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AN INVERSE MASS TRANSFER PROBLEM FOR THE CHARACTERIZATION OF SIMULATED MOVING BEDS ADSORPTION COLUMNS

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Abstract – In this work the formulation and solution of two inverse problems are presented for the determination of physico-chemical parameters in order to characterize adsorption columns to be used in simulated moving beds for biotechnological processes. For the direct problem the Thomas simplified model is used when the axial dispersion may be neglected, and for the other cases the equilibrium transport dispersive model is employed. An implicit formulation is used for the inverse problem in which we seek to minimize the functional of squared residues between calculated and experimental values of the solute concentration at the exit of the adsorption column. Parametric and sensitivity analyses are performed in order to determine which parameters present higher sensitivity.

1. INTRODUCTION

Recent developments in the pharmaceutical industry have led to the discovery of increasingly complex substances, and a large number of drugs going to market at the moment are chiral substances [1] with optical isomers. Even though the physical properties of optical isomers are very similar, their effects on the human organisms may be drastically different, possibly causing harmful side effects. The control agencies are therefore requiring more careful and profound studies on racemic mixtures.

There is a growing demand for efficient methods to purify optical isomers [10], with one of the most promising alternatives being the simulated moving beds (SMB) chromatography.

For the full understanding of the operation of SMBs, and a possible scale-up to industrial production, it requires a knowledge of mass transfer mechanisms and their dependence on the physico-chemical and process parameters. The first step in that direction consists of the characterization of adsorption columns.

In order to design and optimize preparative separations, the knowledge of the adsorption isotherms is of primary importance, and several techniques have been developed for the determination of such thermodynamic functions [9,12,17], with a growing interest towards the inverse problem approach in which the experimental work is coupled to a more comprehensive computational modeling of the phenomena of interest [3,6,7,21-23].

In the present work we model the liquid-solid adsorption phenomenon, which takes place inside an adsorption column for biomolecules separation. For the direct problem solution we use the equilibrium dispersive (E-D) and Thomas models, with the latter being employed when the effects of axial dispersion are negligible in comparison to the other mass transfer mechanisms [6,9].

The inverse problem is formulated implicitly in which we seek to minimize the norm of the squared residues between calculated and measured values for the breakthrough curves, i.e. the time dependent values of the biomolecules concentration at the exit of the adsorption column.

2. MATHEMATICAL FORMULATION AND SOLUTION OF THE DIRECT PROBLEM

2.1 Mathematical Modeling

In Figure 1 a schematical representation is given of an adsorption column. A fixed bed of adsorbent resins composes the column. A mobile phase, composed by a diluted solution of the adsorbate of interest (biomolecule), percolates through the resin bed (fixed phase). The adsorbate is transferred from the bulk of the solution to the vicinity of the resin particles, i.e. mass transfer through the liquid film, and then it diffuses to the interior of the particle pores being then adsorbed by the solid matrix.
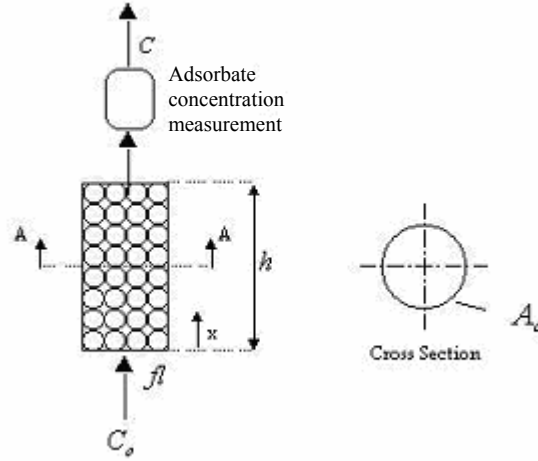
Figure 1. Schematical representation of an adsorption column.

The mathematical model for the chromatography process is based on the mass balance for the two phases; one for the mobile phase that flows through the macro scale porous fixed resin bed, and the other for the resin particles involving the micro scale porous solid matrix [8].

Here we consider the following hypothesis and simplifications [5]: (i) the adsorption process is isothermic; (ii) the mobile phase is a diluted solution; (iii) the mobile phase velocity is constant; (iv) the fixed bed is composed of spherical porous adsorbent particles of uniform size; (v) the concentration gradient in the radial direction is negligible; (vi) there is a local equilibrium between the porous surface and the liquid inside the macro porous; (vii) the axial dispersion coefficient is constant; (viii) the diffusion inside the particles is described by the diffusion inside the pores; (ix) the external mass transfer from the bulk of the liquid to the particles is described by a film mass transfer.

