Journal of Chromatography, 484 (1989) 187–210
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 21 924

MODELLING METHODS TO AID THE DESIGN AND OPTIMISATION OF BATCH STIRRED-TANK AND PACKED-BED COLUMN ADSORPTION AND CHROMATOGRAPHY UNITS

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SUMMARY

In this paper, work is described which has led to the development of a suite of computer programs for the prediction of adsorption and chromatographic processes to aid the design and optimisation of batch stirred-tank and packed-bed column units. Brief descriptions are given of the mathematical models incorporated within the codes, and the complementary small-scale experiments to provide the necessary physical parameter information on adsorption isotherms and mass transfer kinetics.

The models are formulated for single- and multi-component adsorption and for packed-column separation dealing with both frontal analysis and elution chromatography. Two types of predictive method are outlined. The first is based on simple kinetic type rate expressions for mass transfer, the second is a more complex model taking into account liquid film and pore diffusion resistances to mass transfer. For adsorption the models imply a favourable Langmuir type isotherm but they may be adapted for use with linear and irreversible isotherms.

Some details of the mathematics involved in the models and the methods of solution of the resulting equations are presented. In specific cases simplifying assumptions allow analytical solutions to be obtained, whereas in other instances numerical solutions derived by using the Harwell FACSIMILE code are required.

Typical results are given from small-scale and pilot-scale experiments to provide data to validate the codes. These experiments involved studies of the adsorption, washing and elution of single- and multi-component amino acids using Duolite A-162 resin spheres as adsorbent covering a range of conditions. Comparisons are given between code simulations and experimental data, and applications of the codes are discussed.

INTRODUCTION

The development of computer simulation programs to aid the design and optimisation of industrial batch stirred-tank and packed-bed column adsorption and chromatography units continues to attract major attention. In previous work the modelling of adsorption rate processes has been reviewed by Cowan *et al.*[1], and examples of the application of modelling to the design and optimisation of industrial adsorption units has been discussed by Cowan *et al.*[2].

In the present paper, recent publications relevant to the modelling of adsorption and chromatographic processes are reviewed and work is described which has led to the development of computer programs for the simulation of batch stirred-tank and packed-bed column adsorption units to aid in process optimisation and design, given specific information on equilibrium and kinetics derived from small-scale experiments. Brief details are also given of complementary programs which are used for the derivation of the appropriate equilibrium and kinetic parameters from the small-scale experiments. Such parameter fitting codes may be applied to data from small- or preparative-scale operations or from industrial plants to derive physical parameters for modelling and optimisation purposes.

Typical results are presented from small-scale and pilot-scale experiments to provide data to validate the codes. These experiments involved studies of the adsorption, washing and elution of single- and multi-component amino acids using Duolite A-162 resin spheres as adsorbent covering a range of conditions. Comparisons are given between code simulations and experimental data, and applications of the codes are discussed.

RECENT PUBLICATIONS RELEVANT TO MODELLING

Knowledge of capacity and equilibrium relationships and mass transport parameters are required in modelling work. Jacobsen *et al.*[3] have developed a fast, accurate and precise method of isotherm measurement by using a high-performance liquid chromatography (HPLC) technique requiring only milligram quantities of material with frontal development. Kirby *et al.*[4] have also described an HPLC technique suitable for isotherm determination where it is required to contact small quantities of adsorbate with an adsorbent for a short time. A micro-scale system for estimation of isotherm and kinetic parameters used in the modelling of fixed-bed adsorbers is detailed by Weber and Wang[5]. The application of the data from such measurements to the design or analysis of industrial packed-bed columns is of interest. From micro-scale column experiments using carbon particles of different size ranges Weber and Wang[5] concluded that adsorbent particle size did not affect capacity. Similarly Kirby *et al.*[4] found reasonable agreement between isotherm data by using the HPLC technique with 40–50-μm Amberlite XAD-2 particles and larger-scale packed-bed experiments with 700-μm XAD-2 particles. In comparing HPLC data with results from batch cell experiments Kirby *et al.*[4] showed isotherm data to be in sensible agreement, whereas Weber and Wang[5] indicated that batch cell results gave a higher value for adsorbent capacity than obtained from the microcolumn work. Weber and Wang[5] discussed application of the microcolumn data to system scale-up.

A new method of predicting adsorption equilibria for multicomponent liquid solutions on solids which combines the thermodynamic and kinetic treatments of liquid adsorption has been developed by Price and Danner[6]. The method requires the determination of liquid phase and adsorbed phase activity coefficients but provides a simpler computational technique than previous similar treatments. The potential advantage of the method is that complex experimental multi-component equilibrium studies can be replaced by more relatively straightforward experimental studies of binary mixtures. The determination of binding equilibrium constants by numerical simulation in zonal high-performance affinity chromatography has been reported by

Vidal-Madjar *et al.*[7]. The method was applied to the measurement of ligand–protein interactions in zonal elution chromatography to determine the amount of active immobilised protein and the equilibrium constant characterising the affinity interaction. These parameters are of use to compare different methods of protein immobilisation and for determining the contribution of the matrix to the retention.

Arve and Liapis[8] present general equations to describe single- and multicomponent biospecific as well as non-specific adsorption from a finite bath onto porous adsorbent particles whose internal surface is covered by immobilised ligands. The model accounts for the external film resistance and diffusional resistance within the particles and rate expressions for the interaction between the adsorbate and ligand are included. The adsorbate may be monovalent or multivalent and predictions are given for both adsorption and washing stages. Such models are most useful to indicate the effects of changing different parameters on adsorption and washing in complex batch systems, but more extensive comparisons against experimental data are required to validate the model over a wide range.

A mathematical model has been developed by Nigam and Wang[9] to study bioproduct adsorption for small-affinity adsorbent particles immobilised in hydrogel beads for whole-broth processing. The model accounts for diffusion in the hydrogel beads, adsorbent particles and binding within the immobilised adsorbent particles. Code predictions based on the model show that the performance of finely ground immobilised adsorbent particles within the hydrogel can be better than for freely suspended adsorbent. McConvey[10] describes a two-step model for the adsorption of the macromolecule Vitamin B_{12} onto a porous polymeric adsorbent from an aqueous solution in a batch reactor, and the model is used to determine the external film mass transfer and intraparticle surface diffusion coefficients for the process.

Mansour *et al.*[11] give a parametric study of multicomponent adsorption in stirred tanks. A mathematical model was developed by Mansour which takes into account internal and external diffusional resistances and liquid film resistance. A non-linear Fritz–Schlunder[12] type isotherm was used to describe the equilibrium between liquid and solid phases. Predicted transient bath concentration profiles were obtained for the cases of adsorption of single, binary and ternary systems. Predictions for the binary adsorption of 2-butanol and *tert.*-amyl alcohol onto activated carbon showed good agreement with the experimental data of Balzli[13]. Using a simplified model in which it was assumed that internal diffusion is a very rapid process, Mansour *et al.*[14] have also presented a study of the prediction of the effect of parameters influencing the performance of multicomponent adsorption in packed-bed columns. Predictions from the mathematical model satisfactorily agreed with previously published data.

Numerical methods relevant to the solution of adsorption models are discussed by Costa and Rodrigues[15] in the book edited by Rodrigues *et al.*[16], which gives several useful papers relevant to the kinetics of adsorption and fixed-bed processes and modelling. Details of the numerical simulation of fixed-bed adsorption dynamics using the method of lines and accounting for both axial dispersion and intraparticle diffusion are given by Brian *et al.*[17].

An overview of simulation and design for adsorption processes has been given by Weber and Smith[18], including discussion of Freundlich and ideal adsorbed-solution theory equilibrium models, a two-resistance, homogeneous-surface-diffusion dynamic

model, and parameter estimation. Important guidelines given are that continuing research is needed to improve the reliability of parameter estimation techniques, and to validate and enhance the capability of existing models to deal with the complexities encountered in field applications. Comments on possible future directions for process modelling are presented. A comparative study of two models to predict protein adsorption on packed beds of resins has been made by Graham *et al.*[19]. The models are a two-phase resistance model and a shrinking core model. The main difference between the models is the method used to account for diffusion of the protein within the resin particles. In the two-phase resistance model the resin particle is treated as a quasi-homogeneous media through which the protein molecules diffuse. The diffusional process is approximated by a linear driving force using a mass transfer coefficient, related to an effective particle diffusion coefficient which is determined from separate batch experiments. In the shrinking core model, it is assumed that once the protein reaches the resin particle it binds with the active sites and becomes immobilised producing a reacted core, and the concentration of protein diffusing is taken as only that in the pores of the resin. The diffusion equation is solved in the reacted resin region and the pore diffusivity is determined from the free solution diffusivity taking into account the tortuosity of the pores in the resin. Comparison of predictions from the two models with breakthrough curves derived from fixed-bed column experiments for bovine serum albumin (BSA) on Sephadex A-50, and BSA on DEAE-Sepharose indicated that the two-phase resistance model gave the better agreement with experimental data. The shrinking core model predicted broader breakthrough curves possibly because of the more imprecise determination of the pore diffusion coefficient. The optimisation of the process chromatography of proteins has been discussed by Janson and Hedman[20] and a simplified treatment for optimisation of production rate is presented. For such processes these authors conclude that it is more profitable to increase throughput by increasing selectivity rather than column efficiency.

