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VIRTUAL MATERIALS DESIGN

Digital Twins for Polymer-Based Resins

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Introduction

- Liquid chromatography (LC) is widely used for purifying compounds, determining purity levels, and analyzing complex mixtures.
- Interaction between molecules and LC resins are not well understood and hard to predict.
- We present two novel workflows aimed at advancing the understanding of molecular interactions in LC.
- We introduce a virtual design approach to model a commercial multi-modal chromatography (MMC) resin at atomic resolution, inclusive of its polymethacrylic backbone.
- Through binding free energy (ΔG) calculations with 10 linear peptides our model was able to predict Langmuir isotherm constants accurately.

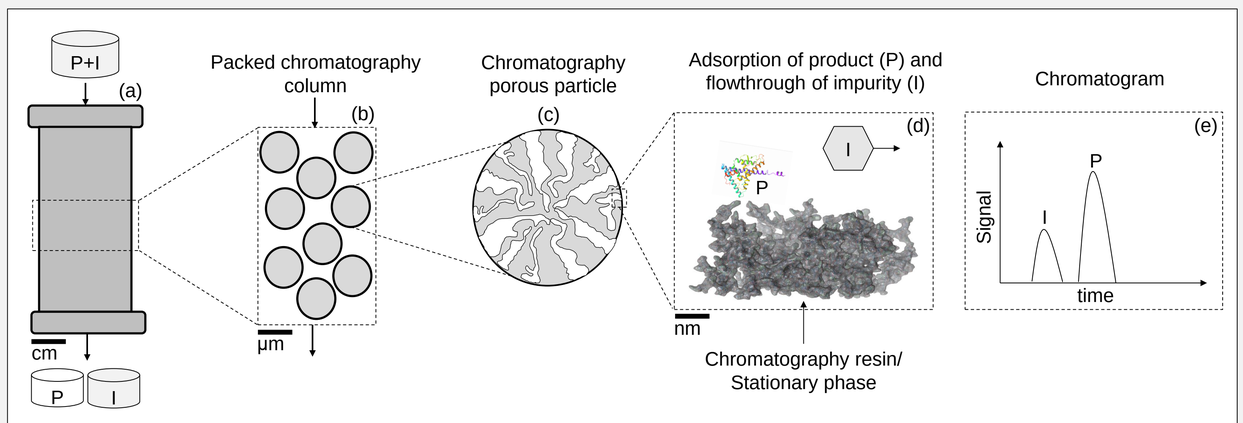

Figure 1: Schematic overview of how LC operates. LC works by passing a liquid sample through a column (a) filled with a chromatography resin (b) and (c). The different molecules interact with the stationary phase based on their physical and chemical properties (d), leading to their separation (e).

Workflows

Virtual Design of Methacrylate-Based Chromatography Resins

We developed a multistage modeling approach to generate all-atom resolution models of methacrylate-based chromatography resins, automated within the workflow management system (WMS) SimStack.