Adsorbent mass balance (fixed phase) A simplified representation of the mass transfer mechanisms in the solid phase [16] considers a time dependent average concentration $\overline{C_i}$, and the resistances to the mass transfer are represented by a global mass transfer coefficient k_l. Being the adsorbate concentration in the bulk of the liquid phase represented by C, the mass balance in the adsorbent spherical particles is written as

$$\varepsilon_i \frac{d\overline{C_i}}{dt} = \frac{3k_l}{R}\left(C - \overline{C_i}\right) - \frac{\partial q_i}{\partial t} \tag{1}$$

where ε_i is the particle porosity, q_i is the adsorbate concentration in the solid matrix, and R is the radius of the adsorbent particles.

The mass transfer rate from the solution to the fixed phase is given by [4]

$$\frac{\partial q}{\partial t} = k_1 C\left(q_m - q\right) - k_2\,q \tag{2}$$

where q is the adsorbate concentration, q_m is the maximum adsorbate concentration which the adsorbent may adsorb (maximum adsorption capacity), k_1 is the adsorption rate constant, and k_2 is the desorption rate constant. Further, the dissociation rate constant k_d is defined as

$$k_d = \frac{k_2}{k_1} \tag{3}$$

Considering a very fast adsorption rate on the surface, an equilibrium can be reached $\left(\partial q / \partial t \equiv 0\right)$, [19], and from eqn. (2) we write

$$\frac{\partial q^*}{\partial t} = k_1\,C^*\left(q_m - q^*\right) - k_2\,q^* = 0 \tag{4}$$

which leads to the nonlinear Langmuir isotherm [11],

$$q^* = \frac{q_m \cdot C^*}{\left(k_d + C^*\right)} \tag{5}$$

Replacing C^* by $\overline{C_i}$, we obtain from eqns (1) and (5),

$$\left(\varepsilon_i + \frac{q_m \cdot k_d}{\left(k_d + \overline{C}_i\right)^2}\right)\frac{d\overline{C}_i}{dt} = \frac{3k_l}{R}\left(C\big|_{r=R} - \overline{C}_i\right) \tag{6}$$

We consider that at the beginning of the process there is no adsorbate in the resin particles. Therefore,

$$\overline{C}_i = 0 \quad \text{for} \quad t = 0 \tag{7}$$

Column Mass Balance (mobile phase) A mathematical model which takes into account mass transfer in the liquid film, axial dispersion and a constant flow rate [8] is given by

$$\varepsilon\frac{\partial C}{\partial t} = \varepsilon D_{ax}\frac{\partial^2 C}{\partial x^2} - u\frac{\partial C}{\partial x} - (1-\varepsilon)\frac{\partial q}{\partial t} \tag{8}$$

where ε represents the bed porosity, D_{ax} the axial dispersion coefficient, u the constant linear velocity and x represents the axial distance from the entrance of the column, see Figure 1. The column has a total length h.

Using the same assumptions considered for the mass balance in the fixed phase, Santacesaria *et al.* [16] derived an approximation for the last term of eqn. (8) arriving at

$$\varepsilon\frac{\partial C}{\partial t} = \varepsilon D_{ax}\frac{\partial^2 C}{\partial x^2} - u\frac{\partial C}{\partial x} - \frac{3k_l(1-\varepsilon)}{R}\left(C\big|_{r=R} - \overline{C}_i\right) \tag{9}$$

Here we use the Danckwert boundary conditions

$$u \cdot C_0 = u \cdot C\big|_{x=0} - D_{ax}\frac{\partial C}{\partial x}\bigg|_{x=0} \quad , \quad \text{for} \quad t > 0 \tag{10}$$

$$\frac{\partial C}{\partial x}\bigg|_{x=h} = 0 \quad , \quad \text{for} \quad t > 0 \tag{11}$$

and the initial condition

$$C = 0, \text{ for } t = 0 \quad , \quad \text{in} \quad 0 \le x \le h \tag{12}$$