A simplified model for multi-component fixed-bed adsorption is described by Moon and Lee[21] based on the assumption that a linear driving force approximation is valid in describing the intraparticle surface diffusion. The Freundlich-type multi-component isotherm (taken as suitable for highly heterogeneous adsorbents such as activated carbon) and the ideal adsorbed-solution theory were incorporated with the model to deal with competitive adsorption. Model parameters were estimated from correlations and obtained from single-component batch experiments. The model was satisfactorily used in predicting breakthrough curves for two-component simultaneous and counter-current adsorptions of phenols on activated carbon in fixed beds. An advantage claimed for the method is that computational times are small compared to those for diffusion models.

In studies of the uptake of various amino acids by two ion-exchange resins Carta *et al.*[22] found that a model for ion-exchange equilibrium which takes into account heterogeneity of functional groups on the resins gave an excellent correlation of binary data. By using parameters determined only from binary measurements the model was successfully extended to the prediction of multi-component equilibria. An equilibrium stage model which incorporates solution and ion-exchange equilibria is also presented for the prediction of packed-bed separation processes. The model which requires only equilibrium data was found to provide an approximate representation of multi-component packed-bed concentration profiles. Ching and Ruthven[23] report results

for the sorption and diffusion of some amino acids in ZX zeolite crystals of 50 μm size. The intercrystalline diffusivities were determined to be in the range of 10^{-7} to 10^{-9} cm^2s^{-1} showing a regular decrease with increasing molecular weight of amino acid. The research showed that it should be possible to obtain an efficient separation of smaller from larger amino acids based on size-selective exclusion.

Adsorption of pollutants onto activated carbon in fixed beds has been studied by McKay and Bino[24], who present a model based on external mass transport and internal pore diffusion for irreversible adsorption to predict breakthrough curves. Effective pore diffusion coefficients were determined for each sorbate carbon system by comparison of the predicted curves with experimental data by using a best-fit method. Reasonable agreement was achieved between predicted and measured breakthrough curves for phenol, *p*-chlorophenol and mercury, but the measured curves for sodium dodecyl sulphate (SDS) were broader than could be fitted. This was explained as due to the assumption of an irreversible isotherm not being applicable to SDS.

The influence of pore and particle size on the frontal uptake of proteins for silica-based anion-exchange packings is discussed by Kopaciewicz *et al.*[25]. Results from a mathematical model used to compute radial adsorption profiles across the adsorbent particles for frontal uptake showed that restricted intraparticle diffusion due to insufficient pore size leads to incomplete use of the internal surface area giving a reduced loading of the packing.

Moon and Tien[26] give details of the use of pseudo-species representation in the modelling of fixed-bed adsorption involving solutions containing unknown adsorbates of favourable adsorption behaviour. To demonstrate the validity of the method experimental data for the fixed-bed adsorption of humic substances from aqueous solutions by activated carbon were compared with model predictions with good agreement. A mathematical model of a fixed-bed ligand-exchange column is described by Bolden and Groves[27]. The model based on a Langmuir isotherm, liquid-phase film resistance and a single-resin phase effective diffusivity gave satisfactory prediction of experimental breakthrough curves for butylamine and diglycolamine on a Cu(II)-loaded carboxylic acid resin. Ching *et al.*[28] discuss the modelling of a counter-current adsorption process for separation of a fructose–glucose mixture at high concentrations where the equilibrium isotherms deviate from linear. It is shown that an equilibrium stage model with due correction for the concentration dependence of the apparent distribution coefficients, provide a good representation of the system behaviour.

A model to simulate the separation of a two-component mixture in preparative-scale non-linear liquid chromatography is presented by Guiochon and Ghodbane[29] with boundary conditions corresponding to the elution of large-concentration profiles, neglecting axial diffusion and assuming that the kinetics of radial mass transfer is infinitely fast. The model consists of two mass balance equations, one for each component, and the equations are solved numerically by a finite difference method. The predicted elution profiles compare reasonably well with experimental data from the literature. Wade *et al.*[30] present the impulse input solution to the equations describing non-linear chromatography and discuss applications to physicochemical measurements in affinity chromatography and the implications for optimisation of preparative-scale separations. The model is used to characterise the retention

behaviour of *p*-nitrophenyl-α-D-mannopyranoside on silica-bound Concanavilin-A affinity columns. The analysis gives information on adsorption–desorption rate constants and the binding site density for the more populous binding site in immobilized Concanavilin-A.

In a comprehensive study Knox and Pyper[31] present details of a framework for maximising throughput in preparative liquid chromatography. The work shows that concentration overload rather than volume overload provides the greatest throughput, and that the plate height concept can be used in optimisation computations. The use of computer simulation to optimise HPLC gradients for the separation of either small or large molecules is discussed in a series of papers by Ghrist *et al.*[32], and Ghrist and Snyder[33,34]. The method is to use a small number of experimental runs to measure sample characteristics which can be related to retention in gradient elution, and then to use computer simulation to predict retention as a function of any gradient conditions. The papers present information on minimising errors in computer simulations, the use of such simulations to determine the effects of different variables, and give recommendations for an efficient approach to the design of optimised gradients for complex samples by using computer simulations. In further papers Snyder *et al.*[35] and Cox *et al.*[36] report the use of the Craig model as a basis for computer simulations for mass-overloaded gradient elution for Langmuir and non-Langmuir isotherms related to the preparative separation of peptide and protein samples by HPLC. It seems possible to quantitatively predict bandwidth and resolution as a function of small-sample retention data, experimental conditions and sample size. The work leads to a proposed systematic approach for designing the preparative- or process-scale separation of protein mixtures by reversed-phase gradient elution. In a complementary development, Hodges *et al.*[37] give details of the use of a computer program to assist workers in devising methods of size-exclusion, cation-exchange, and reversed-phase HPLC for the analytical separation and purification of biologically active peptides and peptide fragments from enzymatic and chemical digests of proteins. It is stated that the program has the ability to examine the effects of flow-rate, gradient rate and sample size on the separation, and that use of the program to simulate experiments eliminates the time consuming trial-and-error methods used to determine suitable separation or purification methods.

The review illustrates the current wide range of applications of modelling to assist the design and optimisation of adsorption and chromatographic separation processes. It is seen that a general approach to modelling involves solution of mass balance and rate relationships for given boundary conditions and with knowledge of equilibrium and kinetic parameters. Models have different degrees of complexity depending on the simplifying assumptions made to achieve the required prediction with a reasonable degree of accuracy and computation time. It is desirable that a model should have as wide an application as possible and yet be of sufficient simplicity that the parameters needed to implement the model can be obtained with accuracy from small-scale experiments or from the literature. Details are now presented of complementary work in our laboratories to meet a general requirement for computer programs to predict the performance of batch stirred-tank and packed-bed column adsorption and chromatography units, whilst also determining equilibrium and kinetic parameters (for input to the simulation programs) by using fitting techniques to experimental data.

MATHEMATICAL MODELLING OF BATCH STIRRED-TANK AND PACKED-BED COLUMN ADSORPTION AND CHROMATOGRAPHIC UNITS

The models are formulated for single- and multi-component adsorption, and for packed-bed column operation deal with both frontal analysis and elution chromatography. In frontal analysis the sample is fed continuously to the column until breakthrough occurs. Loading is stopped at an appropriate time after breakthrough, and is generally followed by a washing stage to remove excess sample from the intersticies of the packed bed. Elution is then commenced to desorb and separate or recover desired components. In elution chromatography a small amount of sample is fed to the column, then the eluent, which has no affinity for the adsorbent and may be the same as the sample solvent, is introduced and separation of the components is achieved in the form of bands. In this paper isocratic elution in which the same eluent is used throughout is dealt with.

Two types of predictive method are described. The first is based on simple kinetic type rate expressions for mass transfer, the second is a more complex model taking into account liquid film and pore diffusion resistances to mass transfer, which may be suitable for cases where the simple kinetic type model is inadequate.

Batch stirred-tank, simple kinetic model

The adsorption process is formulated in terms of a reaction law which leads to a Langmuir type isotherm at equilibrium. The model is one used earlier by Chase[38], and is similar to models described by Thomas[39,40] as applied to ion exchange and chromatography.

The Langmuir isotherm is given by

$$q^* = \frac{Q_m\, c^*}{c^* + K_d} \tag{1}$$

where c^* and q^* are the values of c and q at equilibrium, Q_m is the maximum adsorption capacity of the adsorbent, and K_d is the dissociation constant. Thus Q_m can be evaluated from isotherm measurements as the value q^* tends to asymptotically as c^* tends to a high value, and K_d is the value of c^* when $q^* = Q_m/2$. The dissociation constant K_d is equal to the ratio of backward and forward rate constants K_2/K_1 for the process.

The forward rate constant K_1 can be evaluated from small-scale experiments to determine the rate of uptake of adsorbate, which then allows K_2 to be computed as K_dK_1.

