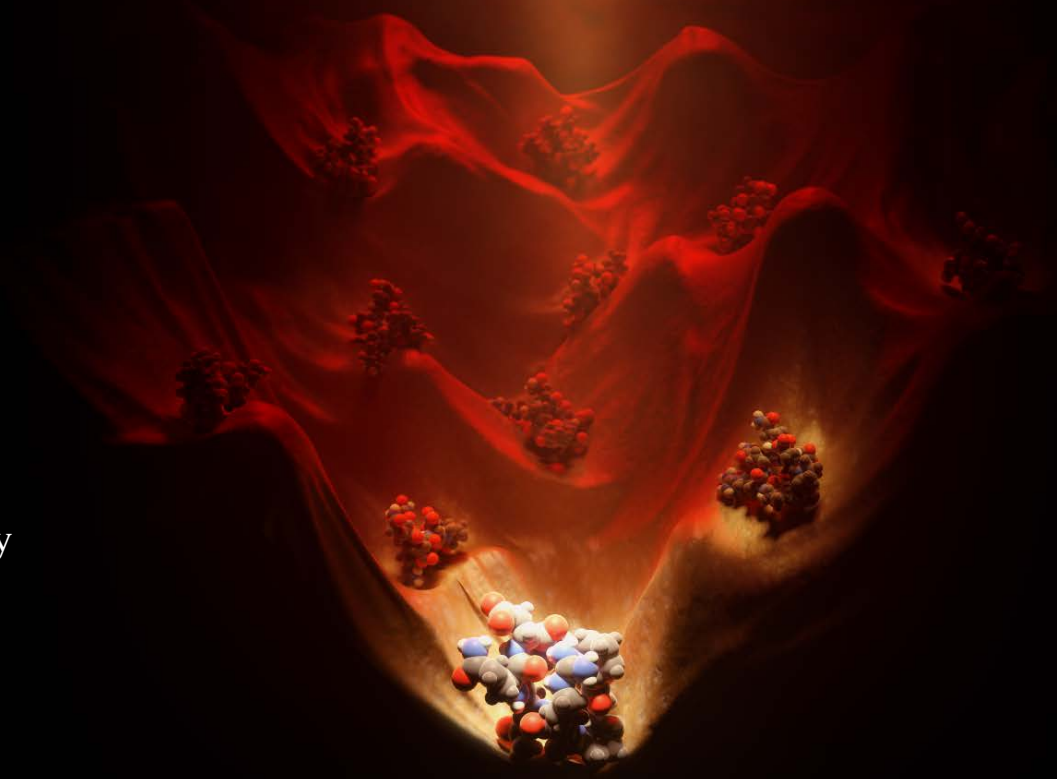
Polypeptides Designed Using the Rosetta Software Suite And the D-Wave 2000Q



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CEO, Menten Biotechnology Labs, Inc.

Tuesday, 24 September 2019

Rosetta Commons

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Menten AI
AI and Quantum-powered Protein Design