2.2 Thomas Model

For the particular case in which the axial dispersion may be neglected, i.e. $D_{ax} = 0$, and the adsorbate inflow is constant, i.e. $C_0 = $ constant, the adsorption problem described in the previous section has an analytical solution [2,4,15] and it was first derived by Thomas [20]. The adsorbate concentration in the mobile phase at the exit of the adsorption column, $x = h$, is given by

$$\frac{C}{C_o} = \frac{J(\eta/\sigma, \eta T)}{J(\eta/\sigma, \eta T) + [1 - J(\eta, \eta T/\sigma)]\exp(1-\sigma^{-1})(\eta - \eta T)} \tag{13}$$

where

$$\sigma = 1 + C_o/k_d \tag{14}$$

$$\eta = q_m k_1 h A_c / fl \tag{15}$$

$$T = flt\left(k_d + C_o\right)/A_c q_m h \tag{16}$$

fl is the volumetric flow rate through the column, and the function $J(a, b)$ is given by

$$J(a,b) = 1 - e^{-b}\int_0^a e^{-\xi}I_0(2\sqrt{b\xi})\partial\xi \tag{17}$$

where I_0 is the modified Bessel function of the first kind and of order zero.

The function $J(a,b)$ may be approximated by an asymptotic series whose two first terms are [20] given by

$$J(a,b) \approx \frac{1}{2}\left[1 - erf(\sqrt{a} - \sqrt{b})\right] + \frac{\exp\left[1 - (\sqrt{a} - \sqrt{b})^2\right]}{2\pi^{\frac{1}{2}}\left[(ab)^{\frac{1}{2}} + b^{\frac{1}{2}}\right]} \tag{18}$$

2.3 Equilibrium Dispersive Model (E-D)

The E-D model given by eqns (6,7,9-12), does not possess a known analytical solution, and therefore a numerical approximation is used. In the present work we use the finite-difference method. For the time derivative we use a forward-difference approximation. For the first derivate in space we use a backward-difference approximation, and for the second derivate in space we use a central-difference approximation.

Defining the following dimensionless variables:

$$\Phi = \frac{C}{C_0}, \quad Y = \frac{x}{h}, \quad \Theta = \frac{\overline{C}_i}{C_0}, \quad Pe = \frac{h \cdot u}{\varepsilon \cdot D_{ax}}, \quad Nu = \frac{k_l \cdot h^2}{R \cdot D_{ax}}, \quad \tau = \frac{t \cdot D_{ax}}{h^2}, \quad \Psi = \frac{1-\varepsilon}{\varepsilon} \tag{19 a-g}$$

the following approximation is obtained for the mass balance in the mobile phase

$$\Phi_{j+1}^{n+1}\left(-\frac{1}{\Delta Y^2}\right)+\Phi_j^{n+1}\left(\frac{1}{\Delta\tau}+\frac{Pe}{\Delta Y}+\frac{2}{\Delta Y^2}+3\Psi Nu\right)+\Phi_{j-1}^{n+1}\left(-\frac{Pe}{\Delta Y}-\frac{1}{\Delta Y^2}\right)=\frac{\Phi_j^n}{\Delta\tau}+3\Psi Nu\Theta_j^n \tag{20}$$

where the index n, with $n = 0,1,..., Nn$, is related to the discretization of the time domain, while the index j, with $j = 0,1,..., Nj$ is related to the discretization of the spatial domain. ΔY and $\Delta\tau$ are related to the spatial and time steps, respectively.

Using a simplification on the Dankwets boundary conditions [8] results in:

$$\Phi_o^n = 1 \quad \text{for} \quad n=1, 2,......,N_n \tag{21}$$

$$\Phi_{N_j}^{n+1} = \Phi_{N_{j-1}}^{n+1} \quad \text{for} \ j = N_j \tag{22}$$

and the initial condition is written as

$$\Phi_j^0 = 0 \quad \text{for} \quad j=1, 2,......,N_j \tag{23}$$

The discretized approximation for the mass balance in the fixed phase is given by

$$\Theta_j^{n+1} = \frac{3\cdot Nu\Delta\tau}{\left[\varepsilon_i+\dfrac{q_m\cdot k_d}{\left(k_d+\Theta_j^n\cdot C_0\right)^2}\right]}\left(\Phi_j^n-\Theta_j^n\right)+\Theta_j^n \tag{24}$$

with the initial condition

$$\Theta_j^0 = 0 \quad \text{for the} \quad j=1, 2,......,N_j \tag{25}$$

The resulting system of linear algebraic equations was solved using the Gauss- Seidel iterative method with the initial guess the values of the concentration available at the previous time step.