For mono-component adsorption, or for multi-component adsorption without competition between species for adsorption sites, the mass balance and rate equations can be solved to give analytical solutions. For multi-component adsorption with competition between species for adsorption sites the rate equations are modified to comply with a model given by Chase[41], and it is then necessary to solve the equations numerically. This is facilitated by writing the computer programs in conjunction with the Harwell code FACSIMILE (Curtis and Sweetenham[42]) which is a program for solving initially valued ordinary differential equations.

Packed-bed column, simple kinetic model

For column simulation two processes within the column have been considered, adsorption and flow of adsorbate down the column. At each point along the column, the system is described by two values, the total concentration of adsorbate in the mobile phase, c, and the local concentration of adsorbate in the stationary phase, q. It is assumed that the system is well mixed across the column so c and q only vary with distance along the column. Transport along the column is governed by the fluid, the solute is assumed to flow with the fluid and to diffuse through it, whereas the adsorbed adsorbate is unaffected by the fluid. The height of the packed bed in the column is taken to be L, and the adsorbate in solution flows down the column with speed V, where V is the interstitial velocity expressed as

$$V = \frac{F}{a\varepsilon_e} \tag{2}$$

where F is the fluid volume entering the column in unit time, a the cross-sectional area of the column, and ε_e the interstitial porosity of the packed bed.

Under these conditions the equations governing the process are

$$\frac{\partial c}{\partial t} = D_a \frac{\partial^2 c}{\partial z^2} - \frac{V \partial c}{\partial z} - K_1 c\,(Q_m - q) + K_2 q \tag{3}$$

$$\frac{\partial q}{\partial t} = K_1 c\,(Q_m - q) - K_2 q \tag{4}$$

where D_a is the axial dispersion coefficient, t the time, z the distance along the column, Q_m the maximum capacity of the adsorbent, and q the concentration of the adsorbed material in consistent units.

For mono-component adsorption for the case where the axial dispersion is negligible eqns. 3 and 4 become

$$\frac{\partial c}{\partial t} = -V \frac{\partial c}{\partial z} - K_1 c\,(Q_m - q) + K_2 q \tag{5}$$

$$\frac{\partial q}{\partial t} = K_1 c\,(Q_m - q) - K_2 q \tag{6}$$

Eqns. 5 and 6 can be solved analytically (Thomas[39], Chase[38] and Cowan *et al.*[1]) the form of the analytical solution depending on the boundary conditions, given by the amount of adsorbate flowing into the column and the amount of adsorbate bound to the bed when the adsorption process starts. In further work analytical solutions have been given to eqns. 5 and 6 for loading, washing and elution conditions (Sweetenham[43]).

When axial dispersion is of importance for given boundary conditions with a single solute eqns. 3 and 4 are solved numerically by use of the FACSIMILE code. Numerical solutions to the equations can be found by assuming the column to be an

array of well mixed cells and then solving ordinary differential equations for the value of c and q in each cell, so that the equations can be solved for a wide range of mathematical models. For multi-component adsorption with competition between species the appropriate forms of eqns. 3 and 4 with axial diffusion, or eqns. 5 and 6 without axial dispersion are solved numerically by use of the FACSIMILE code.

The liquid film plus pore diffusion model

To give an alternative method of calculation when the simple kinetic model proves inadequate (Cowan[44]), particularly where the mass transfer is dependent on diffusion within the porous structure of the adsorbent, equations are presented applicable to a model (Horstmann and Chase[45,46]) taking into account the liquid film and pore diffusion resistances to mass transfer.

From the Horstmann and Chase[45,46] model the material balance in the particle is taken as

$$\varepsilon_i \frac{\partial c_i}{\partial t} = \varepsilon_i D_e \left(\frac{\partial^2 c_i}{\partial r^2} + \frac{2}{r} \frac{\partial c_i}{\partial r} \right) - (1 - \varepsilon_i) \frac{\partial \hat{q}_i}{\partial t} \tag{7}$$

where c_i is the solute concentration in the pore fluid, D_e the effective pore diffusivity of the adsorbate in the particle phase, ε_i the intraparticle porosity, and $\hat{q}_i$ the local solid phase concentration of adsorbed material in mass of adsorbate per unit adsorbent solid volume.

Eqn. 7 is subject to boundary conditions at the centre and radius of the particle as follows

$$\frac{\partial c_i}{\partial r} = 0 \text{ at } r = 0 \tag{8}$$

and, at the surface of the particle, the flux of solute is constant so

$$\frac{\partial c_i}{\partial r} = \frac{k_f}{D_e \varepsilon_i} (c_b - c_i) \text{ at } r = R \tag{9}$$

where c_b is the concentration of the solute in the bulk fluid, k_f the liquid film mass transfer coefficient, and R the radius of the particle.

For adsorption in a stirred tank, Horstmann and Chase[45,46] give the relation at the surface of the particle as

$$\frac{dc_b}{dt} = -3 \frac{V_s k_f}{R V_L} (c_b - c_i)_{r=R} \tag{10}$$

where V_s is the total volume of the adsorbent particles assumed to be spheres, and V_L the volume of external fluid.

Eqns. 7–10 are solved numerically by again implementing the FACSIMILE code.

Measurement of physical parameters

To use the models knowledge of the mono-component equilibrium adsorption isotherms and process kinetics is required. From the adsorption isotherms values of the maximum capacity and dissociation constant can be derived, and from the kinetics curves values of the forward rate constant (for the simple kinetic model), or the liquid film mass transfer coefficient and effective pore diffusion coefficient can be computed (for the liquid film plus pore diffusion model).

A common method (Chase[38], Fowell and Chase[47], and Cowan *et al.*[1,2,44]) of generating adsorption isotherms from small-scale experiments is to shake known amounts of adsorbent with various concentrations of adosrbate solution of known volume, until equilibrium is attained, allowing equilibrium parameters to be determined.

An alternative method for measurement of adsorption isotherms is to use a small packed-bed recirculation system (Horstmann *et al.*[48]) in which aliquots of adsorbate are successively added to a reservoir whose contents are recirculated by being pumped through a fixed bed of adsorbent. The level of adsorbate is continuously monitored at the column outlet by flow spectrophotometry and when the system is in equilibrium as evidenced by the lack of change of the level of adsorbate in the liquid phase, a further aliquot of adsorbate is added. An advantage of the technique is that the adsorbent is kept within the packed bed at all times, removing the possibility of adsorbent disintegration which may occur as the result of the mixing process in stirred-cell systems.

To provide data for the prediction of the elution stage it is desirable to check the isotherms for adsorption in the presence of eluent (Cowan *et al.*[2]), in parallel with the equilibrium measurements without eluent.

To measure kinetic parameters several workers (Chase[38], Horstmann *et al.*[48], and Cowan *et al.*[1,2]) have used a small stirred-cell apparatus to contact adsorbent and adsorbate solution of known concentration and monitored concentration changes of adsorbate by UV spectrophotometry to determine the rate of uptake of adsorbate by the adsorbent. In circumstances where it is not possible to use UV spectrophotometry the same investigators have used discrete sampling techniques with off-line assay to determine solution concentration changes with time. Many adsorption processes are performed in columns and, although small stirred-cell experiments provide useful information, small-scale column experiments may be required to provide appropriate kinetic data particularly if the liquid film mass transfer resistance is of importance (Cowan *et al.*[1], Cowan[44]). By measuring the breakthrough curve for a system it is possible to derive isotherm and kinetic parameters for the adsorption stage, and from the elution curve it is possible to derive data related to the elution kinetics.

Particle and pore size can have a significant effect on adsorption parameters (Horstmann *et al.*[48], Kopaciewicz *et al.*[25]) so it is desirable that experiments be performed on the same size particles as would be used in the actual process. In addition, it is required to simulate the appropriate process physical conditions particularly pH, ionic strength, temperature, and concentrations of other components if these compete or modify the adsorption process.

Codes for physical parameter derivation and simulation of adsorption and chromatographic processes

The modelling work described in this paper has led to the development within the BIOSEP project at Harwell of a suite of computer programs for application to the prediction of adsorption and chromatographic processes. The codes are of two types, those for the prediction of the performance of batch stirred-tank and packed-bed column units, and those for fitting parameters to batch stirred-cell or packed-bed column experimental results to derive requisite physical parameter data. The codes are written for use on appropriate IBM PC AT or compatible microcomputers, or for use on mainframe machines. Brief details of the codes are given in this section.

Derivation of physical parameters from isotherm measurements

The code used for analysis of isotherm data to determine whether a Langmuir isotherm can be fitted is called LANGFIT. The program takes the data and, if a Langmuir isotherm is applicable, fits the parameters K_d, the dissociation constant, and Q_m, the maximum capacity of the adsorbent, to the data. In doing this the code takes into account errors estimated or measured from the experimental protocol. The program gives the 5.0 and 95.0% confidence limits within which the actual values of Q_m and K_d are expected to lie.