Notice

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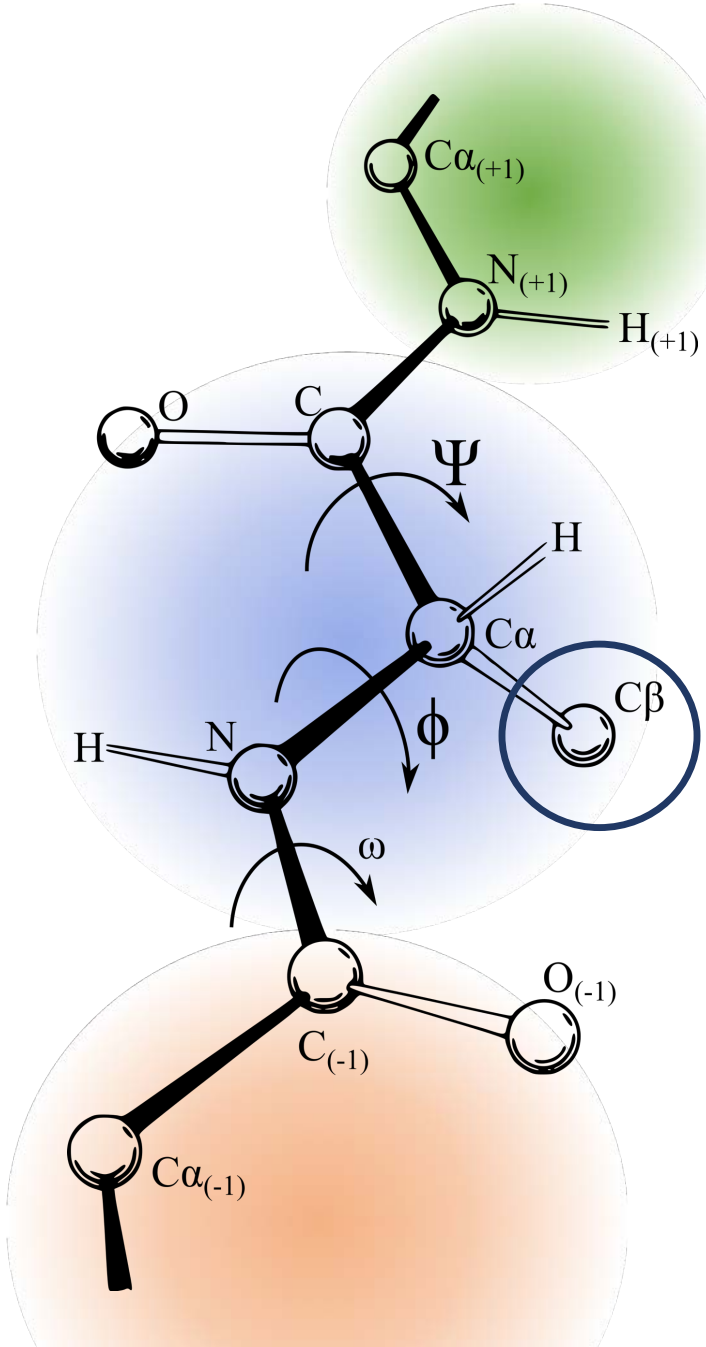
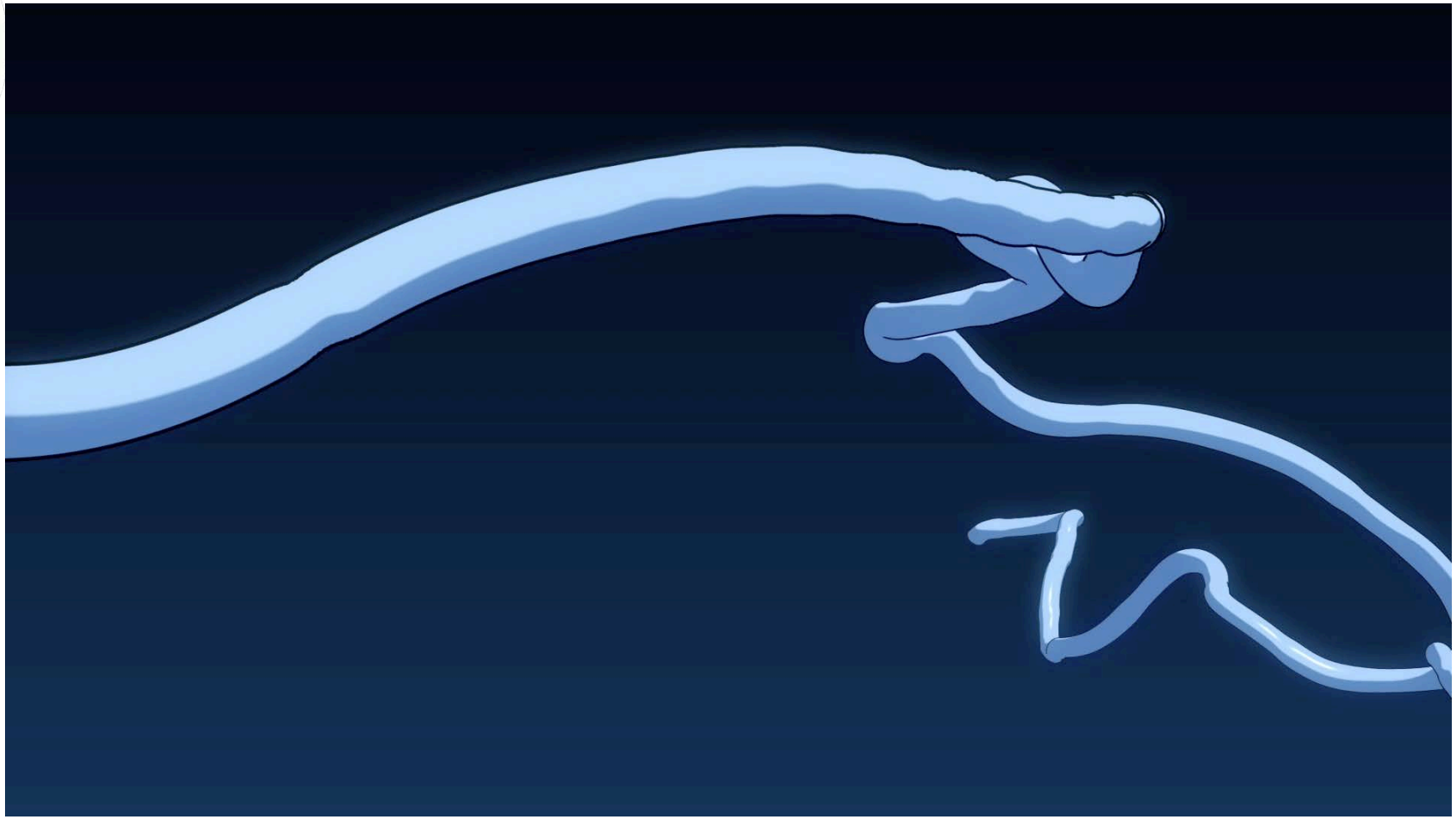