3. MATHEMATICAL FORMULATION AND SOLUTION OF THE INVERSE PROBLEM

In the present work we are interested in determining the parameters of the adsorption isotherm, k_d and q_m, or even other parameters such as the bed porosity ε, and the axial dispersion coefficient, D_{ax}. The unknown parameters are then grouped in a vector of unknowns such as

$$\vec{Z} = \{k_d, q_m\}^T \ \text{ or } \ \vec{Z} = \{\varepsilon, D_{ax}\}^T \tag{26}$$

We consider as experimental data the adsorbate concentration in the liquid phase at the exit of the column, at $x = h$, i.e. $C_{\exp}(t_i)$, $i = 1,2,....,N_e$, where N_e is the total number of experimental data.

As there is more experimental data than unknowns, the inverse problem is formulated implicitly as an optimization problem in which we seek to minimize the cost function given by the summation of the squared residues between the calculated and measured values for the concentration at the end of the adsorption column. Using the dimensionless concentration defined in eqn. (19a), we write

$$Q(\vec{Z}) = \sum_{i=1}^{N_e}\left[\Phi_{calc_i}(\vec{Z})-\Phi_{\exp_i}\right]^2 = \vec{F}^T\vec{F} \tag{27}$$

where the elements of the vector of residues $\vec{F}$ are given by

$$F_i(\vec{Z}) = \Phi_{calc_i}(\vec{Z})-\Phi_{\exp_i}(\vec{Z}), \ i = 1, 2,......, N_e \tag{28}$$

Writing the critical point equation, using a Taylor expansion, and adding a damping factor, λ, to the diagonal of the resulting information matrix, we derive the Levenberg-Marquardt method:

$$[J^T(\vec{Z}^l)J(\vec{Z}^l)+\lambda^l I]\Delta\vec{Z}^l = -J^T(\vec{Z}^l)F(\vec{Z}^l) \tag{29}$$

where

$$\Delta\vec{Z}^l = \vec{Z}^{l+1}-\vec{Z}^l \tag{30.a}$$

because

$$\vec{Z}^{l+1} = \vec{Z}^l+\Delta\vec{Z}^l \tag{30.b}$$

and the elements of the Jacobian matrix J are given by

$$J_{mn} = \frac{\partial\Phi_{calc_m}}{\partial Z_n}, \quad m = 1,2,...,N_e \text{ and } n = 1,2,...,N_u \tag{31}$$

l is the iteration index, and N_u is the total number of unknowns.

In order to solve the inverse problem we start with an initial guess $\vec{Z}^0$. Then eqn. (29) is solved for $\Delta\vec{Z}^0$, and a new estimate, $\vec{Z}^1$ is obtained using eqn. (30b). The iterative procedure for calculating the corrections $\Delta\vec{Z}^l$ with eqn. (29) and the new estimates for the unknowns with eqn. (30b) is repeated until a convergence criterion such as the following:

$$\left|\frac{\Delta Z_n}{Z_n}\right| < \delta \ , \ n = 1,2,...,N_u \tag{32}$$

is satisfield, where δ is a tolerance, say 10^{-4}.

Here the value of the damping parameter λ^l was varied by way of the iterative procedure according to the original proposal of Marquardt [13].

4. RESULTS AND DISCUSSIONS

4.1 Thomas model

In Table 1 the reference values for the process and physico-chemical parameters used in the test cases with the Thomas model are presented. The values shown for the parameters k_d, q_m and k_1, in the second, third and fourth columns of Table 1, were obtained by Chase [4], Pereira [14] and Silva [18], respectively, using several experimental runs.

Table 1: Process and physico-chemical parameters used in the inverse problems with the Thomas model.