Programs for fitting parameters to batch stirred-tank adsorption data

Three computer programs have been written to derive physical parameters by fitting to batch stirred-tank mono-component data. These codes are given the names KIFIT, TANFITK and TANFITP. The KIFIT and TANFIT codes are based on the simple kinetic model. KIFIT allows values of the forward rate constant K_1 to be determined, whereas TANFITK enables values of Q_m, K_d and K_1 to be fitted depending on available data. The TANFITP code is based on the liquid film plus pore diffusion model, and may be used to fit values of the liquid film mass transfer coefficient, k_f, and the effective pore diffusivity, D_e.

Simulation of batch stirred-tank adsorption units

The codes which have been developed for predicting the performance of batch stirred-tank adsorption units are designated as TANSIMK, TANSIMA and TANSIMP. The TANSIMK and TANSIMA programs both incorporate the simple kinetic model. For the prediction of multi-component adsorption TANSIMK assumes that there is no competition between components for sites on the adsorbent, whereas TANSIMA takes into account competition between components for sites on the adsorbent. TANSIMP is based on the liquid film plus pore diffusion model and currently is used for mono-component adsorption in stirred tank adsorbers when pore diffusion is of significance.

Program for fitting parameters to packed-bed column adsorption data

The COLOFITK program utilising the simple kinetic model is used to fit Q_m, K_1 and the backward rate constant K_2 to packed-bed column mono-component adsorption data, and may be applied to experimental results from loading, washing and elution stages.

Simulation of packed-bed column adsorption and chromatographic units

The programs which have been written to predict the performance of packed-bed adsorption columns are COLOSIMK, COLOSIMA and COLOSIMP. The COLOSIMK and COLOSIMA codes include the simple kinetic model and predict the loading, washing and elution stages of packed-bed operation. The COLOSIMK code may be used to predict multi-component adsorption when there is no competition between components for sites on the adsorbent, whereas COLOSIMA predicts multi-component adsorption with competition between adsorbate components for sites on the adsorbent. In addition, COLOSIMA may be used to compute the effect of axial dispersion. The COLOSIMP code which incorporates the liquid film plus pore diffusion model is used to predict the loading, washing and elution stages of packed-bed operation for mono-component adsorption when pore diffusion is of significance.

PARAMETER FITTING

The BIOSEP parameter fitting codes, such as TANFITK and COLOFITK, are written to allow the user to specify the values of some of the parameters governing adsorption and for the code to fit the remaining parameters to the supplied data. The data supplied by the user can come from one or more different experiments which involve the same set of adsorbate species with different initial concentrations for the species in the different experiments.

This provides the user with a lot of flexibility, but means that the user can easily provide insufficient data to fix all the parameter values. For example, suppose that a user uses TANFITK to fit Q_m, K_d and K_1 to data from several kinetics experiments where the data values were only measured at large times when the system had reached equilibrium. In that case, the fitting code may be able to determine values for Q_m, and K_d, which depend only on the isotherm. However, the code would not be able to determine a value for K_1 and the code's output would give values for Q_m and K_d and would state that the value of K_1 could not be determined by the data.

In all the fitting codes, the program first finds the best fit that it can. It then determines whether the fit to the experimental data is within the error estimates provided by the user. Finally, the code determines whether the parameter values are uniquely determined, and if not the code finds how the parameters can be altered without making the fit significantly worse.

EXAMPLES OF CODE VALIDATION WORK

Work to validate and apply the codes is ongoing and typical examples are given here of results from such work for both batch stirred-tank and packed-bed adsorption and chromatographic units. The experimental work associated with this research has involved studies of the adsorption of mono- and multi-component amino acids by the anion exchanger Duolite A-162, and several of the examples are taken from these studies. Duolite A-162 is a macroporous cross-linked polystyrene matrix with $-N^+(CH_3)_2C_2H_4OH$ functional groups to provide ion-exchange capacity, available as rigid beads resistant to attrition and osmotic shocks.

Batch stirred-tank examples

The LANGFIT code has been used extensively to analyse results from small-scale stirred-cell contactor experiments to derive physical parameters from Langmuir isotherms taking into account error estimates in experimental quantities. Fig. 1 illustrates the graphical output from the program showing the fit obtained by using LANGFIT to isotherm results for the adsorption of glutamic acid by Duolite A-162. The values of the maximum adsorbent capacity and dissociation constant were well determined, LANGFIT fitting values of Q_m equal to 295 mg/g (with 5 and 95% confidence limits of 270–321 mg/g) and K_d as 0.015 mg/ml (with confidence limits of 0.0093–0.024 mg/ml), respectively. Computation time for the example using an IBM PC AT microcomputer was 2.7 min.

Results have also been obtained from small-scale batch stirred-cell experiments for the mono-component adsorption of amino acids to Duolite A-162 to determine the rate of loss of the amino acids from solution for various conditions. The TANFITK code has been applied to the analysis of such results to derive in particular values of the forward rate constant K_1. A typical fit obtained by using the TANFITK code to analyse data for the adsorption of glutamine by Duolite A-162 is shown in Fig. 2. From the analysis a value of K_1 was derived as 0.099 ml min/mg with 5 and 95% confidence limits of 0.09–0.109 ml min/mg. Analysis of isotherm data for the adsorption of glutamine by Duolite A-162 yielded a value of the dissociation constant K_d as 0.018 mg/ml. Hence the value of the backward rate constant K_2 for the adsorption of glutamine by Duolite A-162 for the conditions studied can be derived as $K_2 = K_d K_1$

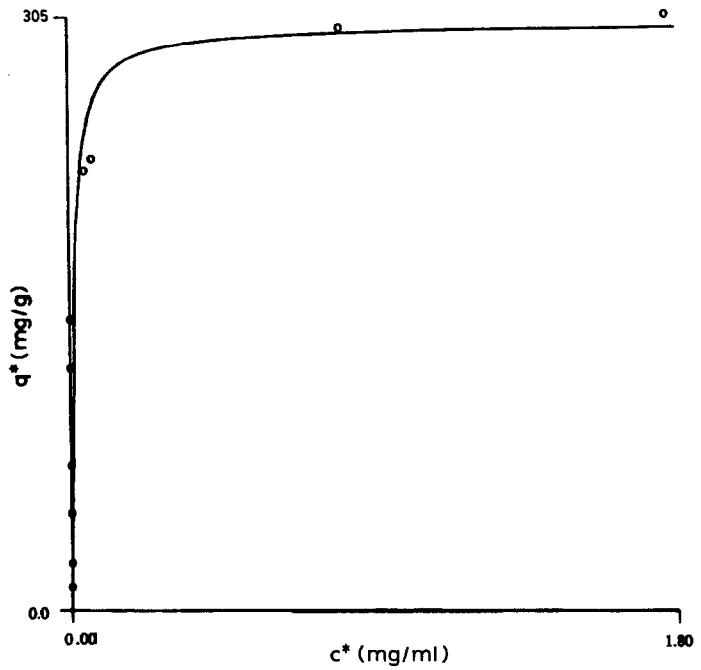

Fig. 1. LANGFIT analysis of isotherm results for the adsorption of glutamic acid by Duolite A-162. ○ = Observed q^*; ——— = calculated q^*.

giving $K_2 = 0.0018\ \text{min}^{-1}$. The computation time for this example was 3.2 min using the IBM PC AT microcomputer.

In further research, a pilot-scale batch stirred-tank rig has been used to study mono- and multi-component adsorption, washing and elution of amino acids by Duolite A-162. The main features and dimensions of the batch stirred tank and the apparatus to monitor adsorbate concentration changes during experiments are shown in Figs. 3 and 4. A 10-l volume of the appropriate amino acid solution was used with 50 g dry mass of Duolite A-162, which had been previously regenerated by using 1 *M* sodium hydroxide solution. To achieve a reasonably uniform suspension of the adsorbent and adequate mixing, the stirred tank was fitted with four stainless-steel baffles and a stirrer operating at a speed of 198 r.p.m. The baffles were sealed to the tank walls to prevent attrition of the Duolite A-162 in any gaps which could otherwise have formed between the baffle and vessel wall. In addition to the on-line monitoring of the experiments using the apparatus shown in Fig. 4, a fraction collector was used to take small samples at predetermined times, and solution concentration changes through the experiments were ascertained from analysis of the samples using HPLC.

The type of analysis which can be applied to results from the pilot-scale batch stirred-tank multi-component amino acid adsorption experiments is illustrated with reference to data for the adsorption of the three-component mixture asparagine, glutamine and serine, each with an initial concentration of 0.6 g/l, by Duolite A-162. The pH of the amino acid solution was not measured in the experiment but was estimated to be between pH 5 and 6. A complimentary code to TANSIMA known as TANFITA was used in the analysis. TANFITA has the ability to fit to multi-component data to derive physical parameters when either there is no competition

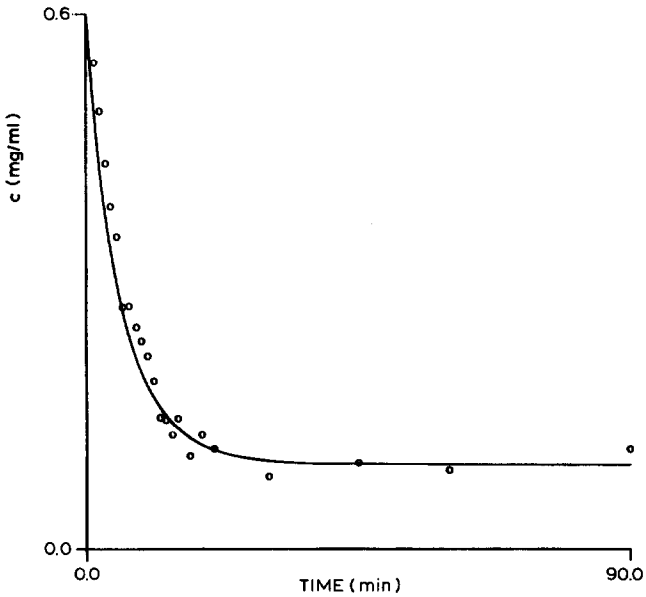

Fig. 2. TANFITK analysis of kinetic results for the adsorption of glutamine by Duolite A-162. ○ = Observed c; ——— = calculated c.

