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Modelling the effect of temperature on the gel-filtration chromatographic protein separation

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ABSTRACT

In this study a mechanistic model for chromatography was taken and the solution to its Laplace transfer function was obtained using the Fast Fourier Transform method. Using previously developed correlations for modelling diffusion, both in solution and intraparticle, and estimating the mass transfer coefficient, the effect of temperature in gel fittration liquid chromatography was investigated. The effect of each individual parameter on the elution curve was systematically explored allowing for reasonable estimates for the different temperature cases. In this case, a system of bovine serum albumin and phenylalanine separated by gel filtration chromatography was simulated to demonstrate how the resolution and the selectivity of the separation will change with physical parameters. Decreasing the particle size and flow rate while increasing the temperature led to higher resolution, which is consistent with experimental literature data.

1. Introduction

The production of biologics has actively employed the use of chromatography to separate the desired from the undesired fermentation products. Purification is one of the major costs associated with protein manufacture and its optimization is of crucial importance to the bioprocessing industry. Detailed mathematical models have been developed to characterize the behavior of the chromatographic system, however the effect of low temperature has rarely been investigated.

There is some data on the chromatographic processes that take place in higher than ambient temperatures. Varied results have been reported with different compounds, however they have not employed detailed mechanistic models to investigate the fundamental effects (Heinisch and Rocca, 2009; Vanhoenacker and Sandra, 2006). This paper presents a model that accurately accounts for the temperature effects on physical parameters and uses it in a predictive manner to describe the column operation. Several aspects of the temperature effect were considered to understand the influence of temperature. The diffusion of the solute, both in the solvent and inside the adsorbing particles had the greatest effect on the chromatogram peak shape, retention time and resolution of the species. Other effects that play a role in chromatography are dispersion and the mass transfer coefficient, both of which vary with temperature as well as flow rate.

Several methods and correlations have been reported (Cussler, 2009) that have used different parameters to characterize the diffusion behavior of solutes. For protein chromatography, correlations that employ the proteins molecular weight (Young et al., 1980) were considered. Another important consideration in this system is the intraparticle diffusivity, which is estimated using the correlation by Boyer and Hsu (1992). The mass transfer coefficient was estimated using three separate correlations, one employed by Schneider and Smith (1968) for a forced convection around a sphere, which is analogous to the heat transfer expression. The other method was the Wilson and Geankoplis (1966) expression, and the one for protein adsorption is the one presented by Liapis et al. (1989). For dispersion occurring inside the bed, the Chung and Wen (1968) correlation was computed. These equations give reasonable estimates of the trends of their respective parameters which are then computed in order to see the pulse response of the column.

Computing the model was accomplished by implementing the Fast Fourier Transform (FFT) technique, first introduced by Cooley and Tukey (1965) for computation of the Fourier integral. The Fourier integral computation can be used in order to numerically invert Laplace transforms, as demonstrated by Hsu for chromatographic systems (Hsu and Dranoff, 1987; Hsu, 1979) and for adsorption related systems. The FFT technique requires a very short computation time compared to the finite Fourier transform computation. The FFT method has been demonstrated to be computation-

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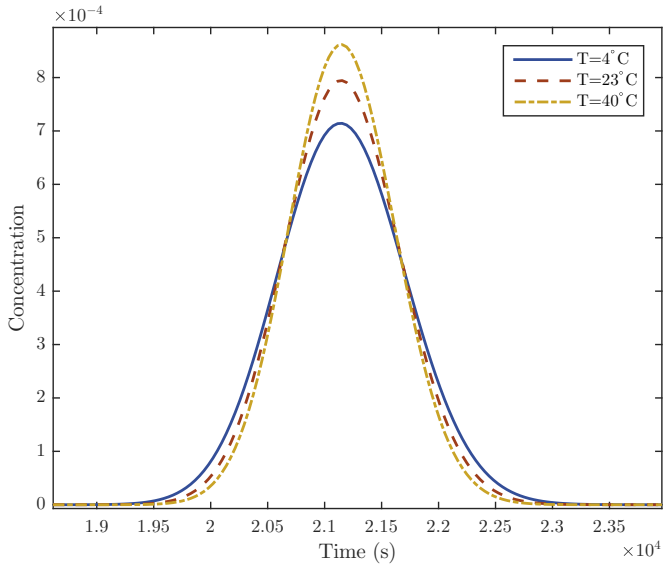

Fig. 1. Elution curves for Bovine Serum Albumin at a fixed mass transfer coefficient ($k_f = 0.0015$ cm/s) and varying dispersion caused by temperature changes. Notice that the peak tailing increases as the temperature decreases.