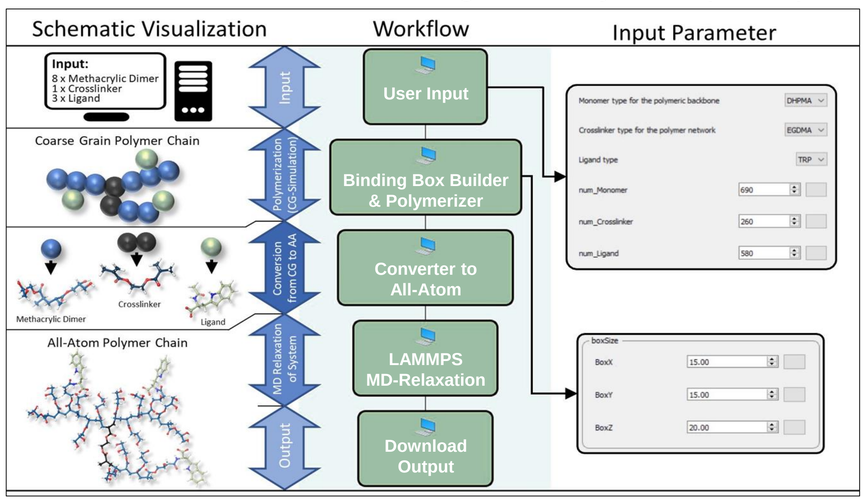

Figure 2: SimStack Workflow - Beginning with user input for polymerization simulation at coarse-grain resolution, transitioning to all-atom resolution conversion, and culminating in MD relaxation.

As a first example we virtually designed a MMC resin from Tosoh Bioscience:

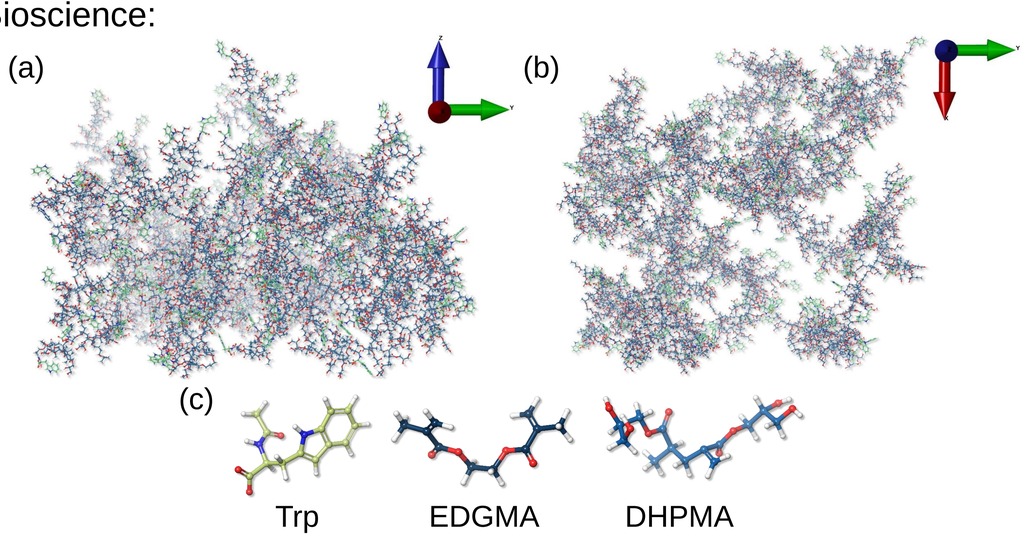

Figure 3: Surface Model of the commercial resin TOYOPEARL MX-Trp-650M - Panel (a) displays the side view, and panel (b) offers a top view of the all-atom model. Panel (c) illustrates the chemical composition of the chromatography resin: Trp: Tryptophan as the ligand, EDGMA: Ethylene glycol dimethacrylate as the crosslinker and DHPMA: 2-hydroxypropyl methacrylate as the monomer.

Computation of Binding Energies with Linear Peptides as Target Molecules

This second workflow demonstrates a use case for our developed model by employing advanced computational methods to determine binding poses and free energies (ΔG) between target molecules and our custom all-atom resin surface model. Our computationally efficient approach enables rapid screenings suitable for standard office computers. We automated the entire multistep simulation using the KNIME workflow management system.

Using this workflow, we calculated four distinct binding poses (Fig. 5) and corresponding ΔG for 10 linear peptides selected as target molecules in this study.