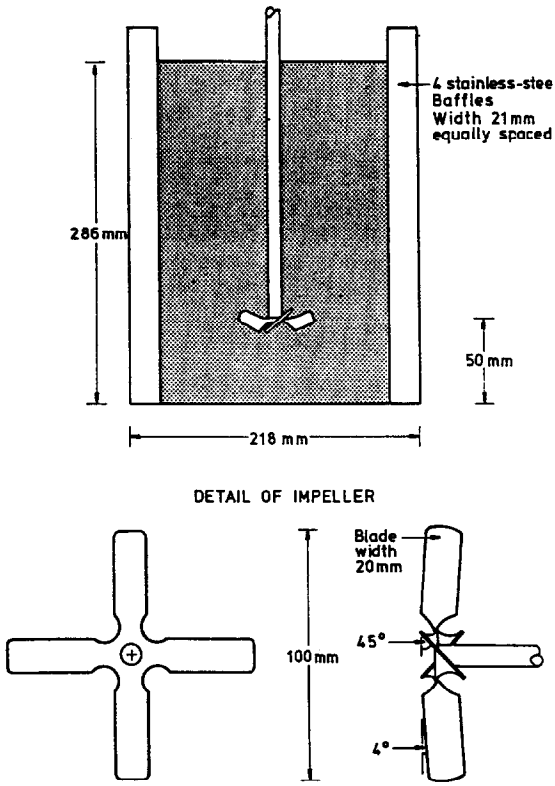

Fig. 3. Detail of pilot-scale stirred-tank adsorption unit.

between components for adsorption sites on the adsorbent, or when there is competition between components for adsorption sites on the adsorbent.

Initially, the TANFITA code was used to try to derive values of the maximum capacity Q_m, and the forward and backward rate constants K_1 and K_2 from

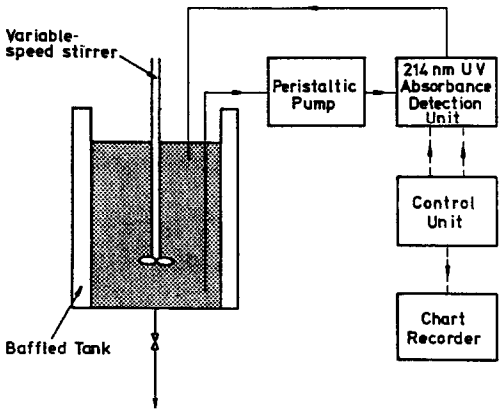

Fig. 4. Pilot-scale batch adsorption rig instrumentation.

mono-component equilibrium and kinetic results for serine, asparagine and glutamine and from the multi-component pilot-scale experiment for the simultaneous adsorption of serine, asparagine and glutamine assuming no competition between the components for adsorption sites. No fits could be obtained for the physical parameters. The exercise was repeated but with the assumption that in the multi-component experiment there was competition between components for adsorption sites. In this case well determined values of the physical parameters were derived. These values of Q_m, K_1 and K_2 were then used with the TANSIMA code to simulate the three-component adsorption of serine, asparagine and glutamine by Duolite A-162. Fig. 5 presents a compari-

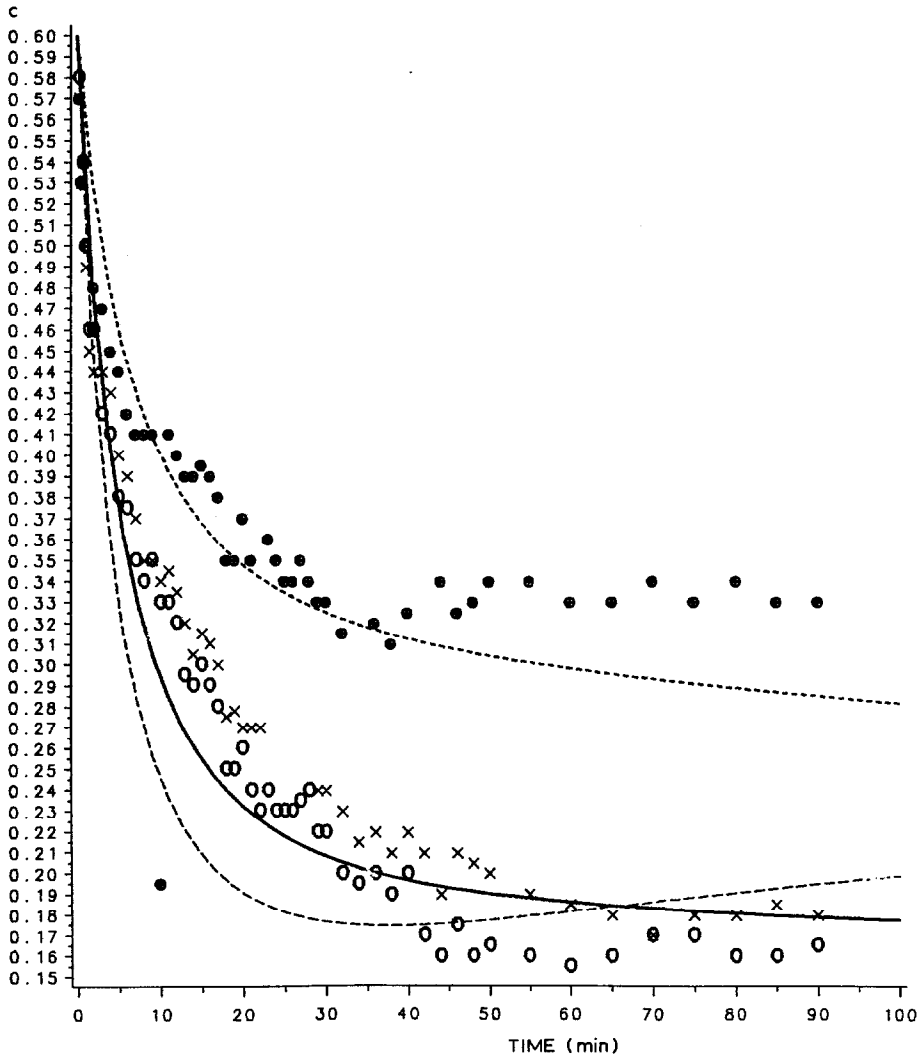

Fig. 5. TANSIMA simulation of the adsorption of serine, asparagine and glutamine by Duolite A-162. Asparagine: O = experimental, ——— = predicted; glutamine: ⊕ = experimental; ---- = predicted; serine: × = experimental; --- = predicted. c in mg/ml.

son between the experimental data and the predicted adsorption characteristics. It is seen from Fig. 5 that the change in concentration of asparagine is well predicted through the experiment. The rate of fall in the concentrations of serine and glutamine are also well predicted over the initial stage of the adsorption process. Subsequently, the model overpredicts the uptake of glutamine and underpredicts the uptake of serine, indicating that in this case the model may require a further degree of refinement.

Packed-bed column examples

The programme of experimental work for code validation is being extended to studies of multi-component amino acid adsorption by Duolite A-162 in packed-bed columns. An example of the use of the modelling codes to support this work has been the use of the COLOSIMA code to predict the adsorption of the binary component mixture tryptophan and aspartic acid by Duolite A-162 in a small-scale packed-bed column. In this exercise the values of the maximum capacity of the adsorbent Q_m, and the dissociation constant K_d were obtained from mono-component isotherm experiments, and the forward and backward rate constants K_1 and K_2 for each component were derived from binary component small-scale batch stirred-cell adsorption experiments. Using this data Fig. 6 shows a prediction from the COLOSIMA code for

