Structure Prediction of Cyclic Peptides via Molecular Dynamics + Machine Learning

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Since the discovery of cyclosporin A in the 1970s, cyclic peptides have shown that they can combine the best attributes of small molecules and biologics. Like biologics, cyclic peptides can potently target protein surfaces; despite their large sizes (generally 5–16 residues with MW 550–1,760 Da) and large numbers of hydrogen-bond donors and acceptors, cyclic peptides can be membrane-permeable and even orally bioavailable, like small molecules. However, there are only ~50 approved cyclic peptide drugs, and most of them are simply natural products or derivatives thereof. While researchers would love to effectively exploit this seemingly privileged class of molecules for targeting specific proteins of interest that are both intra- and extracellular, *de novo* designed cyclic peptide drugs remain exceedingly rare.

A major obstacle to cyclic peptide development is that little structural information is available for these molecules, making it difficult to perform structure-based design or understand why different cyclic peptide sequences display different binding affinity, membrane permeability, and other properties. The lack of structural information is due to the fact that most cyclic peptides adopt multiple conformations in solution, existing as structural ensembles, which are very difficult to characterize using experimental techniques such as solution NMR spectroscopy. In this talk, I will describe how we developed enhanced sampling methods tailored to cyclic peptides to enable efficient simulation of their structural ensembles. Using the simulation results as training datasets, we further built machine learning models that provide simulation-quality cyclic peptide structure predictions in seconds. We expect such a capability to rapidly predict cyclic peptide structures to greatly accelerate the development of this unique class of molecules.