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# A THEORETICAL AND COMPUTATIONAL STUDY OF THE HEAT EFFECTS ON PACKED-BED REACTORS OF IMMOBILIZED ENZYMES

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The effects of heat of reaction and temperature change on an immobilized enzyme reactor have previously been generally neglected. A theoretical analysis of the overall enzyme reaction rate involving nonlinear Michaelis–Menten kinetics was carried out in order that predictions of temperature and concentration profiles in packed columns of fixed enzymes could be made. Numerical solutions of the coupled differential equations describing the overall kinetics are presented and explained.

Note: The notation used in this paper is presented in a separate section at the end of the article.

## INTRODUCTION

Problems of diffusional resistance in immobilized enzyme reactions have been investigated extensively in recent years. The effects of heat of reaction and temperature change on a bound-enzyme reactor, however, have been generally neglected. For small laboratory columns, the surface-to-volume ratio is usually large, and temperature distribution in a column is uniform and true isothermal conditions often hold. Porous glass and ceramics particles that are often used as enzyme supports are also poor thermal conductors. It is conceivable that nonuniform temperature distribution may develop in a large reactor column packed with porous materials. Enzymatic reactions are generally mild because their heats of reaction are not high; on the other hand, enzymes are also very sensitive to heat. For instance, the hydrolysis of maltose to glucose promoted by the enzyme glucoamylase is a very mild reaction. One report (1) indicates an exothermic heat of reaction

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of −4,200 cal/g-mol glucose. Using this figure, a quick estimate will show that a temperature jump of about 10°C will develop if a reactor column is operated adiabatically under the usual industrial conditions. The temperature–enzyme activity of glucoamylase using maltose as its substrate is shown in Fig. 1, which is taken from a previous paper by Marsh, Lee, and Tsao (2). The optimal temperature of immobilized glucoamylase on porous glass is about 60°C. If the feed to an adiabatic glucoamylase reactor is at 60°C, the enzyme activity after a temperature jump of 10° to 70°C will drop to only about 75% of the optimal. Another example is the oxidation reaction of glucose to gluconic acid, which is somewhat exothermic and might cause a severe temperature rise in a packed column.

The temperature effect thus also creates a new problem of reactor optimization. Obviously, the optimal temperature on a temperature–enzyme activity profile may not necessarily be the most desirable input temperature to a large, fixed-bed enzyme reactor. In the case of immobilized glucoamylase as shown in Fig. 1, it might be desirable to feed the reactor at a few degrees lower than the optimal—say, 55°C—and let the heat of reaction warm the reaction mixture to 60°C.

This paper will provide a detailed theoretical analysis of the heat problems involving the nonlinear Michaelis–Menten kinetics. The derived dimensionless equations were solved numerically with the aid of a computer. The computer program is of general use for predicting temperature and concentration (conversion) profiles of enzymatic reactions in fixed-bed reactors. A number of graphs were prepared based on the computation results. It would be ideal if one could read off a chart, say, the temperature jump in a fixed-bed reactor. Because of the large number of dimensionless parameters involved, it is difficult to prepare enough general charts to cover

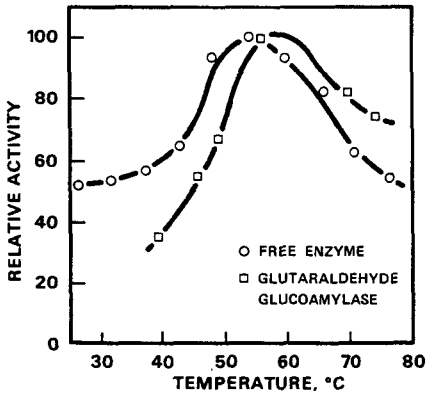


FIG. 1. Temperature–enzyme activity profiles of glucoamylase.

all ranges of possibilities. The graphs that are included in this paper will serve only as examples. In these examples, the effect of deactivation with time of the immobilized enzyme has been considered negligible and thus not taken into account. This disregarding is perhaps reasonable in light of the rapid development of quite stable immobilized enzyme systems that have exhibited long half-lives. In systems that display less stability, this treatise is still valuable in casting light on and explaining differences between laboratory and large-scale performance reactors.