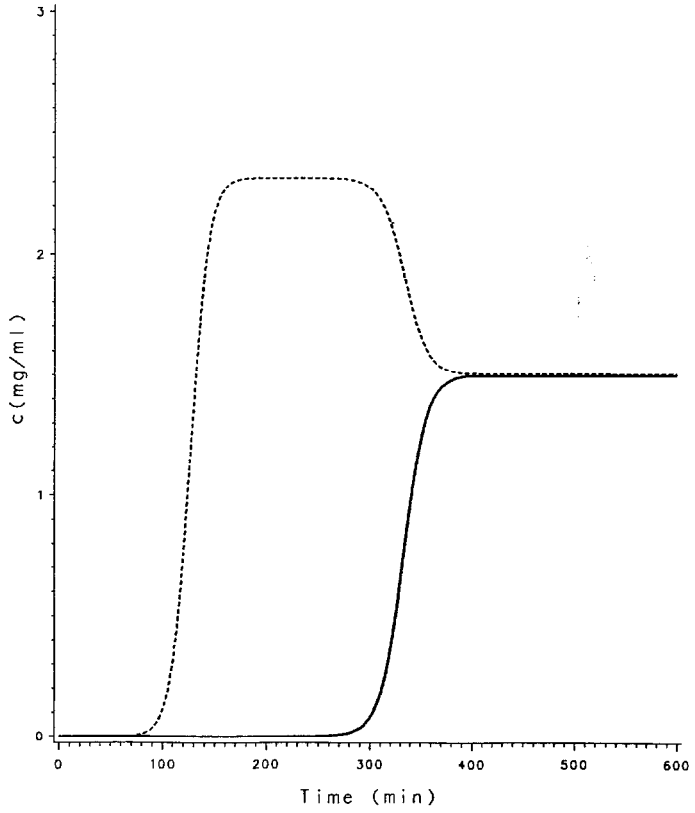

Fig. 6. COLOSIMA simulation of the adsorption of tryptophan (- - - -) and aspartic acid (———) by Duolite A-162.

the adsorption of tryptophan and aspartic acid by Duolite A-162 in a small-scale column operating in frontal analysis mode. It was assumed that both the tryptophan and aspartic acid were fed to the column in solution each at a concentration of 1.5 mg/ml. The predicted breakthrough curves shown in Fig. 6 are typical of competitive adsorption. Fig. 6 indicates that tryptophan will be displaced from the adsorbent by the aspartic acid such that after about 120 min the concentration of tryptophan at outlet becomes greater than at inlet to the column. The tryptophan concentration at column outlet is predicted to reach a maximum and ultimately becomes equal to the inlet concentration when the amount of tryptophan on the column has fallen from its maximum level to its equilibrium level. At this stage the breakthrough curve for aspartic acid is completed and the concentration of aspartic acid at the column outlet becomes equal to the inlet concentration to the column.

To obtain experimental results to compare with predictions from the COLO-SIMP code both small- and pilot-scale packed-bed column experiments have been completed for the loading, washing and elution of aspartic acid onto and from Duolite A-162. The small-scale packed-bed column apparatus is shown diagrammatically in Fig. 7. Aspartic acid solution was pumped downwards through the column which is 1.6 cm in diameter with a packed-bed height of 12.7 cm. The outlet concentration of aspartic acid from the column was monitored on-line by using a UV flow cell, but small samples were also taken from the outlet stream for off-line analysis. This is necessary since care is required with on-line UV measurements at 214 nm to check that correct concentrations are being measured and that there is no interfering absorption from

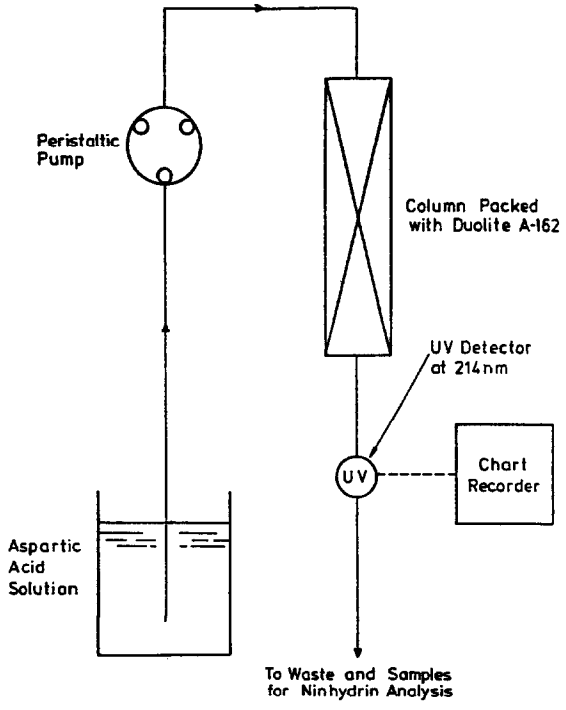

Fig. 7. Diagram of small-scale packed-bed column apparatus.

hydroxyl ions at low aspartic acid concentrations. The flowsheet for the pilot-scale packed-bed column rig is given in Fig. 8. The pilot-scale column was constructed of perspex with a column diameter of 8.8 cm and a packed-bed height of 11.5 cm. The column was normally operated in the downflow mode. As can be seen from Fig. 8 liquid was pumped in sequence from each of the holding tanks to the column to allow regeneration, loading, washing and elution to proceed in turn. The column outlet has a liquid sampling port which is used as a take-off point for liquid to be analysed by an on-line UV absorption detector or to allow samples to be taken for off-line analysis, for example, by HPLC.

Examples are presented in Figs. 9 and 10 of predictions from the COLOSIMP code with experimental data from the small- and pilot-scale columns respectively for both columns operating under similar conditions. In using the COLOSIMP code an estimate of the liquid film mass transfer coefficient was obtained from a correlation given by Wilson and Geankoplis[49] as

$$Sh = \frac{1.09}{\varepsilon_e} Re^{1/3} Sc^{1/3} \text{ for } 0.0015 < Re < 55 \tag{11}$$

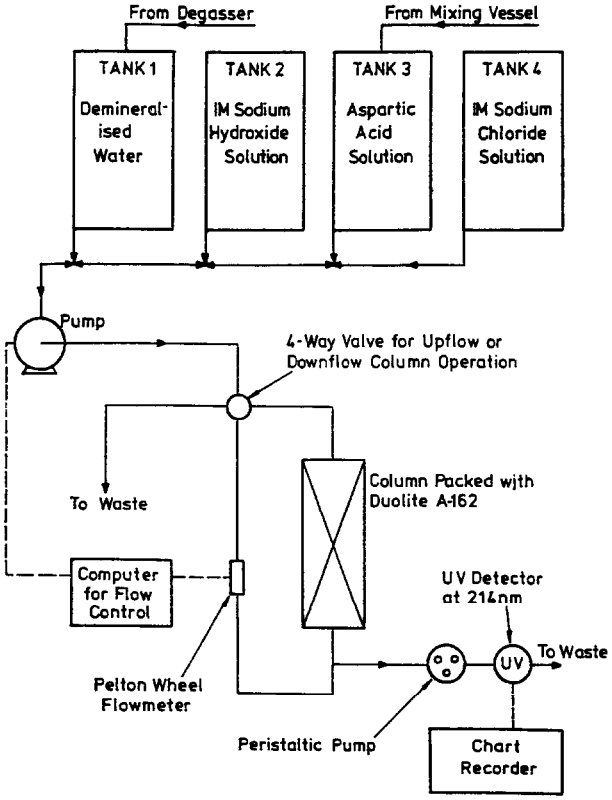

Fig. 8. Diagram of the BIOSEP mass transfer rig.

where Sh is the Sherwood number ($k_f d_p/D_L$), Re the Reynolds number based on the mean particle diameter in the packed bed, Sc the Schmidt number, ε_e the interstitial porosity, d_p the mean particle diameter, and D_L the diffusivity of solute in bulk solution.

An estimate of the diffusivity for aspartic acid in bulk liquid was obtained from an empirical correlation given as

$$D_L = \frac{7.7 \cdot 10^{-16} T}{\mu (V^{1/3} - V_0^{1/3})} \tag{12}$$

where V, the molar volume of aspartic acid, was determined from Kopp's law of additive volumes (Coulson and Richardson[50]), $V_0 = 0.008$ for diffusion in dilute water solutions, T is the absolute temperature of the liquid and μ is the liquid viscosity. The values of the maximum capacity of the adsorbent Q_m and the dissociation constant K_d for use with COLOSIMP for the loading and washing stages were obtained from LANGFIT analysis of equilibrium data for the adsorption of aspartic acid by Duolite A-162, taking into account the 5 and 95% confidence limits. For the elution stage K_d was set to the relatively high finite value of 30 mg/ml as $K_1 \to 0$ for 1 M sodium chloride as eluent.

The mass of resin per unit volume of packed bed was higher in the pilot-scale column than in the small-scale column probably caused by different wall and particle packing effects. The difference was compensated for in the computer analysis by specifying different interstitial porosity values. The value of the interstitial porosity was taken as 0.36 for the small-column experiment and 0.3 for the pilot-scale column experiment.

Consideration of Figs. 9 and 10 indicates (for the cases given) reasonable agreement between the small- and pilot-scale experimental data. Simulations were achieved by using COLOSIMP taking a value of k_f computed from eqn. 11 and varying the effective pore diffusivity, D_e, until a good fit was obtained to the experimental results. It is seen from Figs. 9 and 10, that by using COLOSIMP with values of $k_f = 0.116$ cm/min, and $D_e = 5 \cdot 10^{-4}$ cm^2/min for both the small- and pilot-scale columns acceptable prediction of the breakthrough and washing curves are obtained for both columns. Prediction of the elution stage with K_d taken equal to 30 mg/ml is more approximate. The computation time for examples of the type given in Figs. 9 and 10 was 2.5 h on a COMPAQ 386 microcomputer, for calculations with 20 computational cells along the column and 10 particle segments.