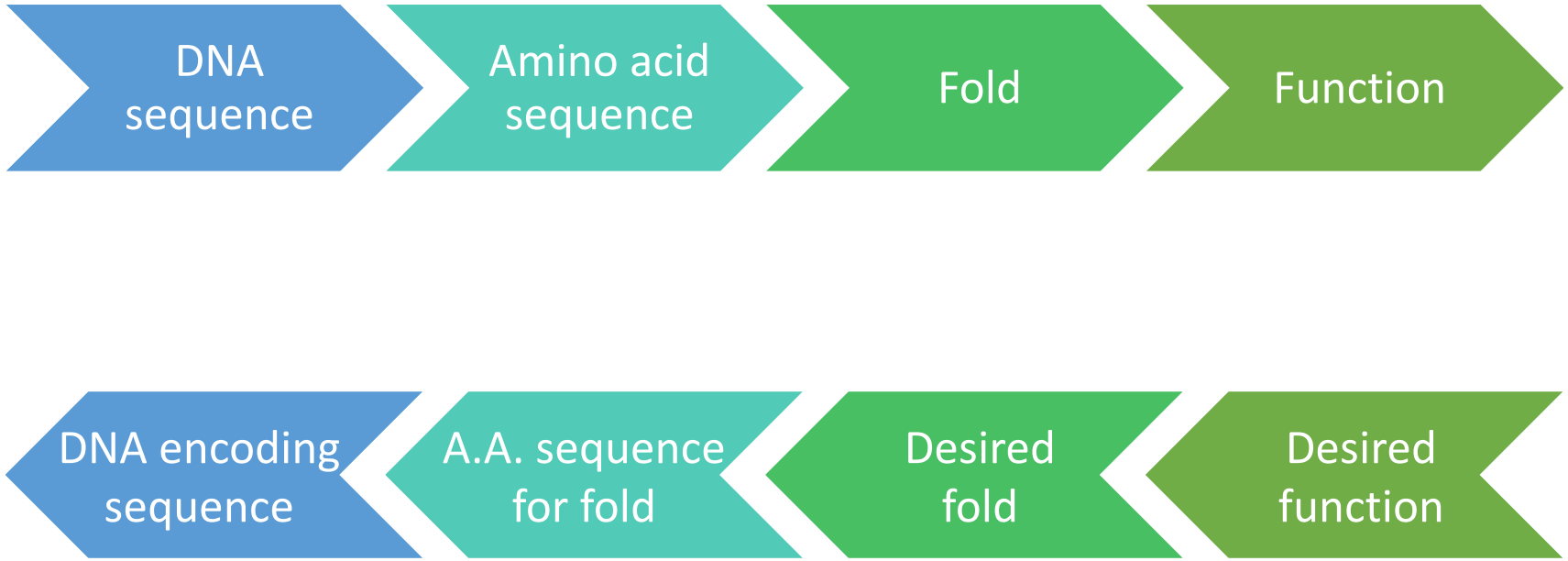
A preprint of the work using the quantum annealer to design peptides and proteins is available from bioRxiv: https://www.biorxiv.org/content/10.1101/752485v1. This work has not yet undergone peer review.