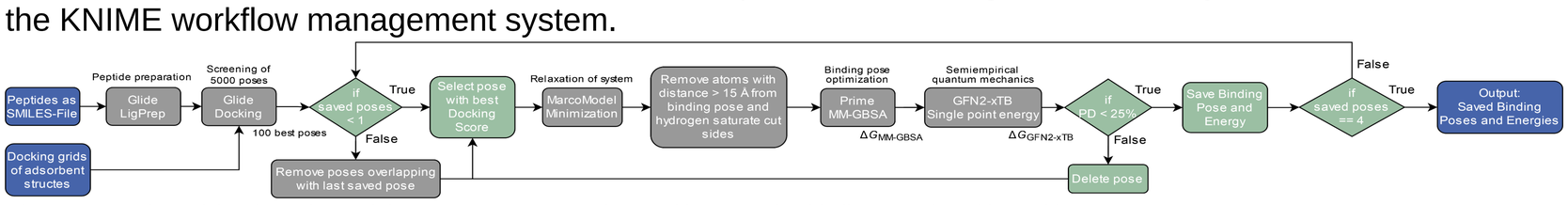

Figure 4: Flowchart of the simulation and data management steps involved in calculating binding energies with peptides.

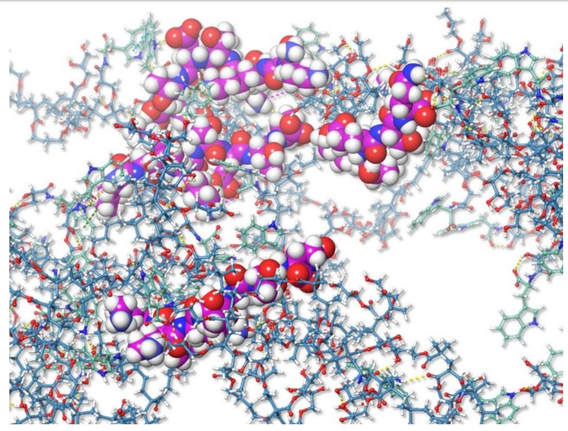

Figure 5: Workflow Output - Four distinct binding poses of Octapeptide-2.

Validation

- For experimental validation, we established a robotic lab to automate high-throughput measurements of adsorption isotherms.
- The obtained Langmuir constants (K_L) showed a strong logarithmic correlation with the previously calculated ΔG values (Fig. 6), consistent with theoretical studies.

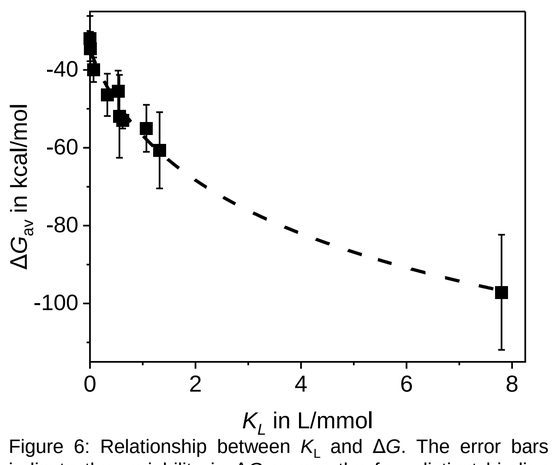

Figure 6: Relationship between K_L and ΔG. The error bars indicate the variability in ΔG across the four distinct binding poses. Taken from [1]

[1]: T. Ballweg, M. Liu, J. Grimm, E. Sedghamiz, W. Wenzel, M. Franzreb, All-atom modeling of methacrylate-based multi-modal chromatography resins for Langmuir constant prediction of peptides, J Chromatogr A 1730 (2024)

Conclusion and Future Studies

- ✓ We introduce and validate two innovative workflows for predicting peptide binding behaviors in multimodal chromatography.
- ✓ The first workflow generates detailed all-atom models of methacrylate-based resin surfaces, including the polymer backbone.
- ✓ The second workflow enables rapid ΔG calculations with linear peptides and effectively predicts experimental K_L values.

- ➢ Future Studies:
- ➢ Introduce various chromatography ligands and validate them using the established workflow.
- ➢ Predict chromatography data for larger target compounds, including oligonucleotides, proteins, and antibodies.