The fixed-bed codes may also be used to simulate the separation of components for isocratic elution chromatography conditions, and to determine the effect of changing different operational parameters. An example to illustrate the use of the COLOSIMK code to simulate the separation of a two-component mixture is shown in Fig. 11. A further example is given in Fig. 12 of the use of the COLOSIMA code to determine the effect of packed-bed length on the resolution of two components in elution chromatography. From Fig. 12 it is seen that as the bed length is increased it is predicted that the resolution of the two components will be increased. However, although resolution is improved, the peaks are broader (and hence the eluted material is more dilute) in the simulations with longer beds.

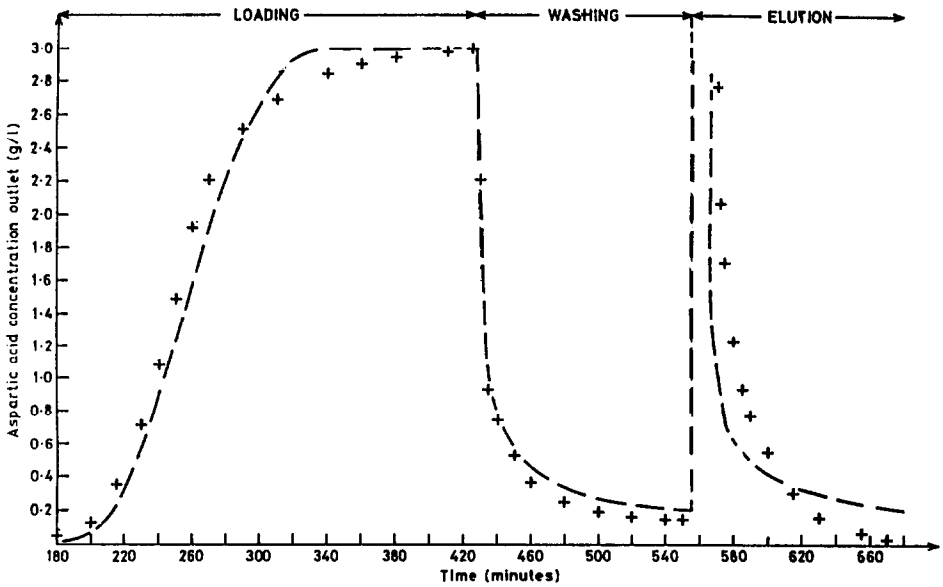

Fig. 9. COLOSIMP simulation of the loading, washing and elution in a small-scale packed-bed column for the aspartic acid–Duolite A-162 system. Column type, small-scale Pharmacia, packed-bed height 12.5 cm, column diameter 1.6 cm; superficial velocity, 1.79 cm/min; bead size range, 710–850 μm. COLOSIMP parameters: Q_m = 270 mg/g, k_f = 0.116 cm/min, D_e = $5 \cdot 10^{-4}$ cm^2/min. K_d = 0.01 mg/ml, interstitial porosity = 0.36, intraparticle porosity = 0.45.

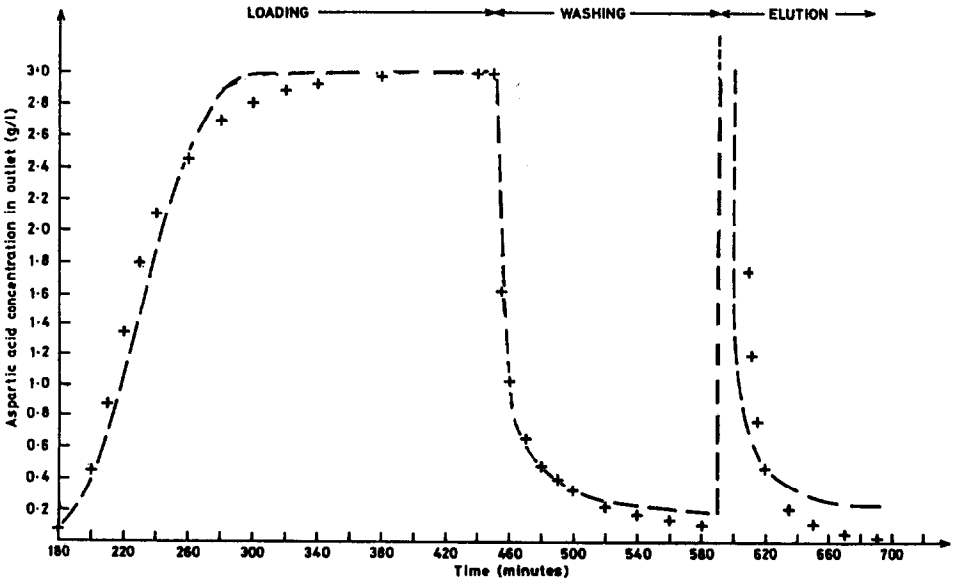

Fig. 10. COLOSIMP simulation of the loading, washing and elution in a pilot-scale packed-bed column for the aspartic acid–Duolite A-162 system. Column type, pilot-scale Perspex, packed-bed height 11.5 cm, column diameter 8.8 cm; superficial velocity, 1.79 cm/min; bead size range, 710–850 μm. COLOSIMP parameters: Q_m = 245 mg/g, k_f = 0.116 cm/min, D_e = $5 \cdot 10^{-4}$ cm^2/min, K_d = 0.01 mg/ml, interstitial porosity = 0.30, intraparticle porosity = 0.45.

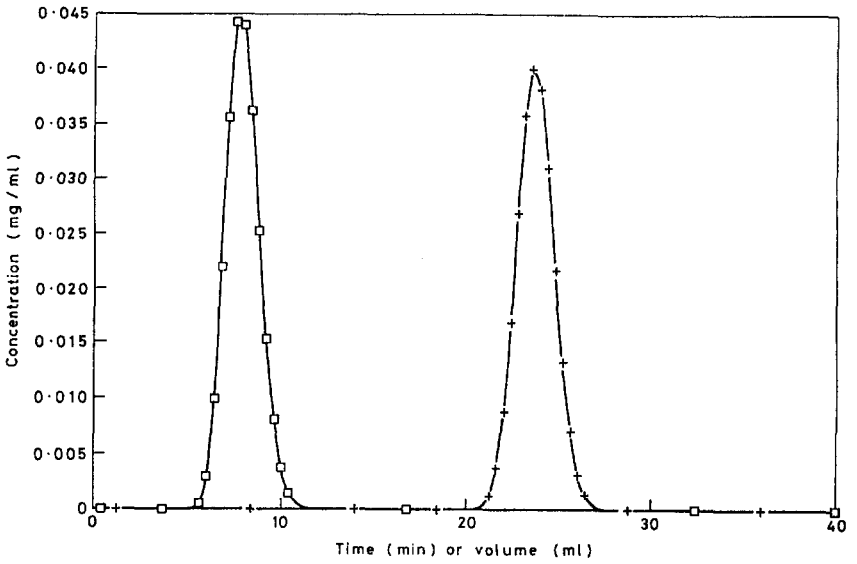

Fig. 11. Separation of components 1 (□) and 2 (+) by elution chromatography.

APPLICATION OF THE CODES

The simulation codes can be used to assist design. In design the requirements of the separation process are specified and it is desired to determine the adsorption equipment options which will meet the process specification. Ideally a design code

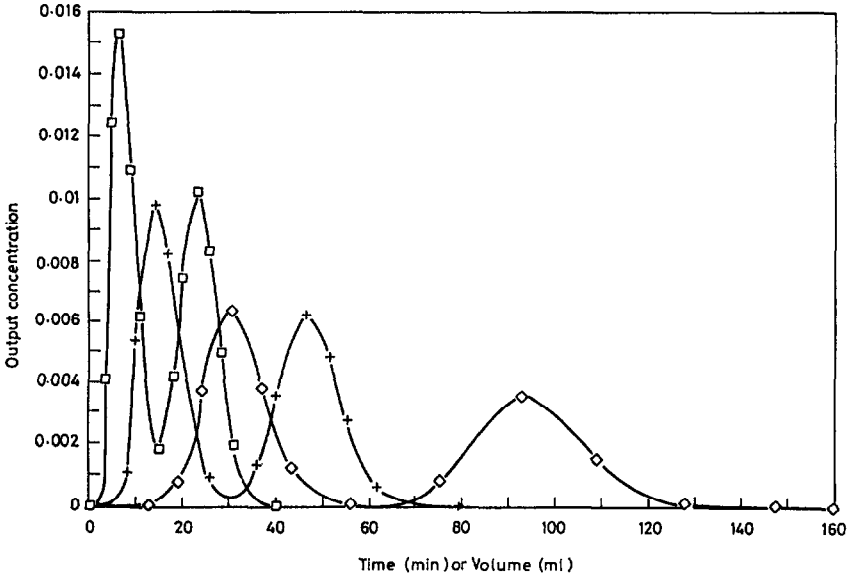

Fig. 12. Effect of column bed length on resolution of two components, column bed length 5 (□), 10 (+) or 20 (◇) cm.

would allow the major options to be computed, and with the incorporation of simple cost formulae would allow the alternative designs to be evaluated on a relative cost basis. Thus, design is concerned with evaluating the geometry of the contacting equipment for given operating conditions. To assist with design, the initial conditions for a separation would be specified to the appropriate simulation codes together with possible stirred-tank or packed-bed geometries for the process, and the codes would be used to predict the performance of the equipment to allow the evaluation of possible designs.

