Biology and Medicine, 2e*, Pearson Prentice Hall, 2004.