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Computational fluid dynamic simulation of axial and radial flow membrane chromatography: Mechanisms of non-ideality and validation of the zonal rate model

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ABSTRACT

Membrane chromatography (MC) is increasingly being used as a purification platform for large biomolecules due to higher operational flow rates. The zonal rate model (ZRM) has previously been applied to accurately characterize the hydrodynamic behavior in commercial MC capsules at different configurations and scales. Explorations of capsule size, geometry and operating conditions using the model and experiment were used to identify possible causes of inhomogeneous flow and their contributions to band broadening. In the present study, the hydrodynamics within membrane chromatography capsules are more rigorously investigated by computational fluid dynamics (CFD). The CFD models are defined according to precisely measured capsule geometries in order to avoid the estimation of geometry related model parameters. In addition to validating the assumptions and hypotheses regarding non-ideal flow mechanisms encoded in the ZRM, we show that CFD simulations can be used to mechanistically understand and predict non-binding breakthrough curves without need for estimation of any parameters. When applied to a small-scale axial flow MC capsules, CFD simulations identify non-ideal flows in the distribution (hold-up) volumes upstream and downstream of the membrane stack as the major source of band broadening. For the large-scale radial flow capsule, the CFD model quantitatively predicts breakthrough data using binding parameters independently determined using the small-scale axial flow capsule, identifying structural irregularities within the membrane pleats as an important source of band broadening. The modeling and parameter determination scheme described here therefore facilitates a holistic mechanistic-based method for model based scale-up, obviating the need of performing expensive large-scale experiments under binding conditions. As the CFD model described provides a rich mechanistic analysis of membrane chromatography systems and the ability to explore operational space, but requires detailed knowledge of internal capsule geometries and has much greater computational requirements, it is complementary to the previously described strengths and uses of the ZRM for process analysis and design.

1. Introduction

Membrane chromatography (MC) is widely used as a purification platform for virus clearance and polishing. Larger pore sizes in membranes (1–1.2 μm) make the mass transfer predominantly convective and permit higher flow rates to be realized at lower pressure drops [1–3]. Recent improvements in membrane surface chemistries have led to higher binding capacities and, consequently, MC is also finding traction in industry as an alternative platform to conventional packed bed chromatography for the purification of complex biomolecules such as, e.g. glycoproteins [4]. In a recent study, Bayer Healthcare has demonstrated a first commercial-scale application of MC in bind and elute mode for blood coagulation factors and has reported a yield improvement of 40% while maintaining high product quality as compared to packed bed chromatography [4]. As MC is becoming increasingly accepted in the biopharmaceutical industry, accurate modeling strategies

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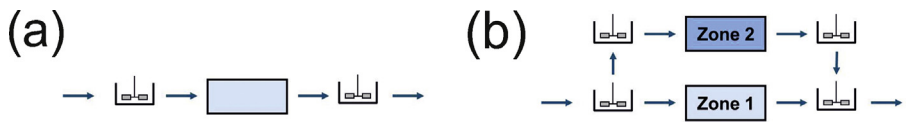

Fig. 1. Representations of (a) the classical one-dimensional Roper and Lightfoot model, and (b) a two zone ZRM configuration for axial flow MC capsules.

have become important for rational process analysis, simulation and design.