Proteins fold spontaneously into rigid conformations determined by amino acid sequence

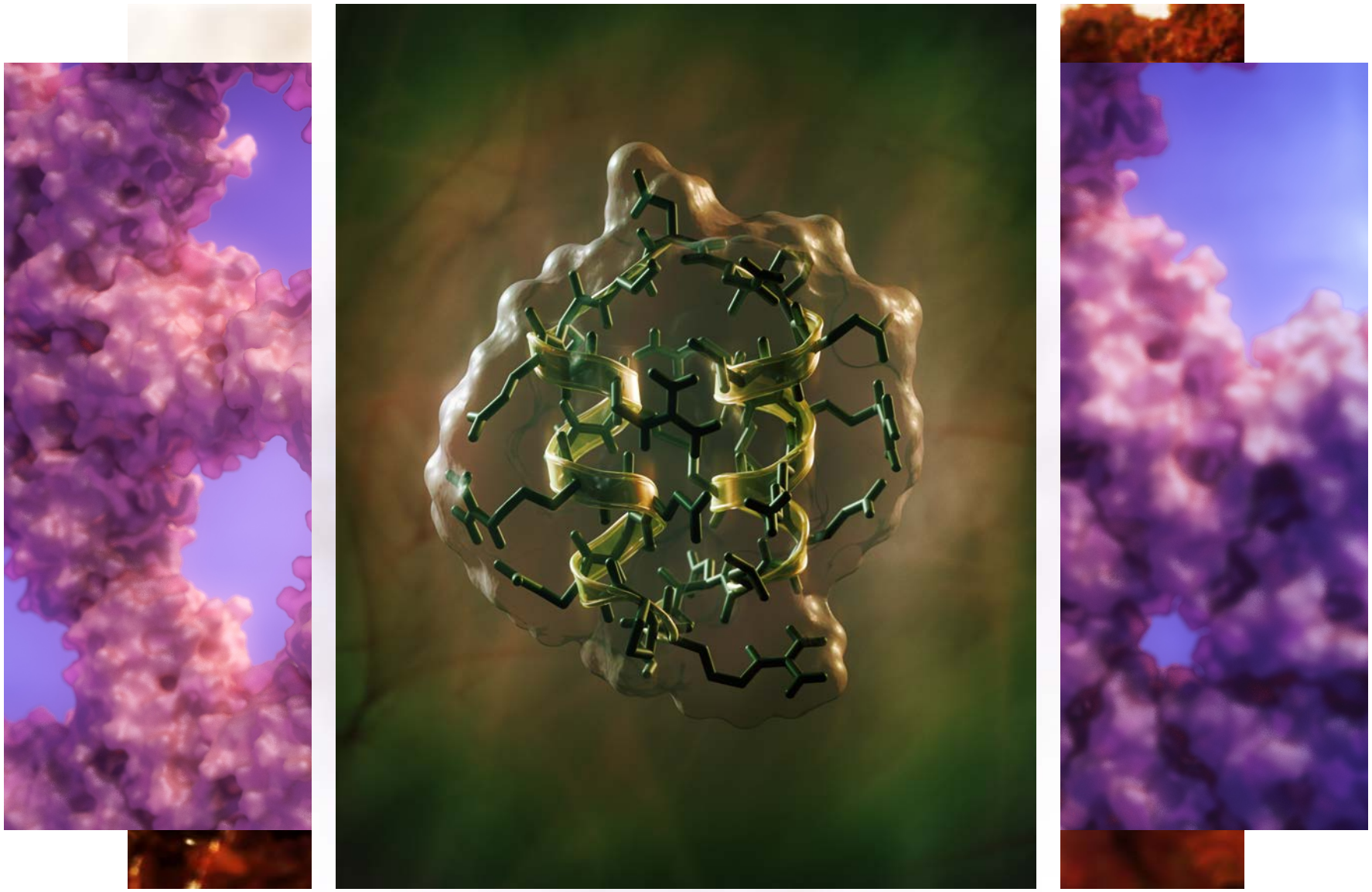