## THEORETICAL CONSIDERATIONS

Temperature change in an adiabatic, packed-column reactor depends on the rate of chemical reaction, which in turn is strongly affected by diffusional rate of the reagents and products in the column packings. Consequently, in analysis of a packed-column reactor, the problems of heat and mass transfer are not independent of each other, and the partial differential equations describing such processes are coupled. Equations (1) and (2) are the general heat and mass balance equations in a reactor column:

$$-\text{div}(\vec{u}C) - \text{div}(-D \text{ grad } C) + R_m = 0 \tag{1}$$

$$-\text{div}(\vec{u}\rho C_\rho T) - \text{div}(-D' \text{ grad } T) + R_h = 0 \tag{2}$$

The first terms are for convective flow, the second for conduction, and $R_m$ and $R_h$ are source terms expressing, respectively, the consumption of a reactant and release of heat of reaction. With the usual assumptions of angular symmetry and zero radial velocity in a packed column, Equations (1) and (2) will reduce, after radial diffusion and convection are disregarded, to Equations (3) and (4):

$$-u\frac{dC}{d\xi} + D_L\frac{d^2C}{d\xi^2} - R_m = 0 \tag{3}$$

$$-u\frac{dT}{d\xi} + \frac{D_{L'}}{\rho C_p}\frac{d^2T}{d\xi^2} - R_h = 0 \tag{4}$$

in which $D_L$ and $D_{L'}$ are mass dispersion and heat dispersion coefficients, respectively. On the assumptions that turbulent diffusion predominates over molecular, and that heat is dispersed axially by the same mechanism of mass dispersion as Bernard and Wilhelm (3):

$$D_{L'} = \rho C_p D_L \tag{5}$$

The following dimensionless equations can therefore be obtained with $Pe_L = ud_p/D_L$:

$$-\frac{L}{d_p}\frac{dC^*}{d\ell}+\frac{1}{Pe_L}\frac{d^2C^*}{d\ell^2}-R_{m'}=0 \tag{6}$$

$$-\frac{L}{d_p}\frac{dT^*}{d\ell}+\frac{1}{Pe_L}\frac{d^2T^*}{d\ell^2}-R_{h'}=0 \tag{7}$$

As often stated in chemical engineering literature, when $Pe_L = 0$, complete dispersion exists, and the reactor column behaves like a stirred tank. When $Pe_L$ is infinity, a true plug flow prevails.

Equations (6) and (7) have been investigated by Carberry and Wendel (4) for first-order kinetics. For Michaelis–Menten kinetics, the following two dimensionless equations can only be solved numerically:

$$\frac{1}{Pe_L}\frac{d^2C^*}{d\ell^2}-\left(\frac{L}{d_p}\right)\frac{dC^*}{d\ell}-\left(\frac{L^2k_V\gamma}{d_puC_{bi}}\right)E(C^*, T^*)\left(\frac{C^*}{\alpha+C^*}\right)=0 \tag{8}$$

$$\frac{1}{Pe_L}\frac{d^2T^*}{d\ell^2}-\left(\frac{L}{d_p}\right)\frac{dT^*}{d\ell}+\left(\frac{L^2k_V\gamma(-\Delta H)}{d_pT_i\rho C\rho u}\right)E(C^*, T^*)\left(\frac{C^*}{\alpha+C^*}\right)=0 \tag{9}$$

where $C^* = Cb/C_{bi}$, $T^* = T/T_i$, $\ell = \xi/L$, and $\alpha = K_{m'}/C_{bi}$.

