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An Accurate Numerical Solution of Biospecific Adsorption in a Stirred Bath

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An Accurate Numerical Solution of Biospecific Adsorption in a Stirred Bath

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Abstract

A mathematical model describing the kinetics of a biospecific adsorption process (affinity chromatography) in a stirred finite bath has been numerically solved by an efficient computer program. The radial adsorption distribution of β-galactosidase onto immobilized anti-β-galactosidase for different times obtained from the present solution has been satisfactorily compared with previously published experimental data, as well as with the theoretical predictions of Chase's and Arve's models. It is also shown that the present solution is more accurate than the one obtained by Chase. The computer program used in this study is a general one that can be used for any number of solutes and for equilibrium and non-equilibrium conditions.

INTRODUCTION

The separation of solutes from a fluid stream by biospecific adsorption (affinity chromatography) is a significant industrial process and is especially important in the purification of proteins, enzymes, hormones, and other materials from complex biochemical mixtures in the areas of microbiology, molecular biology, biochemistry, and biochemical engineering. Among conventional separation processes (such as gel filtration, ion exchange, precipitation, ultrafiltration), it seems that biospecific adsorption has the greatest potential for the purification of proteins from complex biochemical mixtures (*1–11*). The basis of biospecific adsorption is the synthesis of an immobilized phase with a high specific affinity for one particular compound or class of compounds and the use of this material in adsorption processes (*4, 5*). The principle of affinity adsorption can be described as follows: The crude starting material is contacted with an immobilized phase (adsorbent) consisting of molecules, with an affinity for the desired product (adsorbate), firmly attached to an inert insoluble solid support matrix. This adsorbate will bind to the molecules attached to the support matrix and will therefore be adsorbed to the immobilized phase. The adsorption stage is followed by a wash stage in which the concentrations of contaminants present within the porous adsorbent particles are reduced to a lower level and the adsorbent is regenerated by a buffer solution to be prepared for use in another cycle of operation.

A number of reviews of biospecific adsorption are available in the works of Porath and Kristiansen (*8*), Chase (*4, 5*), Parikh and Cuatrecases (*7*), Jenson and Hedman (*6*), Hill and Hirtenstein (*9*), Gribnau et al. (*11*), and Arve (*3, 10*).

In 1985, Arnold et al. (*1, 2*) showed that the analysis of affinity separations has lagged considerably behind the rapid increase in new applications. Many researchers have studied affinity adsorption; however, none of them has accounted for all the following factors: internal and external diffusional resistances, nonlinear equilibrium relationships, nonequilibrium conditions, interphase film resistance, and capability of models to be used for *n*-component systems.

In the present work, all of these factors are taken into account.

PHYSICAL MODEL

The present model can be described by introducing the process raw fluid, which contains the adsorbates to be removed, into a finite bath which is full of spherical porous solid particles (the adsorbent). In the adsorption process the following mass transport and interaction processes are considered: (i) the transport of solute(s) from the bulk fluid to solid (adsorbent) surface; (ii) the diffusion of solute(s) into porous particle; and (iii) the adsorption (interaction) of solute(s) onto the solid surface. The adsorbent particles are suspended in the fluid by continuous agitation to have uniform bulk-liquid concentration throughout the bath.

The following assumptions are made:

1. Isothermal process
2. Constant fluid density
3. Perfect mixing of the bath content
4. Adsorbent particles are spherical in shape
5. Constant effective pore diffusion coefficients
6. Equilibrium conditions exist between liquid and solid phases
7. Mutual diffusional effects are neglected

In the bath adsorption process, the radial concentration profiles of adsorbates inside the pore fluid and on solid surfaces as well as the bulk concentration have to be found as functions of time.

GOVERNING EQUATIONS FOR AFFINITY SEPARATIONS

In this process it is considered that biospecific adsorption occurs in a stirred bath containing n components, and m $(m < n)$ adsorbates compete for the available ligands which are assumed to be immobilized on the internal surface of the porous adsorbent. This means that i $(i = m + 1, m + 2, \ldots, n)$ adsorbates diffuse in the pore fluid of the particles and they do not adsorb.