Parameters	Case 1 [4]	Case 2 [14]	Case 3 [18]
Substance	Lisozyme	β-Galactosidase	Inulinase
h - column height (cm)	10.4	3.2	8.0
A_c – column cross section (cm^2)	0.785	0.196	0.196
fl – volumetric flow rate (ml/min)	1.0	1.0	0.35
C_o - adsorbate concentration at the column inlet	0.1 mg/ml	0.104 mg/ml	1.45 mg/ml
q_m – maximum adsorption capacity	14 mg/ml	32.98 mg/ml	4165.69 UA/ml. g
k_d – dissociation rate constant	0.025 mg/ml	0.04 mg/ml	94.80 UA/ml
k_1 – adsorption rate constant	0.20 ml/mg. min	3.68 ml/mg. min	0.005 ml/UA. min

Before we attempted to use the real experimental data of Chase [4], Pereira [14] and Silva [18], in order to solve the inverse problem we performed a sensitivity analysis.

In Figure 2 the scaled (or modified) sensitivity coefficients are presented, namely

$$X_z(t) = Z\frac{\partial G_{calc}(t)}{\partial Z} \tag{33}$$

for the parameters q_m, k_d and k_1 for the three cases shown in Table 1.

Using the experimental data of Chase [4] and the Thomas model for the direct problem solution, the inverse problem was solved using Levenberg-Marquardt method for the determination of $\vec{Z} = \{k_d, q_m\}$. In Table 2 the values obtained by Chase (Case 1 in Table 1) and the values obtained in the present work are presented. The value of k_1 was considered fixed at 0.2 ml/mg.min.
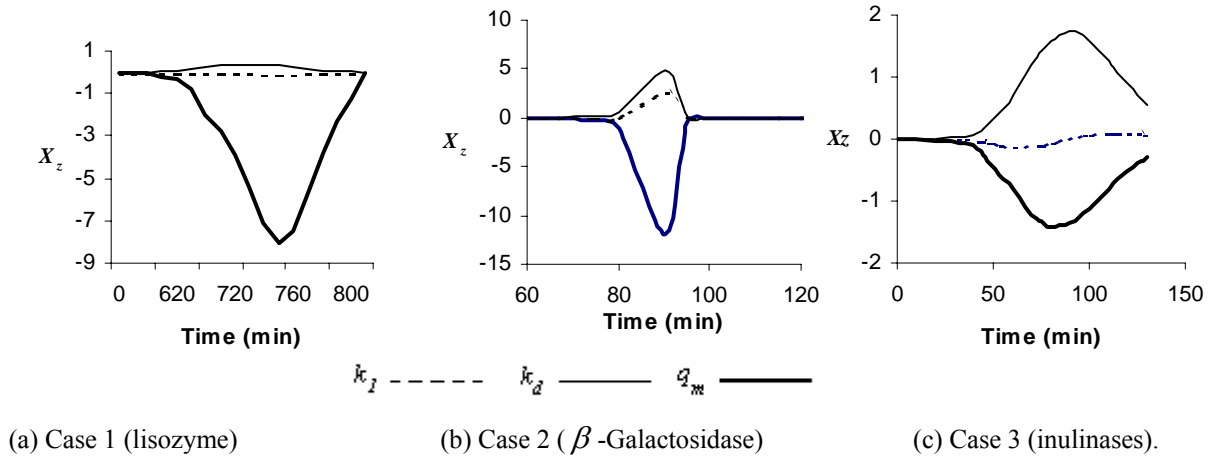
(a) Case 1 (lisozyme)   (b) Case 2 (β-Galactosidase)   (c) Case 3 (inulinases).

Figure 2. Sensitivity coefficients for cases 1-3 in Table 1.

Table 2: Parameters for lisozyme Langmuir´s adsorption isotherm, Case 1 (Table 1).

Source	k_d (mg / ml)	q_m (mg / ml)
Inverse Problem solution	0.029	14
Chase [4]	0.025	14

The estimated value for q_m is in excellent agreement with the value presented by Chase, and a 16% deviation is observed for the estimated value for k_d. This is probably due to the lower sensitivity to this parameter as may be seen in Figure 2(a).

In Figure 3(a) are presented the experimental data for lisozyme breakthrough curves and Chase´s model solution [4], as well as the breakthrough curve calculated with Thomas model and the values estimated for k_d and q_m with the solution of the inverse problem, see Table 2.