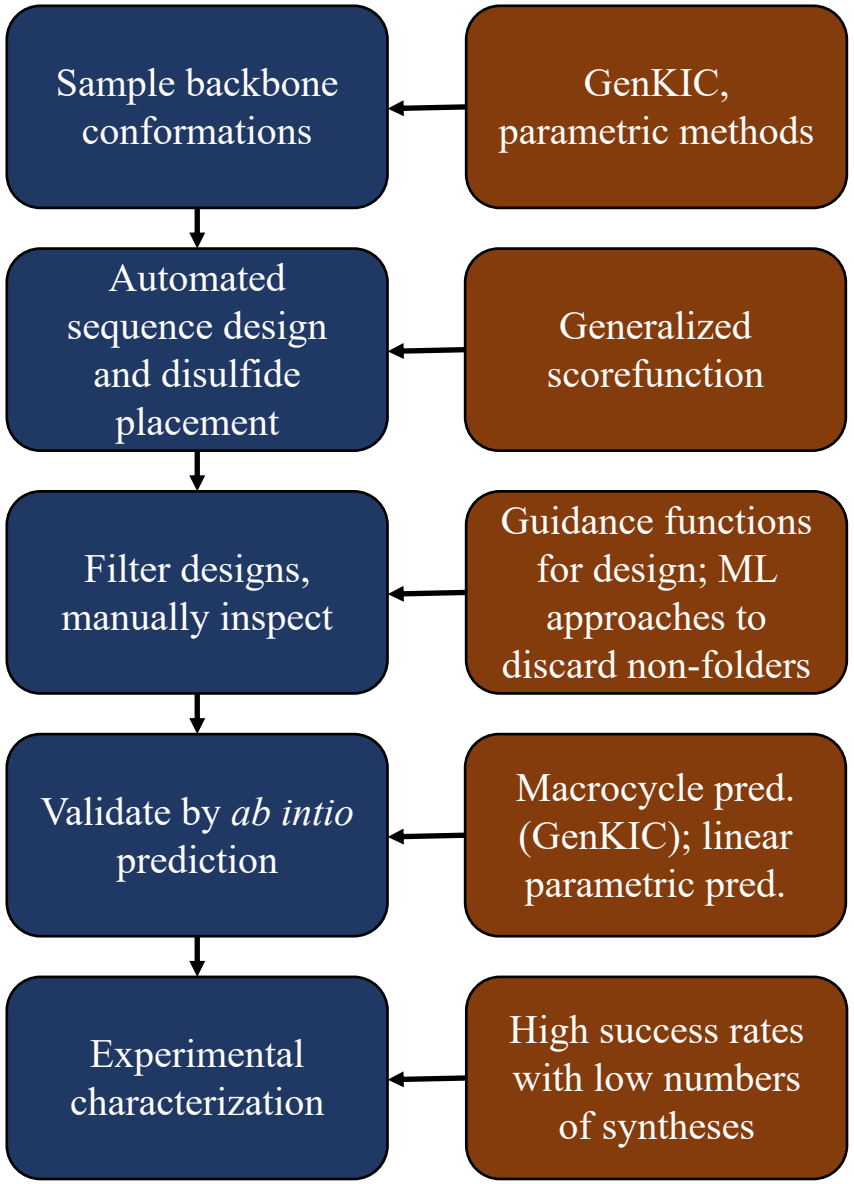
Exploring sequence-structure-function relationship with computation