For any solute i, the following dimensionless differential equation results from the mass balance on the surface and pore concentrations inside the particle (*3*):

$$\frac{\varepsilon_p D_{p1}}{A_0} \frac{\partial C'_{pi}}{\partial \tau} + \frac{C_T}{C_{d0i}} \frac{D_{pi}}{A_0} \frac{\partial C'_{si}}{\partial \tau} = \frac{\varepsilon_p D_{pi}}{R_0^2} \left[6 \frac{\partial C'_{pi}}{\partial \rho} + 4\rho \frac{\partial^2 C'_{pi}}{\partial \rho^2} \right],$$

$$\text{for } i = 1, 2, \ldots, m \tag{1}$$

At equilibrium, the surface concentration is expressed in terms of pore concentration of different components through the following Langmuir equilibrium relationship:

$$C'_{si} = \frac{K_{Ai} C_T C'_{pi}}{1 + \sum_{j=1}^{m} K_{Aj} C'_{pj}}, \qquad i = 1, 2, \ldots m \tag{2}$$

where

$$C'_{pi} = C_{pi}/C_{d0i}; \; C'_{si} = C_{si}/C_T; \; \rho = (r/R_0)^2$$

The initial and boundary conditions necessary to complete the definition of Eq. (1) are

$$C'_{pi}(\rho,0) = 0, \qquad i = 1, 2, \ldots, n \tag{3}$$

$$\frac{\partial C'_{pi}}{\partial \rho}(0,\tau) = 0, \qquad i = 1, 2, \ldots, n \tag{4}$$

$$\frac{\partial C'_{pi}(1,\tau)}{\partial \rho} = \frac{\text{Sh}_{pi}}{4}\left(C'_{di} - C'_{pi}|_{\rho=1}\right), \qquad i = 1, 2, \ldots, n \tag{5}$$

$$C'_{si}(\rho,0) = 0, \qquad i = 1, 2, \ldots, m \tag{6}$$

The concentration of solutes in the surrounding fluid, C'_{di}, varies with time according to the following differential equation:

$$\frac{dC'_{di}}{d\tau} = 6\pi\left(\frac{1-\varepsilon_B}{\varepsilon_B}\right)\varepsilon_p \text{Sh}_{pi} D_{pRi}\left(C'_{pi}|_{\rho=1} - C'_{di}\right), \qquad i = 1, 2, \ldots, n \tag{7}$$

where

$$\text{Sh}_{pi} = \frac{2R_0K_{fi}}{\varepsilon_p D_{pi}}, \qquad i = 1, 2, \ldots, n$$

$$D_{pRi} = D_{pi}/D_{p1}, \qquad i = 1, 2, \ldots, n$$

The initial condition needed to complete the definition of Eq. (7) is

$$C'_{di}(0) = 1, \qquad i = 1, 2, \ldots, n \tag{8}$$

For equilibrium conditions, the derivative of C'_{si} in Eq. (1) can be substituted from the Langmuir model (Eq. 2) as follows:

$$\frac{\partial C'_{si}}{\partial \tau} = \sum_{j=1}^{m}\left(\frac{\partial f_i}{\partial C'_{pj}} \frac{\partial C'_{pj}}{\partial \tau}\right), \qquad \text{i} = 1, 2, \ldots, m \tag{9}$$

where

$$C'_{si} = f_i(C'_{p1}, \ldots, C'_{pm}), \qquad i = 1, 2, \ldots, m \tag{10}$$

The functions f_i represent the equilibrium isotherms for the solutes competing for the available sites.

A second-order reversible interaction is assumed for the adsorption step by the following equation:

$$\frac{\partial C'_{si}}{\partial \tau} = \varepsilon_p P_{0i} D_{pRi} (C_{d0i} C'_{pi} (1 - \sum_{j=1}^{m} C_{sj}) - K_{Di} C'_{si}); \qquad i = 1, \ldots, m \tag{11}$$

where

$$P_{0i} = \text{Porath parameter} = K_{1,i} A_0 / \varepsilon_p D_{pi} \text{ and } K_{Di} = K_{2,i}/K_{1,i}$$

NUMERICAL SOLUTION

A numerical scheme using backward-difference technique together with subroutines developed by Mansour (*12–17*) was used to solve the system of differential equations presented in this work. The details of the numerical solution procedure are available elsewhere (*13, 17, 18*).

RESULTS AND DISCUSSION

The values of parameters used in solving this model were also used by Arve (*10*) in 1987. These values are listed in Table 1.