MC has traditionally been modeled by only considering the axial coordinate [5–8]. In most of these classic studies, the effects of external hold-up volumes on elution band broadening are accounted for by coupling a plug flow model (PFR) for transport within the membrane stack with one or two continuously stirred tank regions (CSTR) in series to account for mixing and residence times within the extra-column spaces (see Fig. 1a). These one-dimensional models assume flow homogeneity over the entire membrane cross-section, which in practice is hard to achieve due to device design constraints. Lab scale MC capsules often have axial flow configurations, employing a stack of flat membrane sheets. Preparative or pilot-scale capsules usually have radial flow configurations with various winding schemes such as spiral wound, hollow fibers, or pleats. Manifold design is long known to significantly impact on the breakthrough performance of MC capsules [9,10]. In a recent report, we showed that the assumption of flow homogeneity over the entire membrane cross-sections does not necessarily hold for commercially available capsules, and that the resulting inhomogeneous mass flows can cause unwanted tailing of breakthrough curves [11]. The zonal rate model (ZRM), which treats this problem, uniquely de-couples the effects of hydrodynamics and binding on the resulting chromatograms by partitioning the entrance and elution hold-up volumes, as well as the membrane stack, into virtual zones that are modeled as a network of inter-connected CSTRs and PFRs [12,13]. The ZRM is thereby able to quantify non-ideal flows, as well as binding non-idealities, and their contributions to band-broadening, and illustrations of these capabilities were provided through application to the Pall Mustang XT5 (axial flow) and Mustang XT140 (radial flow) capsules. Both capsules exhibit admirable performance attributes, but nevertheless exhibit non-idealities at standard operating conditions. ZRM analysis of the axial-flow XT5 capsule suggested that non-ideal flow in the external hold-up volumes upstream and downstream of the membrane stack, which is consistent with the high aspect ratio of the XT5 capsule, contribute to band broadening. In contrast, the ZRM suggested that structural irregularities in the membrane pleats are the primary source of flow non-idealities in the radial flow XT140 capsule. For both studies, the ZRM was able to quantitatively reproduce breakthrough data, a result that cannot be achieved using traditional membrane chromatography models. Moreover, the existence of varying linear velocities in the radial-flow capsule, as suggested by the ZRM, was consistent with magnetic resonance tomography (MRT) images of the internal capsule, which provided evidence of structural irregularities in the membrane pleats. However, direct evidence of linear flow variations within either capsule was not acquired, making it unclear if the ZRM structure and predictions are correct at the mechanistic level. The current study aims to address this shortcoming through the creation and solution of computational fluid dynamic (CFD) models of the axial and radial membrane chromatography modules described above. Although not widely employed in MC modeling, CFD provides a scale-neutral modeling strategy that is able to independently predict hydrodynamic behavior. Linear velocities as a function of position and breakthrough curves under non-binding conditions may therefore be accurately predicted using only knowledge of internal capsule geometries and basic membrane properties. Moreover, when applied to column loading, CFD simulations provide precise hydrodynamics and thereby allow for unambiguous analysis of the ability of different binding models to reproduce measured breakthrough curves. CFD may therefore be used as a powerful tool for gaining a richer and more accurate understanding of mechanisms contributing to band broadening and their relative importance in different MC devices.

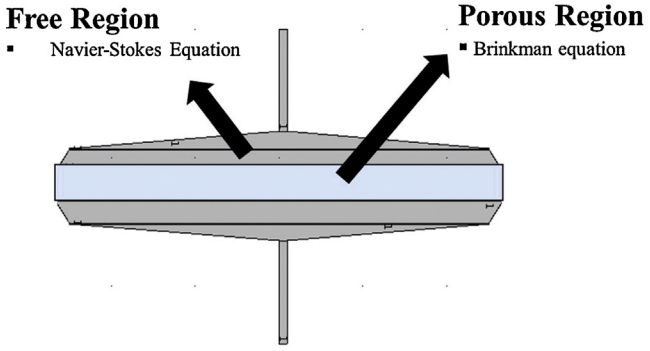

Fig. 2. Longitudinal cross-section of the Pall Mustang XT5 capsule, showing free and porous regions as implemented in the CFD model.

2. Theory

2.1. Computational fluid dynamics

CFD models are based on solution of the fundamental conservation laws of mass, momentum and (sometimes) energy. Mathematically, these laws are described by a set of partial differential equations (PDEs) that have analytical solutions only in a few cases, usually described by rather simple boundary conditions. Hence, numerical methods are required in most applications. In CFD the collective set of PDEs and initial and boundary conditions (the model) is solved to compute fluid flow and related phenomena, such as transport and adsorption of solute molecules.

The system boundaries are defined by the physical geometries of the system, in this case the MC capsules. For example, Fig. 2 shows the internal geometry of a Pall Mustang XT5 capsule. In this capsule, spacer meshes are placed at either sides of the membrane stack. The geometry shown is simplified by omitting these spacer meshes and by considering the membrane stack as one homogeneous region. The model therefore considers the internal geometry as two free regions and one porous region with rotational symmetry. The capsule hold-up volumes before and after the membrane stack constitute the free regions, and the Navier–Stokes equations describe fluid flow in these two regions. The peak Reynolds number within the capsule remains below 5, clearly indicating laminar flow. The incompressible Navier–Stokes equations without external forces are given by Eq. (1) (v denotes the fluid velocity, p the pressure, and μ the kinematic viscosity).

$$\rho\left(\frac{\partial v}{\partial t} + v\cdot\nabla v\right) = -\nabla pI + \nabla\left(\mu(\nabla v + (\nabla v)^T) - \frac{2}{3}\mu(\nabla\cdot v)I\right) + F \tag{1a}$$

$$\nabla\cdot v = 0 \tag{1b}$$