The boundary conditions, according to Wehmer and Wilhelm (5), are:

$$\begin{aligned}&\ell = 0^+, \frac{dC^*}{d\ell}\bigg|0^+ = Pe_L\left(\frac{L}{d_p}\right)(C^*|0^+ - 1)\\ &\ell = 1, \frac{dC^*}{d\ell}=0\end{aligned} \tag{10}$$

and:

$$\begin{aligned}&\ell = 0^+, \frac{dT^*}{d\ell}\bigg|0^+ = Pe_L\left(\frac{L}{d_p}\right)(T^*|0^+ - 1)\\ &\ell = 1, \frac{dT^*}{d\ell}=0\end{aligned} \tag{11}$$

In computer calculations, an explicit marching technique involving the fourth-order Runge–Kutta method (6) was first tried, but was soon found unsatisfactory due to difficult instability problems. Similar instability difficulties have apparently been encountered by many authors in analysis of

fixed-bed reactors, and are discussed by Lee (7) and also by Coste, Rudd, and Amundson (8). A method of quasilinearization described by Lee (7) was adapted to the present problem involving Michaelis–Menten kinetics and internal diffusional resistance of the porous catalyst. Details of the computation procedures are given in a dissertation by Marsh (9). Several important assumptions used in the computation are given below:

(1) Enzyme activity was made dimensionless by expressing it as a fraction of that at a reference temperature. The choice of the reference temperature was arbitrary. The temperature optimum of the temperature–activity profile or a temperature near the optimum would be a good choice.

(2) The temperature–enzyme activity profile (for the glutaraldehyde glucoamylase) in Fig. 1 was used to fit a fourth-order polynomial equation. Because the profile is bell-shaped and apparently a continuous function of temperature over the range where significant enzyme activity is observed, the usage of Arrhenius relationships (possibly two or three) over this range would give rise to discontinuities at points where one function ends its application and another begins. Thus, the description of the profile with a continuous polynomial function was employed in this range. This empirical equation, together with dimensionless temperature based on the selected reference temperature, were employed in the computation, the results of which were the basis of all later figures in this paper. Because the temperature–activity profile was based on the glucoamylase reaction, the computation results have only limited application. On the other hand, most temperature–enzyme activity profiles of enzymatic reactions are bell-shaped. The curves in Fig. 1, if they were expressed in dimensionless temperatures based on a suitable reference temperature, might approximate dimensionless temperature–enzyme activity profiles of many other enzymes. If so, the computation results of this study expressed in dimensionless parameters might have much generalized application.

(3) For an immobilized enzyme on porous support, there are both external film resistance and internal pore diffusional resistance to mass transfer. In this calculation, the internal pore diffusion was assumed to be rate-controlling. This assumption is reasonable, since the external film resistance is important only when the feed rate through the reactor is very slow. If necessary, the computation procedure can be easily modified to take into account the film resistance. Details of the modification are given in Marsh's dissertation.

(4) Throughout the whole reactor column, pH was assumed to be uniform and maintained at its optimal value. For reactions that form no acid or base, such as starch hydrolysis, this assumption is reasonable. For some enzymatic processes, pH may not be uniform in a reactor column and, in fact, not even in a single pore. The effect of a nonuniform pH distribution will require another optimization study.

(5) As stated in paragraph (3) above, pore diffusion was assumed to be rate-controlling. Consequently, we need a subroutine for computing the effectiveness factor, which varies throughout a column reactor. In making this computation, it is assumed that temperature is uniform within each of the individual pores. Mass transfer and diffusional problems of immobilized enzymes are discussed in a previous paper by Marsh, Lee, and Tsao (2), in which the numerical methods for computing the effectiveness factor were given.

(6) In the graphs included in this paper the input temperature, $T_i$, to the reactor column was taken to be the same of the reference temperature, $T_{ref}$; i.e., the dimensionless input temperature was taken to be 1.000. This is, however, not a necessary restriction. In some computations, dimensionless input temperatures other than 1.000 were used.