Figure 1 shows good agreement between the theoretical predictions of this work (Curve 3) and experimental data presented by Arve and Liapis

TABLE 1

Numerical Values of Parameters Used for the Adsorption Model Used for Curves 1, 2, and 3, Fig. 1

$C_{d01} = 1.58 \times 10^{-2}$ kg/cm^3	$D_{p1} = 6.9 \times 10^{-8}$ cm^2/s
$C_T = 2.2$ mg/cm^3	$\mathrm{Sh}_{p1} = 254$, $P_{01} = 481$ cm^3/mg
	$\varepsilon_B = 0.985$
$K_{A1} = 4.54 \times 10^{-4}$ cm/s	$\varepsilon_p = 0.5$
$K_{f1} = 5.84 \times 10^{-4}$ cm/s	$R_0 = 7.5 \times 10^{-3}$ cm
$K_{1,1} = 0.235$ cm^3/mg·s	$K_{2,1} = K_{D1}, K_{1,1} = 5.17 \times 10^{-6}$ s^{-1}
Langmuir isotherm:	$C_{s1} = K_{A1} C_T C_{p1} / (1 + K_{A1} C_{p1})$

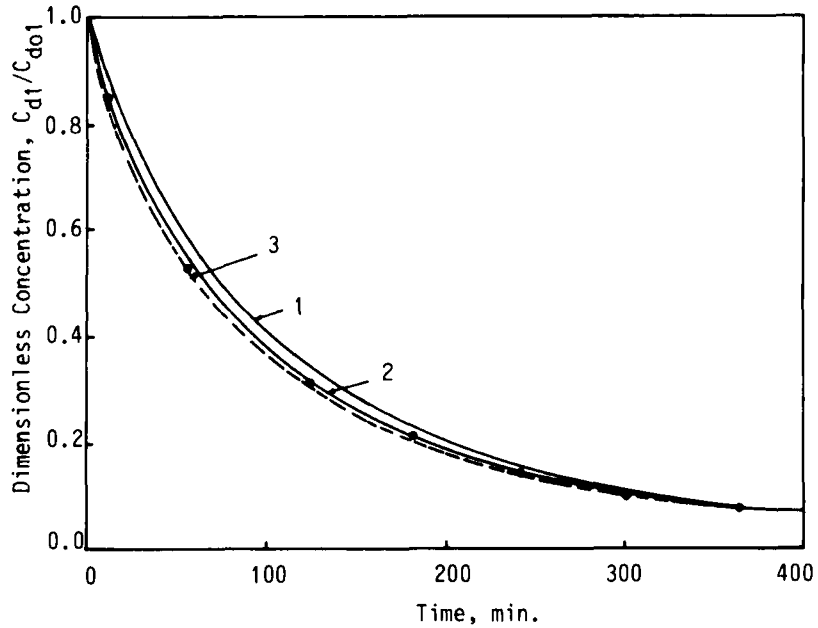

FIG. 1. Variation of the β-galactosidase concentration in the bulk fluid phase with time. Experimental data. Curve 1, Chase's model; Curve 2, Arve's model; Curve 3, predictions of present solution.

(*10*). The predictions obtained in this study are also shown to have excellent agreement with the theoretical predictions obtained by the method of orthogonal collocations (*3, 10*). In previous works (*13–17*) it was shown that the finite difference solution is advantageous to that of orthogonal collocations since it consumes less computer time and it can be used for any number of solutes while a new, different model and different computer program is needed for each different case of orthogonal collocations. Moreover, the present solution is convenient for both equilibrium and nonequilibrim conditions.

It is noted that there are some sorts of deviations between the present predictions and Chase's model (Curve 1) (*3, 4*). These deviations are expected since Chase's model ignores both the diffusion resistance inside the particles of the adsorbent and the mass transfer resistance of the fluid film surrounding the adsorbent particles.

Figures 2 and 3 show the variation of the dimensionless pore concentration of β-galactosidase and the surface concentration of β-galactosidase-anti-β-galactosidase complex with the dimensionless particle radius for different times, respectively. Note that there is a sharp increase in C'_{pi} near the outer surface of the particle where the C'_{pi} value is close to the initial bath concentration, $C'_{di}(0)$.

The concentration profiles of the adsorbate-ligand complex in Fig. 3 are similar to those in Fig. 2 for the unbound solute. It is also noted that a long time (approximately 500 h) is needed to reach equilibrium conditions, which suggests the inclusion of the equilibrium term $K(C'_{si} - C_{si})$ in the model described by Eq. (1) in order to account for the nonequilibrium conditions usually encountered in practice.

CONCLUSIONS

A general computer solution has been successfully applied to predict theoretical results for biospecific adsorption of β-galactosidase onto anti-

