



# A new general method for designing affinity chromatography processes



Lei Ling, Lee-Wei Kao, Nien-Hwa Linda Wang\*

School of Chemical Engineering, 480 Stadium Mall Drive, Purdue University, West Lafayette, IN 47907-2100, USA

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## ABSTRACT

Affinity chromatography is widely used for selectively recovering a target solute from a complex mixture. The challenge in designing a capture process is to achieve high yield, high column utilization, and high sorbent productivity while satisfying loading time and pressure limit requirements. The conventional design method based on constant-pattern waves cannot be used for small feed batches or short columns, which do not allow the formation of such waves. Other design methods in the literature rely on simulations or experimental trials, and can be time-consuming and costly. In this study, a new design method with no need of simulations is developed for constant pattern and non-constant pattern systems with Langmuir isotherms. Given feed conditions, loading time, and desired yield, the design requires only the values of certain intrinsic parameters, which can be estimated from a small number of bench-scale experiments. The minimum column volume for capture can be estimated either graphically or analytically. The method is tested with Protein A chromatography data for antibody purification. It is applicable to a wide range of production scales and design requirements. The effects of material properties, feed composition, feed volume, and design requirements on the column volume for capture can be found graphically. When the loading time relative to a characteristic diffusion time is 0.5 or larger, the minimum column volume approaches that of an ideal system. A short loading time increases sorbent productivity, but increases the minimum column volume. A high feed concentration, a high equilibrium capacity, and a small diffusion time relative to the loading time can reduce the minimum column volume and increase productivity.

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## 1. Introduction

Affinity chromatography is widely used for selectively recovering a target solute from a complex mixture [1]. The separation is based on specific interactions between a sorbent and a solute. Examples are Protein A chromatography for antibody purification [2], immobilized metal affinity chromatography (IMAC) for protein fractionation [3], and capture chromatography for medical isotope precursor recovery [4].

In general, an affinity chromatography process consists of four steps: (1) pre-equilibrating the column with a buffer; (2) loading the feed and capturing the target solute; (3) washing the column with the buffer to remove non-adsorbing impurities; and (4) eluting the target solute using a stripping agent. The most challenging aspect of designing a capture process is the selection of column size and operating velocity to achieve high yield and high column utilization, while satisfying the requirements of loading time and

pressure limit. Achieving these goals by experimental trial and error can be costly and time-consuming. Furthermore, the results of a specific design may not apply if the feed concentration, feed volume, loading time, operating velocity, column length, or sorbent are different from those in the tested case. It is also difficult to predict how material properties, such as particle size, particle porosity, bed void fraction, adsorption isotherm, and intra-particle diffusivity, affect the column volume or the operating velocity.

The yield and column utilization in a capture process depend on the shape of the frontal wave, which depends on the adsorption isotherm and mass transfer rates. For linear isotherm systems, Rosen considered film diffusion and intra-particle diffusion effects. He obtained an analytical solution of the effluent concentration as a function of the loading time for sufficiently long columns [5,6]. For nonlinear isotherm systems, most of the published design methods are based on the solutions for “constant-pattern” waves, and apply only if the feed volume and the column length are sufficiently large for the frontal wave to reach a constant pattern [7–10]. In many affinity chromatography systems, a constant pattern is unattainable when the column length, the feed volume, or the loading time is small. For high affinity systems with highly

\* Corresponding author. Tel.: +1 765 494 4081; fax: +1 765 494 0805.  
E-mail address: [wangn@ecn.purdue.edu](mailto:wangn@ecn.purdue.edu) (N.-H.L. Wang).

non-linear “rectangular” adsorption isotherms, Carta and co-workers obtained correlations between the dynamic column capacity and the solute residence time [11,12]. The correlations, which are valid for constant pattern or non-constant pattern systems, can be used to predict the maximum loading time for a given column if the breakthrough concentration and the velocity are specified.

Recently, Ling et al. developed a graphical design method for systems with Langmuir isotherms to determine the minimum column volume ( $V_{Cmin}$ ) for a required capture yield and loading time [4]. In this method, the column volume is found from the intersection point of a constant breakthrough limit curve (BL curve) and a constant loading time curve (LT curve). Numerical simulations are required to generate the BL curve. This method was tested using data of Mo-99 recovery from uranium fission products. In this example, only one sorbent with one set of Langmuir isotherm parameters was tested, and the feed concentrations were mostly in the linear isotherm region [4].

In this study, we build on the previous minimum-column-volume design method [4] and develop a more efficient method, which does not require any simulations for affinity chromatography systems with Langmuir isotherms. The goal of the design method is to achieve the desired yield and loading time while maximizing sorbent productivity for either constant pattern or non-constant pattern systems. The method is tested with published affinity chromatography data. We also aim to understand how the loading time, the material properties, and the feed concentration affect the minimum column volume required for capture.