## COMPUTATION RESULTS

In Fig. 2, the diffusional–kinetic modulus, $\phi_R$, and effectiveness factor, $E$, are plotted with the dimensionless concentration (conversion) and temperature profiles at the given conditions. The modulus $\phi_R$ varies with the temperature and is shown to reach a maximum at about 1.012 of $T_{ref}$.

The dimensionless groups in the following figures are assigned values to cover broad ranges of immobilized enzyme reactions. The group $(Lk_{V_{ref}}\gamma/uC_{bi})$ is a mass "reaction-to-convection" ratio, and is given the value unity to insure a near-complete conversion over the length, $L$, of the column reactor. Because of dispersion, complete conversion is, of course, not always achieved. The dimensionless group $(C_{bi}(-\Delta H))/T_i\rho C_p)$, an energy "reaction-to-convection" ratio, is given low values to indicate that the heat of reaction of enzyme reactions is generally not very high, but yet sufficient to cause significant temperature changes in temperature-sensitive enzyme reactions. The value of $\alpha$ $(= K_{m'}/C_{bi})$ is low, since many enzymes have Michaelis constants in the range $10^{-3}$–$10^{-2}$ M, and for initial substrate concentrations 0.1–1.0 M, the quantity, $\alpha = 0.01$, is justified. The

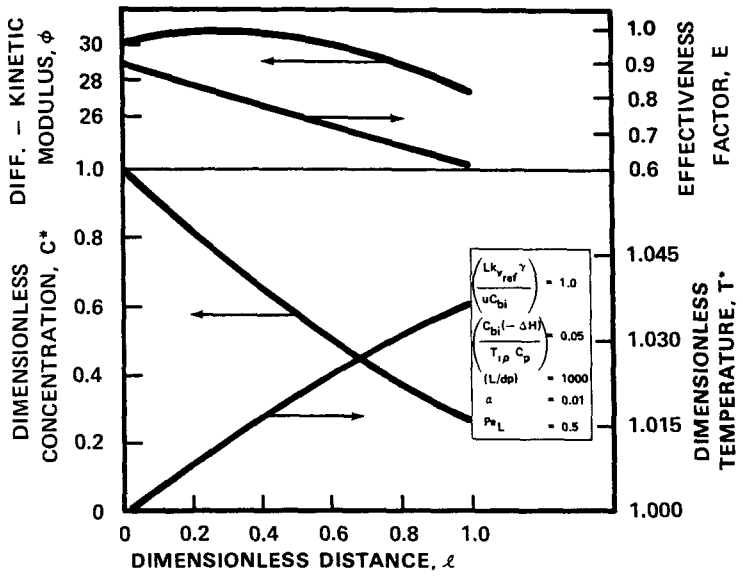


FIG. 2. Profiles of concentration (conversion), temperature, effectiveness factor and diffusional–kinetic modulus in a fixed-bed enzyme reactor.

immobilized enzyme modulus, $\phi_{ref}$, was taken arbitrarily as 30. It would be impossible to construct a generalized chart for behavior of immobilized enzyme reactions in packed columns because of the many parameters involved, but one can speculate how such a reaction might behave by observing the change in conversion or temperature due to variation in one particular parameter with the others fixed.

In Figs. 3 and 4 are shown dimensionless concentration and temperature profiles at different $Pe_L$ values. At the low Peclet number, $10^{-5}$, complete backmixing is achieved, since the concentration is essentially constant throughout the reactor. At this high level of dispersion, the behavior of a packed-column reactor approaches that of a continuously stirred tank. At the other extreme is plug flow, which, as expected, gives the highest conversion. It is interesting to observe that the dispersion effect at $Pe_L = 0.1$ has decreased the conversion by 4% as compared to a true plug flow reactor.