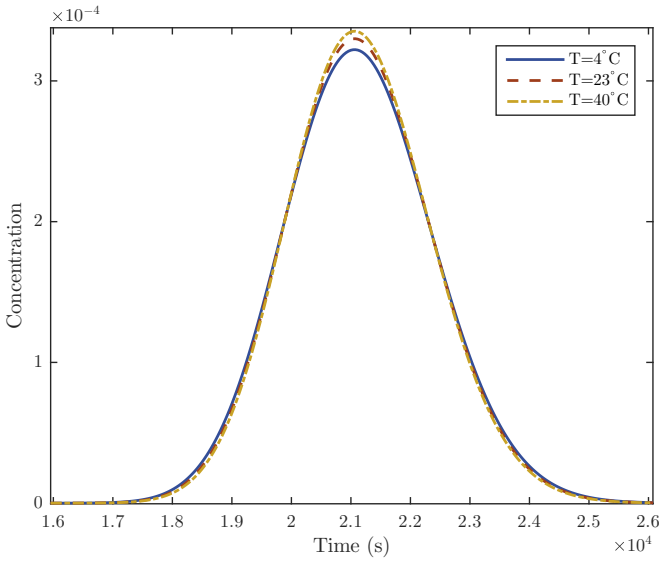

Fig. 2. Effect of the mass transfer coefficient at different temperatures at fixed dispersion ($D_L = 0.0015$ cm^2/s). The peak height decreases slightly at lower temperatures.

ally superior, even to the direct evaluation of the time-domain solution as in some cases the evaluation of the oscillatory integrand converges very slowly (Hsu and Dranoff, 1987; Rasmuson, 1985). Obtaining the time domain solution is very important in investigating the performance of the column when compared to the moments method introduced by Schneider and Smith (1968).

This study aims to study the effect of diffusion, dispersion and mass transfer coefficient on the chromatograms in gel filtration chromatography. After computing the elution curves, they were analyzed in order to investigate how the peaks are affected by fundamental mass transfer phenomena. These insights were taken into account to model and analyze the best way of chromatographic separation at low temperatures. Results were obtained for a model system of bovine serum albumin and phenylalanine and their subsequent resolutions at different superficial velocities, temperatures and gel particle radii.

2. Theory

2.1. Model development

Boyer and Hsu (1992) used a model for an axially dispersed liquid flow with external film diffusion and intraparticle diffusion. The model is for an isothermal chromatographic column packed with spherical particles. The protein adsorption on unsubstituted agarose matrices is negligible, so there is no adsorption accounted for in this model.

For the mobile phase

$$\frac{\partial C}{\partial t} + V\frac{\partial C}{\partial z} - D_L\frac{\partial^2 C}{\partial z^2} = -\frac{-3k_f}{mR}(C - C_p|_{r=R}) \tag{1}$$

Intraparticle mass balance

$$\epsilon_p\frac{\partial C_p}{\partial t} = D_e\left(\frac{\partial^2 C_p}{\partial r^2} + \frac{2}{r}\frac{\partial C_p}{\partial r}\right) \tag{2}$$

The initial and boundary conditions

$$C(z,0) = 0 \tag{3}$$

$$C(0,t) = \begin{cases} C_0, & 0 \le t \le t_0 \\ 0, & t_0 < t \end{cases} \tag{4}$$

$$C(\infty,t) = 0 \tag{5}$$

$$C_p(r,z,0) = 0 \tag{6}$$

$$C_p(0,z,t) \neq \infty \tag{7}$$

$$k_f(C - C_p|_{r=R}) = D_e\frac{\partial C_p}{\partial r}\Big|_{r=R} \tag{8}$$

The variables introduced are : C - solute concentration in mobile phase, C_p - solute concentration in the pores, C_s - solute concentration on solid, C_0 - initial pulse concentration, V - mobile phase velocity, D_L - axial dispersion coefficient, $m = \epsilon/(1-\epsilon)$, ϵ - column void fraction,ϵ_p particle porosity, q - concentration in particles, D_e - intraparticle diffusivity, k_f - external mass transfer coefficient, t - time, z - axial position, r - intraparticle radial position, R - radius of the bead. A solution can be obtained by inverting the equations into the Laplace domain. The result is:

$$\bar{C}(z,s) = C_0\exp\left[\left(\frac{V}{2D_L} - \sqrt{\frac{V^2}{4D_L^2} + \frac{s}{D_L} + \frac{3k_f}{mD_LR}\alpha(s)}\right)z\right] \tag{9}$$

$$\alpha(s) = \frac{\sqrt{\frac{\epsilon_p s}{D_e}}\cosh\sqrt{\frac{\epsilon_p s}{D_e}}R - \frac{1}{R}\sinh\sqrt{\frac{\epsilon_p s}{D_e}}R}{\sqrt{\frac{\epsilon_p s}{D_e}}\cosh\sqrt{\frac{\epsilon_p s}{D_e}} + (\frac{k_f}{D_e} - \frac{1}{R})\sinh\sqrt{\frac{\epsilon_p s}{D_e}}R} \tag{10}$$

2.2. Computational method

The inversion of this transfer function was then computed using MATLAB and the built-in IFFT function. The frequency spectrum of this function is symmetrical, it was specified in the function which aids the algorithm and decreases computation time. The formula utilized by MATLAB is:

$$\bar{f}(t) = f(n\ \Delta T) = \frac{N}{2T}\left[\ \left(\frac{1}{N}\right)\ \sum_{k=1}^{N} F\left(\frac{i(k-1)\pi}{T}\right)\right.$$
$$\left.\exp\left(i\frac{2\pi\,(n-1)(k-1)}{N}\right)\right] \tag{11}$$