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Multi-scale modeling of protein fouling in ultrafiltration process

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A B S T R A C T

The aim of this work was the formulation of a theoretical multi-scale model simulating the membrane separation of proteins. The proposed approach integrated the knowledge about separation process, as attained at different lengths and timescales. The fouling progress, as determined by protein layers deposited on the membrane surface, and the permeate flux decay of dead-end ultrafiltration were predicted without resorting to adjustable parameters. With reference to Bovine Serum Albumin (BSA) the electrostatic surface charges were calculated by accurate quantum mechanics approaches, along with the contact molecular surface and the BSA effective diameter. These quantities were exploited to estimate the BSA surface potential necessary to formulate, at a microscopic scale, a balance of the forces acting on each BSA particle. The additional resistance due to the accumulated protein layers was then calculated, thus allowing the transition to a macroscopic scale. A transport model describing the unsteady-state mass transfer of BSA was eventually formulated to predict the behavior of dead-end UF process as a function of the operating conditions. The predictions of the proposed multi-scale model were compared with a set of experimental data collected filtering a BSA aqueous solution through a polyethersulfone ultrafiltration membrane.

1. Introduction

Process systems engineering is concerned with the understanding and development of systematic procedures for the design and operation of chemical systems. In membrane technology, modeling is of paramount importance since it allows either designing high performance membranes with maximized permeability and molecular rejection or improving the performance of existing separation processes. The choice of an appropriate material (material design) definitely allows reducing membrane fouling, which occurs during proteins separation or purification by UltraFiltration (UF). In addition, a proper choice of the operating conditions to be utilized (process design) may achieve the reduction of concentration polarization effects.

The permeate flux in ultrafiltration process was traditionally expressed as the ratio between the process driving force, i.e. the transmembrane pressure, and the transport resistance [1]. This, according to the resistance-in-series model, was computed as the sum of two contributions: the hydrodynamic resistance of the clean membrane, constant in time and related to the reciprocal of its permeability, and an overall, time-dependent resistance accounting for membrane fouling [2,3]. Many different studies dealing with membrane fouling, as caused by colloids or proteins, were carried out in order to determine the permeate flux decay as a function of the operating conditions [4–7]. A great number of papers have proved that both surface and pore fouling do actually have a profound influence on the permeate flux and the retention characteristics of UF membranes [8–11]. In a recent paper, Polyakov and Zydney [12] gave a detailed presentation of the most common theories aimed at evaluating the effects of complete blocking and pore constriction on membrane transport. In particular, it was shown that a proper coupling of models for steric/electrostatic solute rejection and of models for solute fouling, based on either complete blocking or pore constriction, might allow mathematically describing the relationship existing between selectivity and permeability in UF process. The most common modeling approaches exploited in membrane technology, however, made use of empirical or semi-empirical parameters, obtained by direct experimental measurements or by fitting sets of available experimental data [13–16]. In some cases, membrane fouling and permeate flux decay were predicted by empirical models, based on artificial neural networks, ANN [17–20], or by hybrid neural models, which were developed combining either a transport model and an ANN model, together concurring to the obtainment of UF process responses [21], or the film layer model to an ANN [22]. Many different theoretical approaches, describing

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the mass and momentum transport occurring in membrane modules, were also formulated [23–26].Bowen and Jenner [27] proposed a dynamic mathematical model for predicting the rate of ultrafiltration of charged colloidal dispersions, using accurate descriptions of the particle–particle interactions. The disjoining pressure was expressed according to the Deryaguin–Landau–Verwey–Overbeek (DLVO) theory [28,29]. This theory is based on the assumption that the electrostatic double layer repulsion force, the Van der Waals attraction and the short-range forces, referred as Born repulsion or hydration force, can be added. The latter forces were often cataloged as ‘non-DLVO forces’, even if their relevance in the calculations of the interactions between colloidal particles or biological systems was widely demonstrated [30]. DLVO theory has been traditionally preferred over other theories to describe the interactions among nanoparticles, essentially for the simplicity of the analytical expression of the potentials involved in the calculation of attraction/repulsion forces. DLVO theory, however, may be reasonably applicable only for solutions with low salt concentrations. In several situations, it demonstrated to be unable providing even a proper qualitative description of protein-solution behavior; one important example is protein salting-out, namely the precipitation of protein with the addition of salt [31]. Harmant and Aimar [32] made use of the colloidal interaction forces, deriving from DLVO theory, in a force balance written for each particle composing the cake. The balance accounted for the viscous forces and allowed obtaining both the colloidal deposit structure and the values of cake additional resistance necessary to perform the permeate flux calculation. Both Aimar's and Bowen's approaches provided accurate predictions of membrane process behavior and of permeate flux decay [33–37]. However, some of the quantities, actually belonging to the sub-nanoscopic or nanoscopic scale and exploited to express the additional resistance or the disjoining pressure, were not the results of theoretical calculations but were obtained by experimental measurements.