The effects of the mass "reaction-to-convection" ratio on concentration (conversion) and on temperature profiles in a reactor column are given in Figs. 5 and 6, respectively, covering fairly broad ranges in which most enzyme reactors will fall. The effects of energy "reaction-to-convection"

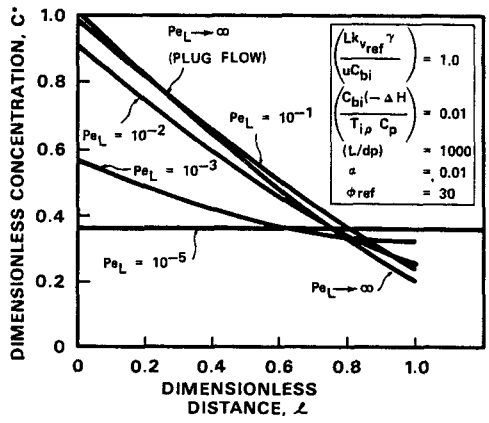


FIG. 3. Dimensionless concentration versus dimensionless distance affected by Peclet number.

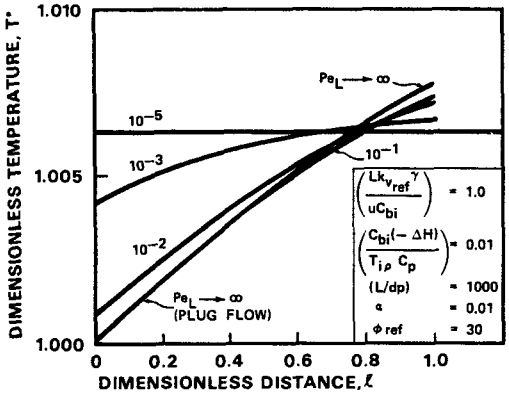


FIG. 4. Dimensionless temperature versus dimensionless distance affected by Peclet number.

ratio are given in Figs. 7 and 8. Over a 10-fold change from 0.05 to 0.5, the degree of conversion varies little, as shown in Fig. 7. This limited variation is due chiefly to the general bell shape of most temperature–activity profiles of enzymes.

Many additional charts that describe graphically the effects of dimensionless Michaelis constant $\alpha$, feed temperature, diffusional–kinetic modulus, and other factors on the concentration and temperature profiles in column reactors are given in Marsh's dissertation and will not be repeated here. The complete IBM 360/65 computer program is also given in the dissertation (9).

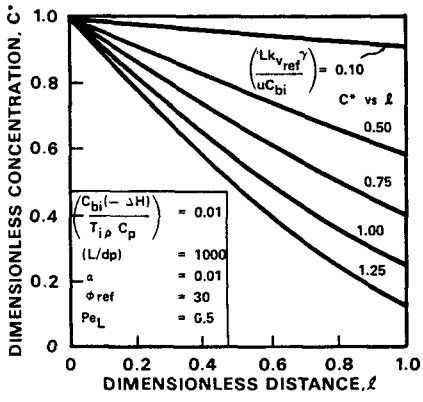


FIG. 5. Dimensionless concentration (conversion) profile affected by mass "reaction-to-convection" ratio.

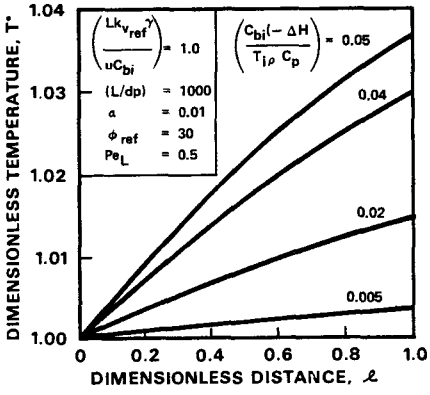


FIG. 6. Dimensionless temperature profile affected by mass "reaction-to-convection" ratio.