In Figure 3(b) is presented the Langmuir adsorption isotherm for lisozyme calculated using eqn. (5) and the estimated values for k_d and q_m shown in Table 2. Also presented are the Chase experimental data and the adsorption isotherm obtained in [4].
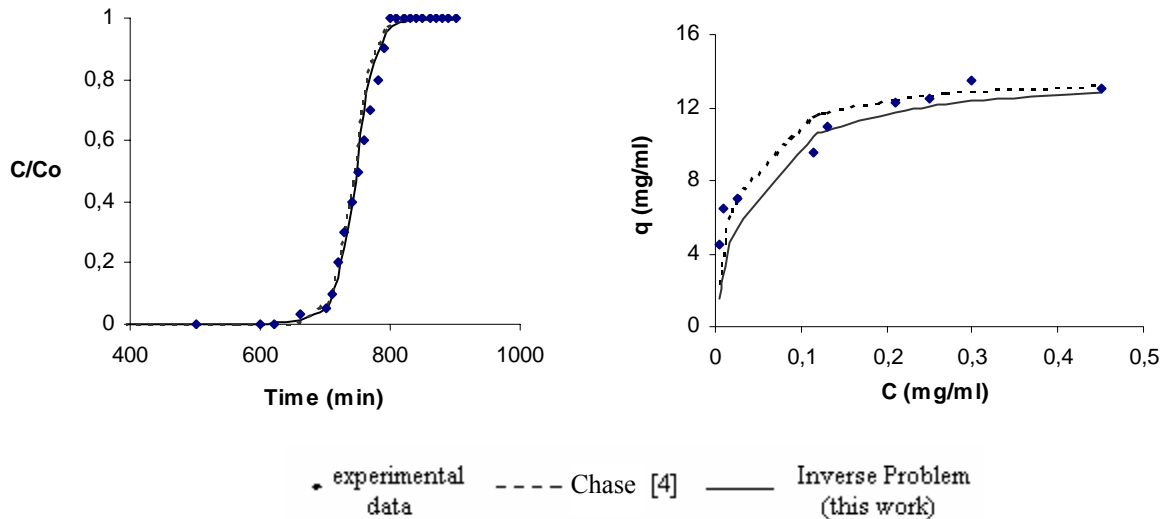

Figure 3. (a) Breakthrough curves, and (b) adsorption isotherm, for lisozyme.

Results shown in Table 2 and Figures 3(a) and 3(b) demonstrate the good quality of the solution obtained.

Using the experimental data of Pereira [17], and the Thomas model for the solution of the direct problem, the estimated values for k_d and q_m shown in Table 3 were obtained.

Table 3: Parameters for β-Galactosidase, Case 2 (Table 1).

	k_d *(mg / ml)*	q_m (mg / ml)
Inverse problem solution	0.123	33.0
Pereira [17]	0.04	32.98

The value of k_l was considered fixed at 3.0 ml/mg.min. This value was chosen after a parametric analysis was performed starting at the value given by Pereira (Case 2 in Table 1).

Here the estimate for q_m was good and the estimate for k_d was poor. Again, this behavior was expected because of the sensitivity analysis results shown in Figure 2(b).

In Figure 4 the Langmuir adsorption isotherm for β-Galactosidase calculated using eqn. (5), and the estimated values for k_d and q_m shown in Table 3, are presented. In the figure the experimental data and the adsorption isotherm obtained in [14] is also shown.

Using the experimental data of Silva [18], and the Thomas model for the solution of the direct problem, the estimated values for k_d and q_m shown in Table 4 were obtained.

Table 4: Parameters for inulinase, Case 3 (Table 1).

	k_d *(UA / ml)*	q_m (UA / ml. g).
Inverse problem solution	253.77	5002.87
Silva [18]	94.80	4165.69

The value of k_l was considered fixed in 0.001 ml/UA.min. This value was chosen after a parametric analysis was performed starting at the value given by Silva (Case 3 in Table 1).

Here both the estimates for k_d and q_m are poor, probably due to the fact that they may be correlated as shown in Figure 2(c).

