Computational modelling for membrane permeation of cyclic peptides

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Cyclic peptides have become a standard tool of modern drug discovery. Cyclization restrains the conformational freedom, thus reducing the entropic penalty upon binding. This allows cyclic peptides to bind relatively large and flat targets such as protein-protein interfaces. Nevertheless, they are often still flexible enough to adapt to environments with different polarity by switching between conformations. This effect is commonly called chameleonicity, and it often allows for a very advantageous combination of solubility and membrane-permeability, even at molecular weights significantly beyond the traditional rule-of-five space.

In-silico approaches such as conformer generation and molecular dynamics provide important resources to study the conformations of cyclic peptides. Here, we present recent computational findings on the structural principles governing cyclic peptides as well as their process of passive membrane permeation. By improving our mechanistic understanding of passive membrane permeation, we hope to provide novel opportunities for drug development, and to facilitate the design of compounds with favorable biophysical properties such as oral bioavailability.