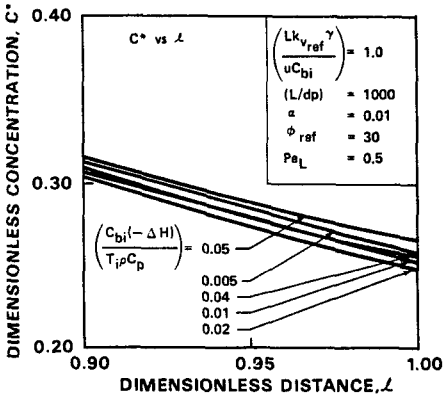


FIG. 7. Dimensionless concentration (conversion) profile affected by energy "reaction-to-convection" ratio.

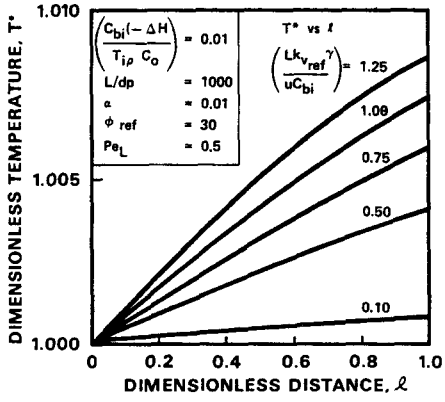


FIG. 8. Dimensionless temperature profile affected by energy "reaction-to-convection" ratio.

## DISCUSSION

In designing a fixed-bed reactor, it is desirable to have a means of predicting the maximum temperature jump and its possible adverse effect on reactor performance. The work reported in this paper is for developing such a capability. For an obvious reason, temperature and concentration distributions in fixed-bed reactors are frequent topics of chemical engineering research. Theoretical prediction of such distributions, however, has been generally difficult for most chemical reactions due to the complexity and diversity of their kinetics. The fact that many enzymatic reactions do obey the Michaelis–Menten equation provides an opportunity for computation work that might have generalized applications.

The dimensionless Equations (8) and (9) and the boundary conditions (10) and (11) contain 5 adjustable dimensionless parameters: (a) the Peclet number, (b) $L/d_p$, (c) the dimensionless Michaelis constant, (d) the mass "reaction-to-convection" ratio, and (e) the energy "reaction-to-convection" ratio. These equations will have a unique solution and thus determine a definite set of temperature and concentration profiles once the values of the 5 dimensionless parameters are fixed. Unfortunately, there is no way to plot a chart that can include all 5 adjustable parameters. With a number of partial charts, however, it is possible to evaluate these parameters, one at a time, regarding their effects on the temperature and concentration profiles of the reactor. Very often, even the capability of identifying parameters that have strong effects on the reactor performance will aid greatly in reactor design.

The two "reaction-to-convection" ratios were defined based on $k_V$ at the reference temperature. To relate $k_V$ at any temperature to $k_{V_{ref}}$, we thus also include the temperature–enzyme activity profile in the numerical solution of Equations (8) and (9). Whether or not there can be a "generalized temperature–enzyme activity profile" is a subject of future research. In this study, the profile of immobilized glucoamylase in Fig. 1 was first converted into dimensionless temperature units, then used to fit a fourth-order polynomial equation, which was incorporated into the computer program. This of course poses a limitation on the application of the computation results. As discussed in a previous section, the dimensionless temperature–activity profile is a reasonable approximation and can at least give an estimate of the heat effects of other enzyme systems. Since most temperature–activity profiles are bell-shaped, it will be interesting to collect a large number of such published curves and examine closely the possibility of developing a "generalized dimensionless temperature–enzyme activity profile." The fourth-order polynomial equation used in this work contains 5 adjustable coefficients. with this many parameters, it might be possible to develop a "generalized equation" for the activity profiles.