In Figure 5 the Langmuir adsorption isotherm for inulinases, calculated using eqn. (5), and estimated values for k_d and q_m shown in Table 4 are presented. The experimental data and the adsorption isotherm obtained in [18] are also shown.
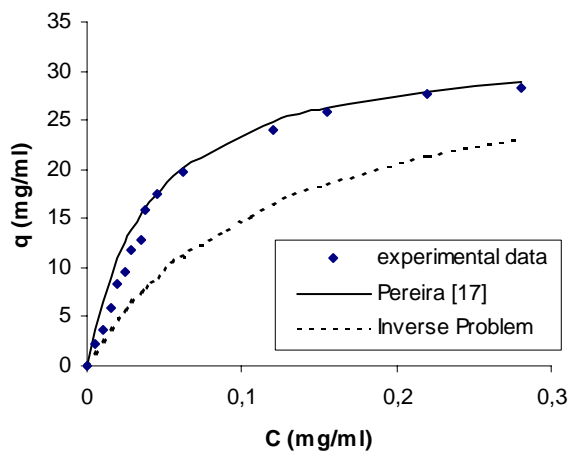

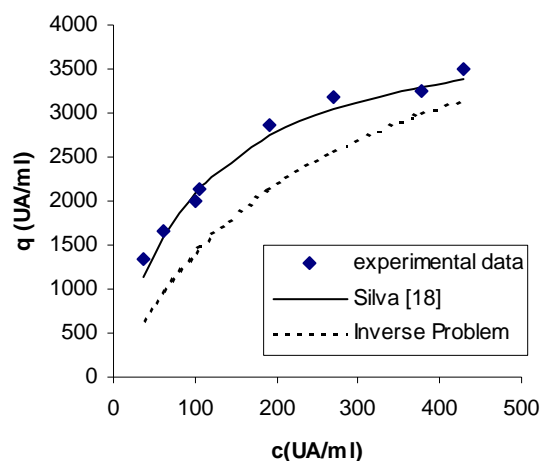Figure 4. β-Galactosidase adsorption isotherm.

Figure 5. Inulinase adsorption isotherm.

From Tables 3 and 4 and Figures 4 and 5 it can be seen that there is a large discrepancy between the results presented in [17, 18] and those obtained in the present work. In addition to the difficulties related to the sensitivity to the parameters of interest, k_d and q_m, we observe that for β-Galactosidase and inulinase the effects due to the axial dispersion can not be neglected in comparison to the other mass transfer phenomena, and therefore the Thomas model can not be used for the solution of the direct problem. In the next section the results

for the estimation of the bed porosity and the axial dispersion coefficient for inulinase using the equilibrium dispersive model for the direct problem are presented.

4.2 Equilibrium (E-D) Dispersive Model

In Table 5 the reference values for the process and physico-chemical parameters used in the test case with the E-D model are presented.

We then performed a parametric analysis by varying the values of D_{ax}, ε, ε_i, R, q_m, k_d and k_1 by $\pm 5\%$, and observing the effects on the breakthrough curves. The highest sensitivities were observed for the axial dispersion coefficient, D_{ax}, and the bed porosity, ε, as may be observed in Figures 6(a) and 6(b).

Table 5: Process and physico-chemical parameters used in the inverse problem
with the Equilibrium Dispersive Model (E-D).

| Parameters	Case 3 [18]
Substance	Inulinase
h - Column height (cm)	8.0
A_c – Column cross section (cm^2)	0.785
f – Volumetric flow rate (ml/min)	0.25
C_o - Adsorbate concentration at the column inlet (UA/ml)	15.6
q_m – Maximum adsorption capacity (UA/ml.g)	4165.69
k_d – Dissociation rate constant (UA/ml)	94.68
kl – Global mass transfer coefficient (cm/min)	6 x 10^{-6}
R – Radius of the adsorbent particles (cm)	0.0045
ε – Bed porosity	0.557
ε_p – Particle porosity	0.501
D_{ax} – Axial dispersion coefficient (cm^2/min)	0.0273
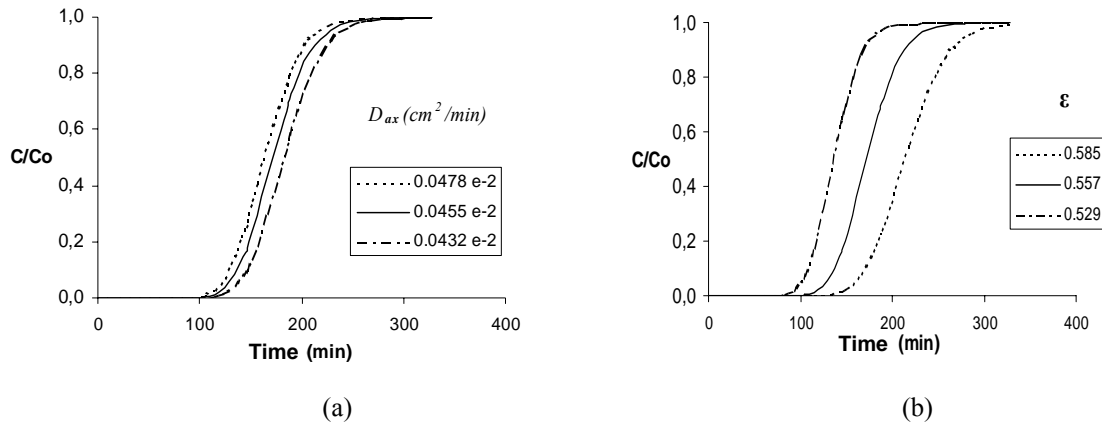
Figure 6. Effects on the inulinases breakthrough curves due to a variation of $\pm 5\%$ on
(a)   the axial dispersion coefficient, and   (b) the bed porosity.

