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# Computational methods to design cyclic peptides

Sean M McHugh[1], Julia R Rogers[1], Sarah A Solomon[1], Hongtao Yu[1] and Yu-Shan Lin

Cyclic peptides (CPs) are promising modulators of protein–protein interactions (PPIs), but their application remains challenging. It is currently difficult to predict the structures and bioavailability of CPs. The ability to design CPs using computer modeling would greatly facilitate the development of CPs as potent PPI modulators for fundamental studies and as potential therapeutics. Herein, we describe computational methods to generate CP libraries for virtual screening, as well as current efforts to accurately predict the conformations adopted by CPs. These advances are making it possible to envision robust computational design of active CPs. However, unique properties of CPs pose significant challenges associated with sampling CP conformational space and accurately describing CP energetics. These major obstacles to structure prediction likely must be solved before robust design of active CPs can be reliably achieved.

**Address**
Department of Chemistry, Tufts University, Medford, MA 02155, United States

Corresponding author: Lin, Yu-Shan (yu-shan.lin@tufts.edu)
[1] These authors contributed equally.

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## Introduction

Many biological processes proceed via protein–protein interactions (PPIs). A robust capacity to target and modulate any specific PPI would facilitate diverse mechanistic studies to dissect the functional roles of PPIs, and could lead to novel therapeutic interventions [1,2]. Cyclic peptides (CPs) are among the most promising PPI modulators owing to their ability to bind large protein surfaces with high affinity and specificity and their enhanced biostability and bioavailability as compared to linear peptide counterparts [3,4,5]. Successful applications of CPs as PPI modulators include griselimycins [6], CP CXCR4 antagonists [7], cyclo-(CLLFVY) that inhibits HIF-1α/HIF-1β [8], and the examples shown in Figure 1.

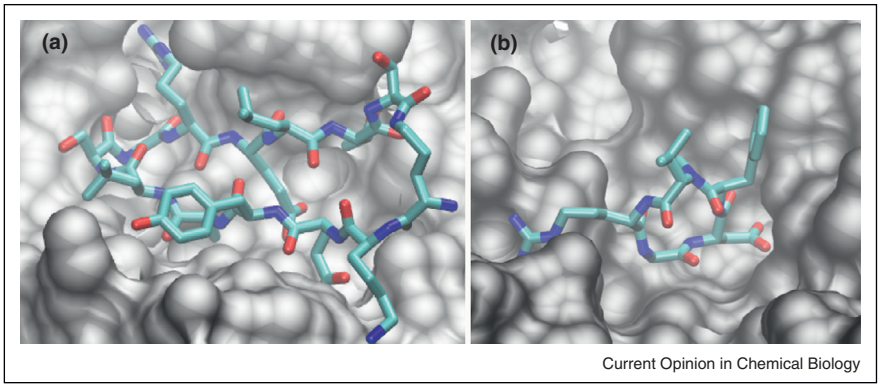
A number of CP features must be considered during the design process. Various cyclization strategies are available, including head-to-tail, disulfide, other side-chain to side-chain, and side-chain to terminus bonding [11,12]. Incorporating multiple cyclizations to generate peptides that are bicyclic, tricyclic, etc., can provide additional restraints to rigidify the peptide and provide further complexity of design space. Furthermore, in addition to the canonical amino acids, D-amino acids, *N*-methylated residues, and other non-natural amino acids can be implemented to improve binding affinity or pharmacokinetic properties [13–17]. With many variables to optimize, experimentally generating, testing and analyzing large and synthetically challenging CP libraries can be arduous and time consuming. Therefore, computational approaches to design CPs and provide a better understanding of their sequence–structure relationships would greatly aid CP development efforts. Below, we discuss a number of computational methods for CP structure prediction and development, as well as current challenges faced within the field.

