PROTEIN BINDING AFFINITY IN ION EXCHANGE CHROMATOGRAPHY AND QUANTITATIVE STRUCTURE-PROPERTY RELATIONSHIP MODELING FOR CHROMATOGRAPHIC SYSTEMS AND PROTEOMICS

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ABSTRACT

Protein adsorption on an ionic surface is dominated by electrostatic interactions and is a complex function of resin chemistry and mobile phase effect (e.g. pH and salt). Experimental work was first carried out to investigate the effect of resin chemistry on protein binding affinity. Protein batch desorption profiles were determined for a set of multi-modal cation exchange chromatographic materials. These carboxylic acid based materials enabled a secondary interaction in addition to traditional electrostatic interaction. The results demonstrated that protein binding affinity was significantly enhanced by these multi-modal resins under high salt conditions and that the overall selectivity was altered as compared to traditional cation exchange chromatography. In addition, novel elution strategies were developed for amine based multi-modal anion exchange materials which possessed stronger secondary interactions.

Quantitative Structure-Property Relationship (QSPR) modeling techniques were then employed to study a variety of chromatographic systems. QSPR models were generated to correlate the structural components and physicochemical properties of multi-modal ligands with their binding affinity with proteins. The important binding characteristics between the various ligand molecules and proteins were examined from the selected features of the models. A multi-scale modeling approach which combines QSPR models for the *a priori* prediction of adsorption parameters with a macroscopic mass transport model was then used to predict complex non-linear protein chromatography in gradient systems. This work was extended to multiple pH conditions by using a set of novel pH dependent descriptors that represent protein charge/EP properties. These descriptors were employed in concert with the multi-scale modeling approach for the prediction of column separations under different pH conditions.

Finally, the structure-property modeling technique was extended to the field of diagnostic proteomics. Two dimensional molecular descriptors were calculated based on peptide sequences and QSPR models were generated for peptide retentions in capillary reverse phase chromatography. This predictive QSPR model may enable the identification of low abundance peptides which are not easily detected by LC/MS and may eventually facilitate the use of LC/MS for complex diagnostic applications.