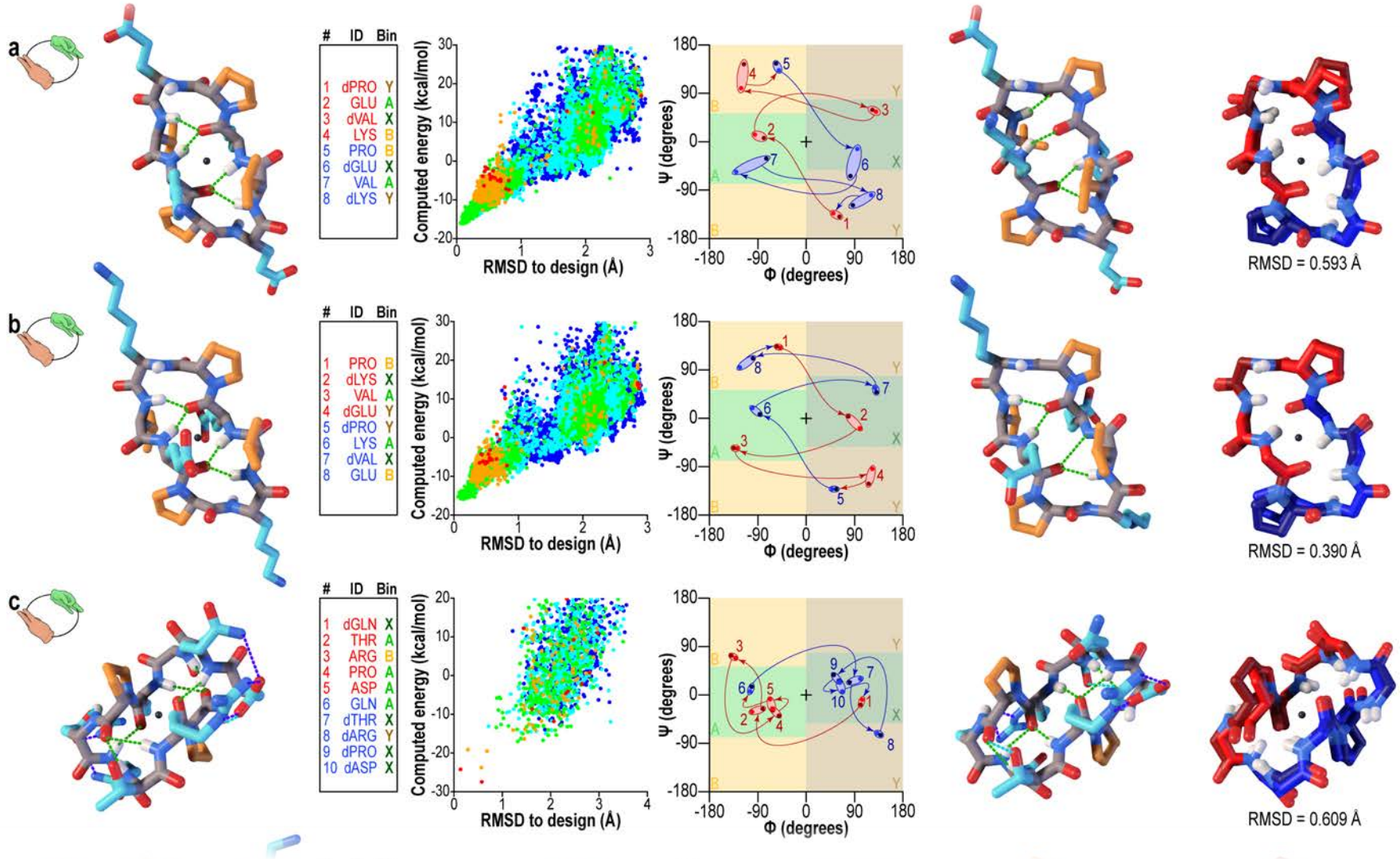
Successes of the Rosetta software suite



The generalized pipeline for *de novo* design of synthetic heteropolymers

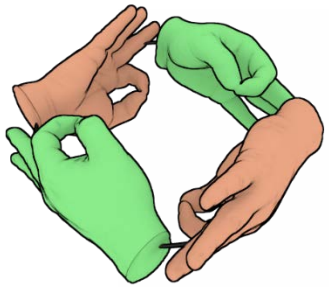


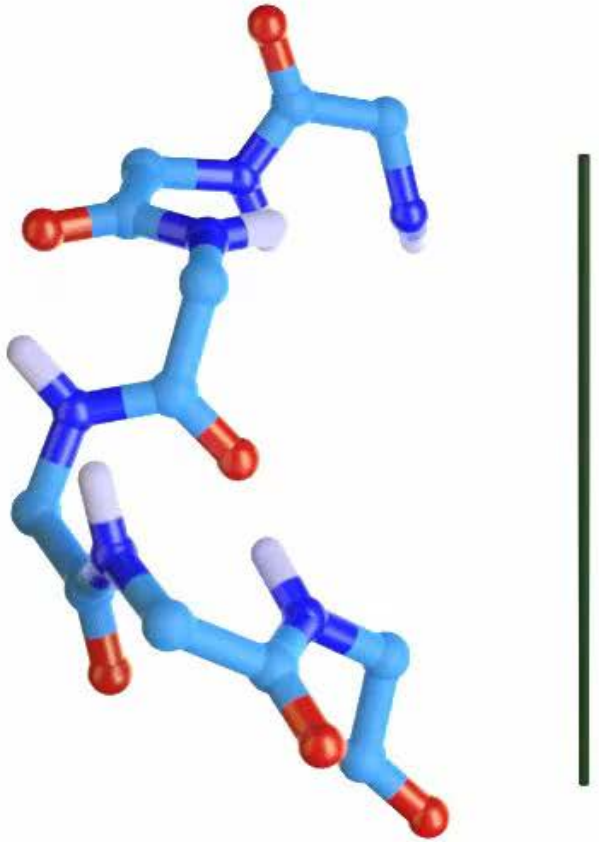
Designing folding peptide macrocycles with internal symmetries