## Methods to generate cyclic peptide libraries for virtual screening

Virtual screening a large library of CPs can be key to identifying high affinity binders [18,19]. Effective virtual screening may include exploration of sequence space, for instance to test a variety of sequences containing residues crucial for binding to a specific protein surface. For example, CycloPs generates a virtual library of all constrained peptide sequences that meet a user's specifications about which cyclization methods or amino acid types to include, and excludes peptides that are likely to prove difficult to synthesize [20••]. Recently, a CP with drug lead-like activity to inhibit thrombin, a protein involved in blood platelet formation, was identified by screening sequences generated by CycloPs with pharmacophore matching [21]. Although an efficient method to explore sequence space, additional algorithms need to be used to fully explore conformational space.

To generate conformer libraries for a given CP sequence, at least three major types of conformational search algorithms have been used. These algorithms primarily differ in how they reduce the dimensionality of the conformational space. (1) Distance geometry algorithms utilize distance restraints to describe a molecule. Rubicon (Rubicon, Daylight Chemical Information Systems), which implements a distance geometry

**Figure 1**




**(a)** A cyclic peptide mimicking the β-hairpin of CdiA-CT binds to CdiL (PDBID = 4ZQW; Cdi: contact-dependent growth inhibition; CdiA-CT: C-terminal toxin domain of CdiA) [9]. **(b)** A cyclic peptide containing the RGD motif binds to integrin αVβ3 (PDBID = 1L5G) [10].

algorithm, selects various distances that meet the restraints to generate many conformers for a CP. Other methods such as stochastic proximity embedding [22] and self-organizing superimposition [23], also implement distance geometry algorithms, but instead refine random initial atomic positions until the restraints are satisfied. (2) Stochastic search algorithms first define variables that characterize the system, such as bond lengths or dihedrals. Then, discrete values are randomly assigned to each variable, and the generated conformers are scored to obtain a manageable number of variable values for exhaustive structure generation. Methods using stochastic search algorithms to generate CP structural libraries include Catalyst (Catalyst, Accelrys), MacroModel (MacroModel, Schrödinger), MOE (MOE, Chemical Computing Group) and others [24]. (3) Systematic search algorithms assemble a variety of likely conformations of individual fragments to construct full structures, and are used in methods such as CAESAR [25] and Omega [26]. Analysis of the conformational diversity produced by these various search algorithms for a variety of CPs indicates that the distance geometry methods generate libraries with the widest variety of structures [27].

Loop closure algorithms can also be used to generate CP conformer libraries. For example, inverse kinematic algorithms determine the possible dihedrals to close a loop consisting of rigid segments and pivot points. Kinematic algorithms for peptides have been implemented in the Rosetta suite and the BRIKARD package [28,29,92], among others. A different strategy, PLOP (Protein Local Optimization Program) initiates a dihedral angle buildup procedure from both ends of the loop to generate halves of a CP. The distances between the end residues are evaluated to determine whether the two halves can be appropriately joined to complete the cycle [30].

## Structure prediction of cyclic peptides using fragment-based algorithms

A major impediment to the full exploration of CPs as therapeutics is the difficulty in structure prediction. The conformational search algorithms mentioned above can also provide low-energy structures upon integration with additional software and program functions, such as using kinematic algorithms in combination with additional Rosetta functions or specifying a reduced number of structures to be generated by PLOP after energetic evaluation (further details about PLOP can be found in Table 1) [29,30]. Additional structure prediction methods available for linear peptides have also been modified or developed to identify the low-energy conformations of CPs [31,32]. Peplook [33,34], PEPstrMOD [35], PEP-FOLD [36,37], and I-TASSER [38] methods first determine likely conformations for individual residues or specific fragments of the peptide and then evaluate all generated conformations to predict the structure of a given sequence. The applicability of a structure prediction method to model a given CP depends on the size, cyclization method, and residue types incorporated in the peptide (see Table 1 for which CP characteristics each method can model). Of the described methods, Peplook can model the smallest CPs and has been tested on several small CPs of five to seven residues with known structures [33]. All of the described methods can model disulfide-bonded CPs and have been applied most for CPs of 10+ residues that are cyclized through disulfide bonds [33,35,36]. Peplook and PEPstrMOD can also model CPs with non-canonical amino acids. However, the reliability of these structure prediction algorithms greatly depends on their ability to generate all plausible structures a CP can adopt, and the accuracy of the energetic functions used, which remains an active field of study.

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