The effectiveness factor, $E$, in Equations (8) and (9) varies throughout a reactor column with the local temperature and local substrate concentration; it is also dependent on the physical properties of the immobilization carrier. Fortunately, this variation does not pose a serious limitation on the application of the computation results. The physical properties of a support material can usually be described with only one parameter, namely the diffusional–kinetic modulus at the reference temperature. Often, such physical properties can be predetermined by the supplier of the immobilization carriers.

An examination of the components that make up the 5 dimensionless parameters of Equations (8) and (9) will show the basic data that are needed before the heat effect on a column reactor can be evaluated. In order to assign specific values to the 5 parameters, first needed are the local Michaelis constant of the immobilized enzyme, the heat of reaction, kinetics constant, and carrier particle size, in addition to the temperature–enzyme activity profile and the diffusional–kinetic modulus at the reference temperature of the enzyme–carrier complex. In addition, a tracer study should be carried out to determine the dispersion coefficient and the Peclet number of reactor columns. The technique of such tracer studies is conventional, and is also fully described in Marsh's dissertation (9).

Once the basic data are collected from preliminary experiments, the use of the type of graphs reported in this paper will allow estimation of temperature and concentration profiles in reactor columns. With the computer program reported in (9), very precise predictions can also be

calculated. In addition, by varying the input substrate concentration and the input temperature in the computation procedures, optimization of input conditions for optimum reactor performance can be made.

## NOTATION

| | | | |
|---|---|---|---|
| $A_{c.s.}$ | cross-sectional area of packed column | $R$ | mass transfer rate per unit volume of matrix, in mol/cm$^3$-sec, or effective radius of porous catalyst |
| $C_b$ | substrate concentration in solution bulk, in mol/cm$^3$ | $Re_p$ | particle Reynolds number ($= d_p u\rho/\mu$) |
| $C_{bi}$ | inlet bulk concentration at $\xi = 0$ | $t$ | time |
| $C_0$ | Concentration at exterior surface of catalyst particle, in mol/cm$^3$ | $T$ | temperature of fluid in packed bed |
| $C_p$ | heat capacity of fluid | $T_{ref}$ | reference temperature (= 55°C in this analysis) |
| $C^*$ | dimensionless bulk concentration ($= C_b/C_{bi}$) | $T_i$ | inlet fluid temperature (at $\xi = 0$) |
| $d_p$ | particle diameter, cm | $T^*$ | dimensionless temperature ($= T/T_i$) |
| $D_{eff}$ | effective volume diffusivity | $u$ | interstitial velocity in packed column |
| $D_L$ | longitudinal mass dispersion coefficient | $v_0$ | volumetric flow rate |
| $D_{L'}$ | longitudinal heat dispersion coefficient | $\alpha$ | $K_m/C_{bi}$ |
| $E$ | effectiveness factor | $(-\Delta H)$ | heat of enzymatic reaction |
| $k_e$ | effective thermal conductivity in porous catalyst | $\varepsilon$ | external void fraction in packed bed |
| $k_V$ | velocity constant based on unit volume of catalyst | $\gamma$ | $\frac{1-\varepsilon}{\varepsilon}$, volume of catalyst per unit volume of reacting solution |
| $k_{V_{ref}}$ | value of $k_V$ at reference temperature, $T_{ref}$ | $\mu$ | viscosity of fluid, centipoise |
| $K_m$ | Michaelis constant of free enzyme | $\phi_R$ | diffusional–kinetic modulus, $R\sqrt{k_V/(D_{eff}K_{m'})}$ (spherical geometry) |
| $K_{m'}$ | local Michaelis constant for enzyme attached to porous matrix | $\phi_{ref}$ | value of $\phi_R$ at reference temperature, $T_{ref}$ |
| $\ell$ | dimensionless distance along packed bed ($-\xi/L$) | $\rho$ | density of fluid, in g/cm$^3$, or dimensionless radius |
| $L$ | length of packed-bed reactor | $\xi$ | distance along packed-bed reactor |
| $Pe_L$ | longitudinal Peclet number ($= ud_p/D_L$) | | |

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