The simulation codes may also be used to assist with process optimisation. In process optimisation it is assumed that the scale and geometry of the batch stirred-tank or packed-bed column adsorption equipment is fixed, and it is necessary to consider the effect of changing operating variables on performance. Such variables may include the initial feed concentration or composition in a batch stirred tank or volumetric flow-rate in a packed-bed column, the physical characteristics of the solution and the operating protocol. Optimisation is necessary to ensure that the plant is running at its most effective, which usually means highest productivity or yield at acceptable purity. Increasing productivity means increasing the amount of material which is processed per unit time, which can be achieved by reducing the overall process time or by increasing the amount of material for a set process time. For optimisation purposes the conditions for the separation would be specified to the simulation code together with the adsorption plant geometry, for example, packed-bed height, column diameter. The simulation code would then be used to predict systematically the performance of the plant for different operating conditions, to allow the optimum conditions to be evaluated.

CONCLUSION

A suite of computer programs has been developed for application to adsorption and chromatographic processes. The programs are of two types, those for simulation of adsorption, washing and elution in batch stirred-tanks and packed-bed columns and to simulate elution chromatography in packed-bed columns, and those which may be used for the derivation of physical parameters relevant to equilibrium or kinetics in terms of adsorbent maximum capacity, dissociation constant, forward and backward rate constants, liquid film mass transfer coefficients and effective pore diffusion coefficients. The programs provide aids to the design and optimisation of adsorption processes.

ACKNOWLEDGEMENTS

The contributions of Dr. H. A. Chase and Miss B. J. Horstmann of the Department of Chemical Engineering, University of Cambridge, Mrs. A. Malleson of Tessella and Mr. A. Rodway, Mr. A. Reading and Miss H. M. Kellett of the Harwell Laboratory, to the work outlined in this paper, are acknowledged. Acknowledgement is also made to BIOSEP, Harwell Laboratory, Harwell, Oxfordshire OX11 0RA, U.K., for permission to publish the work presented in this paper.

REFERENCES

1 G. H. Cowan, I. S. Gosling, J. F. Laws and W. P. Sweetenham, *J. Chromatogr.*, 363 (1986) 37.
2 G. H. Cowan, I. S. Gosling and W. P. Sweetenham, in M. S. Verrall and M. J. Hudson (Editors), *Separations for Biotechnology*, Ellis Horwood, Chichester, 1987, p. 152.
3 J. Jacobsen, J. Frenz and Cs. Horváth, *J. Chromatogr.*, 316 (1984) 53.
4 N. F. Kirby, N. K. H. Slater, K. H. Weisenberger, F. Addo-Yobo and D. Doula, *Chem. Eng. Sci.*, 41 (1986) 2005.
5 W. J. Weber and C. K. Wang, *Environ. Sci. Technol.*, 21 (1987) 1096.
6 P. E. Price, Jr. and R. P. Danner, *AIChE J.*, 33 (1987) 551.
7 C. Vidal-Madjar, A. Jaulmes, M. Racine and B. Sébille, *J. Chromatogr.*, 458 (1988) 13.
8 B. H. Arve and A. I. Liapis, *AIChE J.*, 33 (1987) 179.
9 S. C. Nigam and H. Y. Wang, in J. A. Asenjo and J. Hong (Editors), *Separation, Recovery and Purification in Biotechnology*, American Chemical Society, Washington, DC, 1986, p. 153.
10 L. F. McConvey, *Chem. Eng. Res. Des.*, 65 (1987) 231.
11 A. R. Mansour, A. B. Shahalam and M. A. Sotari, *Sep. Sci. Technol.*, 20 (1985) 1.
12 W. Fritz and E. V. Schlunder, *Chem. Eng. Sci.*, 29 (1974) 1279.
13 M. W. Balzli, *Ph.D. Thesis*, Eidgenossiche Technische Hochschule, Zürich, 1977.
14 A. R. Mansour, A. B. Shahalam and N. Darwish, *Sep. Sci. Technol.*, 19 (1984–85) 1087.
15 C. Costa and A. E. Rodrigues, in A. E. Rodrigues, M. D. LeVan and D. Tondeur (Editors), *Adsorption: Science and Technology* (*NATO ASI Series E: Applied Sciences*, Vol. 158), Kluwer, Dordrecht, 1989, p. 257.
16 A. E. Rodrigues, M. D. LeVan and D. Tondeur (Editors), *Adsorption: Science and Technology* (*NATO ASI Series E: Applied Sciences*, Vol. 158), Kluwer, Dordrecht, 1989.
17 B. F. Brian, I. Zwiebel and R. S. Artigue, *AIChE Symp. Ser.*, 83 (259) (1988) 80.
18 W. J. Weber, Jr. and E. H. Smith, *Environ. Sci. Technol.*, 21 (1987) 1040.
19 E. E. Graham, A. Pucciani and N. G. Pinto, *Biotechnol. Prog.*, 3 (1987) 141.
20 J. C. Janson and P. Hedman, *Biotechnol. Prog.*, 3 (1987) 9.
21 H. Moon and W. K. Lee, *Chem. Eng. Sci.*, 41 (1986) 1995.
22 G. Carta, M. S. Saunders, J. P. DeCarli and J. B. Vierow, *AIChE Symp. Ser.*, 84 (264) (1988) 54.
23 C. B. Ching and D. M. Ruthven, *Chem. Eng. J.*, 40 (1989) B1.
24 G. McKay and M. J. Bino, *J. Chem. Technol. Biotechnol.*, 37 (1987) 81.
25 W. Kopaciewicz, S. Fulton and S. Y. Lee, *J. Chromatogr.*, 409 (1987) 111.
26 H. Moon and C. Tien, *AIChE Symp. Ser.*, 84 (264) (1988) 23.
27 W. B. Bolden and F. R. Groves, Jr., *AIChE Symp. Ser.*, 84 (264) (1988) 62.
28 C. B. Ching, C. Ho, K. Hidajat and D. M. Ruthven, *Chem. Eng. Sci.*, 42 (1987) 2547.
29 G. Guiochon and S. Ghodbane, *J. Phys. Chem.*, 92 (1988) 3682.
30 J. L. Wade, A. F. Bergold and P. W. Carr, *Anal. Chem.*, 59 (1987) 1286.
31 J. H. Knox and H. M. Pyper, *J. Chromatogr.*, 363 (1986) 1.
32 B. F. D. Ghrist, B. S. Cooperman and L. R. Snyder, *J. Chromatogr.*, 459 (1988) 1.
33 B. F. D. Ghrist and L. R. Snyder, *J. Chromatogr.*, 459 (1988) 25.
34 B. F. D. Ghrist and L. R. Snyder, *J. Chromatogr.*, 459 (1988) 43.
35 L. R. Snyder, G. B. Cox and P. E. Antle, *J. Chromatogr.*, 444 (1988) 303.
36 G. B. Cox, P. E. Antle and L. R. Snyder, *J. Chromatogr.*, 444 (1988) 325.
37 R. S. Hodges, J. M. R. Parker, C. T. Mant and R. R. Sharma, *J. Chromatogr.*, 458 (1988) 147.
38 H. A. Chase, *J. Chromatogr.*, 297 (1984) 179.
39 H. C. Thomas, *J. Am. Chem. Soc.*, 66 (1944) 1644.
40 H. C. Thomas, *Ann. N.Y. Acad. Sci.*, 49 (1948) 161.
41 H. A. Chase, personal communication, 1986.
42 A. R. Curtis and W. P. Sweetenham, *FACSIMILE Release H User's Manual, AERE-R11771*, Harwell Laboratory, Harwell, 1985.
43 W. P. Sweetenham, personal communication, 1986.
44 G. H. Cowan, in A. E. Rodrigues, M. D. LeVan and D. Tondeur (Editors), *Adsorption: Science and Technology* (*NATO ASI Series E: Applied Sciences*, Vol. 158), Kluwer, Dordrecht, 1989, p. 517.
45 B. J. Horstmann and H. A. Chase, presented at the *SCI Meeting on Separations for Biotechnology, Reading, 1987.*
46 B. J. Horstmann and H. A. Chase, *Chem. Eng. Res. Des.*, 67 (1989) 243.
47 S. L. Fowell and H. A. Chase, *J. Biotechnol.*, 4 (1986) 1.
48 B. J. Horstmann, C. W. Kenney and H. A. Chase, *J. Chromatogr.*, 361 (1986) 179.
49 E. J. Wilson and C. J. Geankoplis, *Ind. Eng. Chem. Fundam.*, 5 (1966) 9.
50 J. M. Coulson and J. F. Richardson (Editors), *Chemical Engineering*, Vol. 1, 3rd ed., 1977, p. 278.