Starting with the values obtained by Silva [18], $\varepsilon = 0.557$ and $D_{ax} = 0.0273$ cm²/min, we have performed a few runs of the direct problem with the E-D model trying to find a better fit for the experimental data.

The results for all runs are shown in Table 6, from which it can be seen that the values $\varepsilon = 0.55$ and $D_{ax} = 0.0252$ cm²/min seem to provide a better fit with a slightly smaller value for the cost function $Q(\vec{Z})$ given by eqn. (27).

In Figure 7 the experimental data for the inulinase breakthrough curves and the solution of Silva using the E-D model [18], as well as the breakthrough curve calculated with the E-D model and the values estimated for ε and D_{ax} according to Table 6 are presented.

Table 6: Cost function results, $Q(\vec{Z})$, for the inulinase test case 4 in Table 5 and different values for the bed porosity ε and axial dispersion coefficient, D_{ax}.

ε	D_{ax} (cm^2/min.)	$Q(\vec{Z})$, Eq. (27)
0.557	0.0273	0.04
0.5	0.0240	1.53
0.5	0.0300	2.8
0.5	0.0180	2.2
0.6	0.0300	1.23
0.55	0.0270	0.12
0.55	0.0252	0.03
0.55	0.0246	0.05

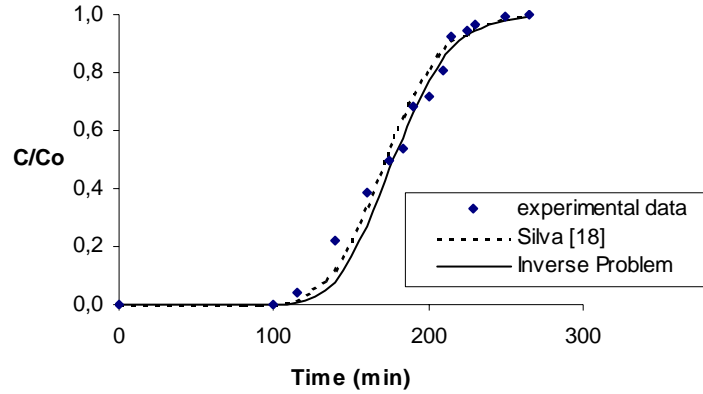

Figure 7. Breakthrough curves for inulinase, Case 4 in Table 5. The inverse problem solution was obtained with the equilibrium dispersive model and ε = 0.55 and D_{ax} = 0.0252 cm²/min.

5. CONCLUSIONS

The use of the inverse problem approach for the estimation of the adsorption isotherm may be competitive in comparison to the other methods available, such as the frontal analysis, mainly when the adsorbate is of high cost. With the measurements of the adsorbate concentration and a model which describes the relevant mass transfer phenomena involved, the present work uses the Levenberg-Marquardt method for the estimation of parameters related to the adsorption isotherm, the adsorption column porosity and the axial dispersion coefficient.

For lisozyme the direct problem was solved using the Thomas model and for β-Galactosidase and inulinases the equilibrium dispersive model was used. For the first substance the effects of the axial dispersion were negligible in comparison to the other mass transfer phenomena, and the use of the Thomas model yielded good estimates for the maximum adsorption capacity.

For the inulinases, the E-D model was required and a parametric analysis indicated the higher sensitivity to the bed porosity and axial dispersion coefficient. The calculated values for the breakthrough curve were in excellent agreement with the experimental data.

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