In order to describe all the various aspects involved in membrane separation processes, more efficient and innovative modeling methodologies, based on a higher-level physical description of the phenomena, are required. A more rigorous and systemic problem formulation is, definitely, worth a proper investigation. Such novel methodologies have to accommodate a greater variety of models, ranging from the molecular level to the macroscopic scale (multi-scale modeling). Multi-scale simulation can be defined as “the enabling technology of science and engineering that links phenomena, models, and information between various scales of complex systems” [38]. The idea of multi-scale modeling is straightforward: one computes information at a smaller (finer) scale, by using the appropriate computational approach, and passes it to a model at a larger (coarser) scale by leaving out, i.e., coarse-graining, degrees of freedom.

In the case of proteins UF, the formulation of an efficient multi-scale modeling strategy, which starts from the knowledge of protein molecular structure and eventually leads to the prediction of process behavior, is crucial to attain a deeper knowledge of the complex phenomena involved in membrane separation. With particular reference to proteins ultrafiltration, it is worthwhile observing that non-covalent intermolecular interactions do actually govern the adsorption and the packing of various macromolecules, like proteins, on the membrane surface [39,40]. The distribution of the electrostatic charges on the protein surface represents one of the most important features, which is to be carefully evaluated since it controls the physical interactions among proteins and, therefore, affects the deposit build-up on the membrane surface. Thus, any multi-scale model properly describing membrane fouling requires, as a starting point, an accurate computation, without using any adjustable parameter, of the electrostatic charge distribution on the protein surface. Quantum Mechanics (QM) approaches are generally exploited for the determination of the partial charges on the atoms of any molecular system. A QM approach, although characterized by a rather significant computational effort, definitely represents the most reliable method since it does not make use of any adjustable parameter. In the open literature, the available models describing protein separation or purification by UF, rarely made use of the physical–chemical properties evaluated by ab-initio calculations [41]; rather, it was preferred to exploit adjustable parameters or fit experimental data. Up to date, literature exhibits a significant lack of information concerning the use of proper computational methodologies in conjunction with the microscopic-, mesoscopic- and macroscopic-scale theoretical approaches. In addition, theoretical models integrating the sub-nanoscale properties calculated by QM methods with a set of conservation equations typical of larger length- and timescales could not be found, at least with reference to membrane processes.

The present study was intended to fill such a gap. With reference to the ultrafiltration process of Bovine Serum Albumin (BSA), different modeling aspects, each of them characteristic of a definite scale, were analyzed to formulate an integrated multi-scale model independent of any adjustable parameter; in fact, only the crystallographic structure of BSA was used. BSA was chosen since it is relatively easy to isolate and to purify and, due to its characteristics, it was often considered as a reference molecule [42,43]. As explained in the following sections, the additional resistance as caused by the deposit of proteins on the membrane surface was described introducing a set of key structural proprieties, computed by a QM approach and accounting for the strong relationship existing between the chemical structure of the protein and the microscopic and macroscopic properties affecting UF performance. In particular, the electrostatic charges on each atom of BSA external amino acids, the contact molecular surface, the effective diameter and the BSA average surface charge were preliminarily computed. Quantum calculations, based on Density Functional Theory (DFT) were performed since they allowed a correct evaluation of the electrostatic charges, in various chemical environments, with reasonable computational efforts [44]. Although both electrostatic long-range and short-range intermolecular interactions should be considered in the analysis, only long-range interactions were taken into account, leaving out other interactions, such as hydrogen bonding and London interactions. Long-range electrostatic and massive forces, indeed, mostly control the surface fouling, as caused by the deposit of macromolecules on the membrane surface. The description of long-range interactions was based on the evaluation of average surface charge, which was computed by a free-from-adjustable-parameters calculation. Such a QM calculation allowed computing the BSA surface potential, which was exploited to estimate the electrostatic interactions existing between different nanoparticles and, then, to formulate a microscopic scale model according to the approach already proposed by Harmant and Aimar [32]. This model allowed calculating the main characteristics, namely the separation distance among the particles and the void fraction, of the protein layers accumulated on the membrane. The so-obtained parameters were exploited to estimate the specific cake resistance, which was eventually used in a macroscopic model describing the mass transfer occurring in an unstirred dead-end UF cell. It was, therefore, possible to formulate a predictive model aimed at calculating the permeate flux decay, as a function of process and operating variables.

As described in the following, the present multi-scale model did not take into account the effects of the interactions between BSA and both membrane surface and the inner wall of the pores. The effects of steric and electrostatic exclusion, which play a major