We first review the key dimensionless groups and the previous graphical design method introduced in Ling et al. [4], in which numerical simulations were used to generate a BL curve for a specific breakthrough limit. In this study, general correlations of the BL curves for various dimensionless breakthrough limits (0.05, 0.1, and 0.15) are developed for Langmuir isotherm systems. The correlations allow the determination of the column volume and the operating velocity without any simulations. Relations between the breakthrough limits and the capture yields are also developed so that the minimum column volume can be found to meet a specific yield requirement. The accuracy of the design method based on the analytical correlations is tested by comparing the column volumes found from the new method with the experimental column volumes reported in the literature [13–17]. In Ling et al. [4], the minimum column volume was found from the intersection of the BL and LT curves in the  $L_f$  vs.  $N_D$  graph. In this study, we generate new graphs of dimensionless column volume as a function of dimensionless loading time for various breakthrough limits. If the feed volume, feed concentration, and material properties are known, the minimum column volume for a specific loading time is directly found from the graphs without the need to generate the BL and LT curves. Alternatively, if the capture column volume is fixed, the loading time and loading velocity to meet the yield requirement can be found from the graphs.

The design method developed in this study is applicable to all the systems with Langmuir adsorption isotherms. The  $V_{Cmin}$  for the desired yield and loading time can be found without simulations. Only certain material properties (adsorption isotherm parameters, bed void fraction, diffusivity, and porosity) are needed for the design and they can be obtained from a small number of bench-scale experiments. The conditions for the formation of constant pattern waves are found. The effects of material properties and design criteria (feed concentration, feed volume, loading time, and yield) on the column volume are elucidated. In general, high productivity can be achieved with a small loading time. A small column volume for capture can be achieved with a high feed concentration, a high equilibrium capacity, and a small diffusion time relative to the loading time.

## 2. Review of the previous design method based on simulated breakthrough limit curves

The key dimensionless groups used to characterize mass transfer and column utilization are summarized in Section 2.1. How the breakthrough limit curves and the loading time curves are related to the key dimensionless groups are explained in Sections 2.2 and 2.3. The algorithm for finding the minimum column volume for a specific breakthrough limit and loading time is described in Section 2.4. The method for calculating the maximum column length and velocity allowed by a pressure-drop limit is explained in Section 2.5.

### 2.1. Key dimensionless groups

During the feed loading step, the frontal wave spreads as a result of various mass transfer effects. This wave spreading prevents complete utilization of the equilibrium column capacity if all of the target solute in the feed needs to be captured. Column utilization is related to the degree of wave spreading and dimensionless breakthrough concentrations (Fig. 1), which is linked to the capture yield as discussed in Section 3.2. Wave spreading can be affected by many factors, such as the sorbent particle size ( $R$ ), the column length ( $L$ ), the bed void ( $\epsilon_b$ ), the particles porosity ( $\epsilon_p$ ), the superficial velocity ( $u_s$ ), the feed concentration ( $C_f$ ), the Langmuir isotherm parameters ( $a$  and  $b$ ), the intra-particle diffusivity ( $D_p$ ), the axial dispersion coefficient ( $E_b$ ), and the film mass transfer coefficient ( $k_f$ ). Studying the individual effects of these factors on wave spreading can be quite tedious. To reduce the number of variables, several dimensionless groups are used for characterizing column utilization and the effects of mass transfer and thermodynamic sharpening on wave spreading.

The general rate-model equations in terms of dimensionless variables for batch and simulated moving bed chromatography have been reported previously [18]. The equations are solved numerically for specific isotherms and operating conditions. The solutions of the effluent history and column profiles are governed by the dimensionless groups in the differential mass-balance equations, the isotherm equations, and the boundary conditions. The resulting independent dimensionless groups related to convection, axial dispersion, film diffusion, and intra-particle diffusion are  $Pe_b$ ,  $N_f$ , and  $N_D$  [4]. The definition and the physical significance of each group are summarized in Table 1. The spreading of a frontal wave is related to the three dimensionless groups.

For low-pressure chromatography systems ( $R > 20 \mu\text{m}$ ), it has been shown that  $N_D$  ranges from 0.1 to 1,  $Pe_b$  is about  $10^2$ , and  $N_f$  is about  $10^3$ , indicating that intra-particle diffusion, or only the value of  $N_D$ , controls the wave spreading [4].

Thermodynamic sharpening, which counters diffusional spreading, also affects the shape of a frontal wave. Its effects are controlled by the dimensionless group  $bC_f$  in the Langmuir isotherm.

$$q_f = \frac{aC_f}{1 + bC_f} = a^*C_f \quad (1)$$

where  $q_f$  is the equilibrium concentration of the adsorbed solute (adsorbed solute per packing volume) at a feed concentration of  $C_f$ . The Langmuir  $a$  value is also defined based on per packing volume;  $a^*$  is defined as  $a^* = a/(1 + bC_f)$ , which can be considered as an effective  $a$  value at a specific concentration for a nonlinear isotherm system. The group  $bC_f$  can be considered as an “overloading” factor or a “thermodynamic wave sharpening” factor.

The column utilization can be described by another dimensionless group, the loading fraction  $L_f$ , which is defined as the ratio of

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