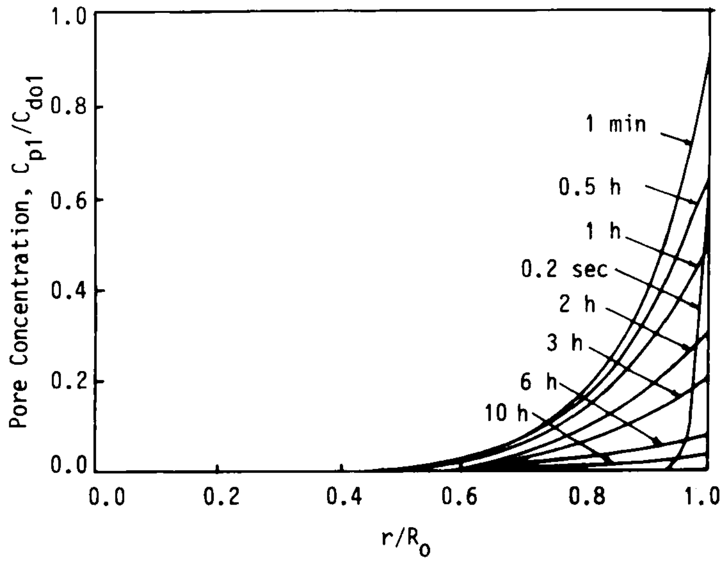

FIG. 2. Pore concentration profiles of β-galactosidase inside the solid particles for different times.

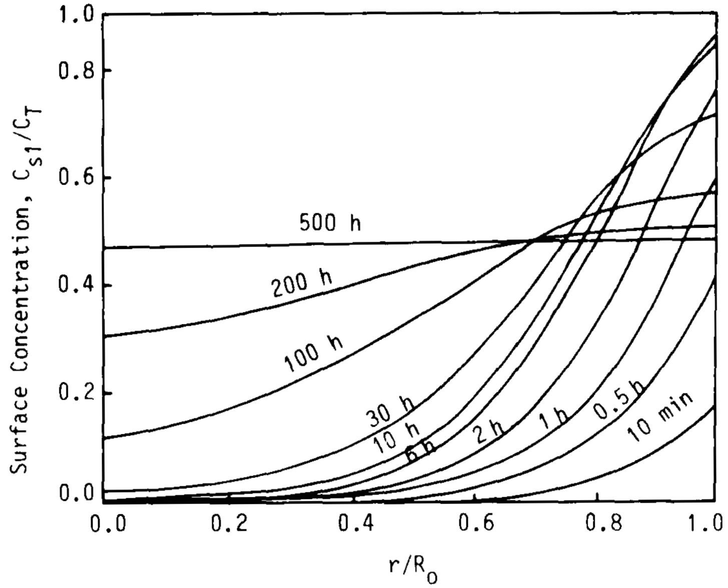

FIG. 3. Surface concentration profiles of β-galactosidase-anti-β-galactosidase complex inside solid particles for different times. $\mathrm{Sh}_{p1} = 254$, $\mathrm{P}_{01} = 481$ cm^3/mg.

β-galactosidase immobilized on a porous silica support matrix in a finite stirred bath. The simulation results are satisfactorily compared with previously published experimental data and theoretical results.

SYMBOLS

A_0	external surface area of particle = $4\pi R_0^2$ (m^2)
C_{di}	bulk fluid concentration of solute i (kg/m^3)
C_{d0i}	initial value of C_{di} (kg/m^3)
C'_{di}	dimensionless $C_{di} = C_{di}/C_{d0i}$
C_{pi}	pore-fluid concentration of solute i (kg/m^3)
C'_{pi}	dimensionless concentration of $C_{pi} = C_{pi}/C_{d0i}$
C_{si}	surface concentration of the adsorbed solute i (kg/m^3 solid particle)
C'_{si}	dimensionless value of $C_{si} = C_{si}/C_T$

C_T	total concentration of ligand (kg/m^3 particle)
D_{pi}	effective pore diffusion coefficient of solute i (m^2/s)
D_{pRi}	D_{pi}/D_{p1}
f_i	equilibrium functions for solutes adsorbed onto ligands
$K_{1,i}$	forward interaction rate constant of solute i (m^3/kg · s)
$K_{2,i}$	backward interaction rate constant of solute i (s^{-1})
K_{Ai}	association equilibrium constant of solute i (m^3/kg)
K_{Di}	dissociation equilibrium constant of solute i (kg/m^3)
K_{fi}	film mass transfer coefficient of solute i (m/s).
m	number of solutes adsorbed
n	number of solutes available in the bath
P_{0i}	Porath parameter = $K_{1,i}A_0/\varepsilon_p D_{pi}$ (m^3/kg)
r	radial distance inside particle (m)
R_0	radius of particle (m)
Sh_{pi}	Sherwood number of solute i = $2R_0K_{fi}/\varepsilon_p D_{pi}$
t	time (s)

Greek Letters

ε_B	bath void fraction
ε_p	particle void fraction
ρ	dimensionless radial distance = $(r/R_0)^2$
τ	dimensionless time = tD_{p1}/A_0

Subscripts

d	bulk fluid
i	integer
j	integer
p	pore
s	solid
0	initial

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