475e A Molecular Design Approach to Peptide Stabilization

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Over the last twenty years peptides have emerged as a new class of potent and effective therapeutic drugs, but their susceptibility to chemical degradation has made it impossible to realize their full potential. One solution, which has been demonstrated experimentally to be effective using the polymer poly (vinyl pyrrolidone), is to complex the peptide with a polymer. However, it is difficult to take advantage of this stabilizing effect without more knowledge of the mechanism of action. This work performs molecular simulations and uses optimization techniques to provide insight into the stabilizing effect of the polymer, and this insight allows polymer candidates to be designed for peptide stabilization via computational molecular design. The first goal of this research was to understand how a polymer decreases the rates of degradation reactions that commonly render a peptide drug ineffective, by modeling the peptide-polymer complex using simulation techniques. The peptide's range of torsion angle movement was calculated with and without the polymer, providing an understanding of the polymer's effect on peptide flexibility. Simulated annealing experiments were conducted to determine what effect the polymer has on the peptide's most likely secondary structures. Steric and electrostatic effects were also investigated as a function of polymer chain length. Given an understanding of how a polymer prevents peptide degradation, we are able to link polymer properties to chemical properties of the peptide-polymer complex, allowing us to discern which polymer properties are important for peptide stabilization. This link allows the use of computational molecular design (CMD) to develop novel polymer structures for peptide stabilization. In our CMD formulation, topological indices are used to predict properties of the pure polymer, and then specific properties of the peptide-polymer system are determined. These properties include stabilization effects, toxicity, and solubility. These property prediction equations are then combined with structural constraints resulting in a mixed-integer linear program. The formulation is solved using the Tabu search algorithm, which provides a set of near-optimal solutions that serve as candidate polymers for peptide drug stabilization. Examples are provided which show the efficacy of the approach.