With Christine Kang, Stephen Rettie, Xinting Li, and Tim Craven

Using S4 symmetry to design for metal binding





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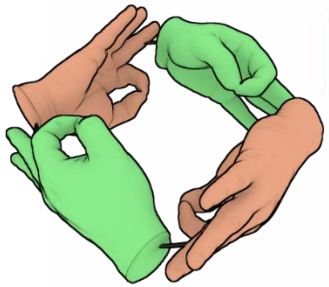
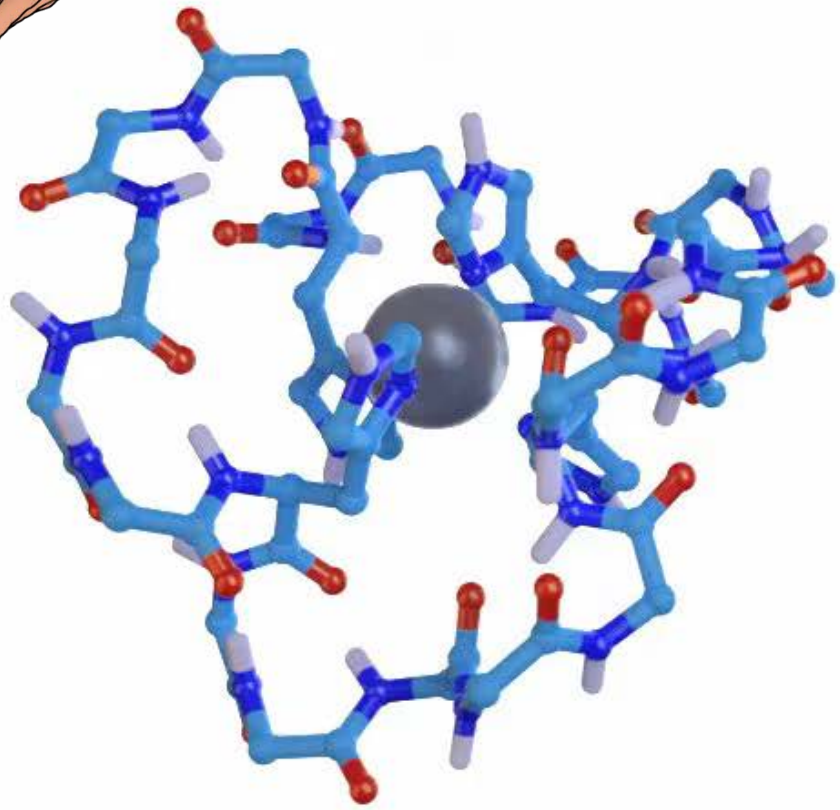
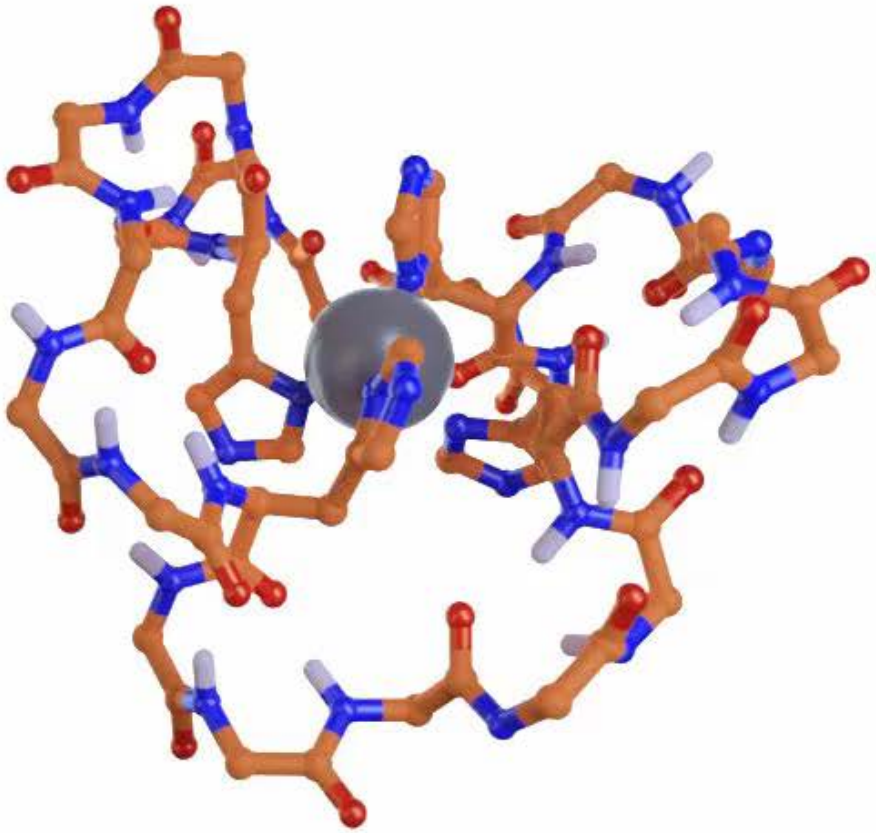


Design model

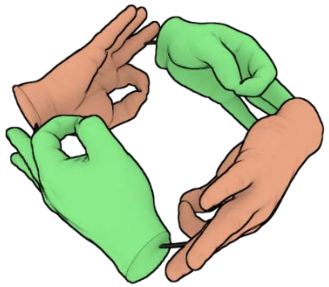


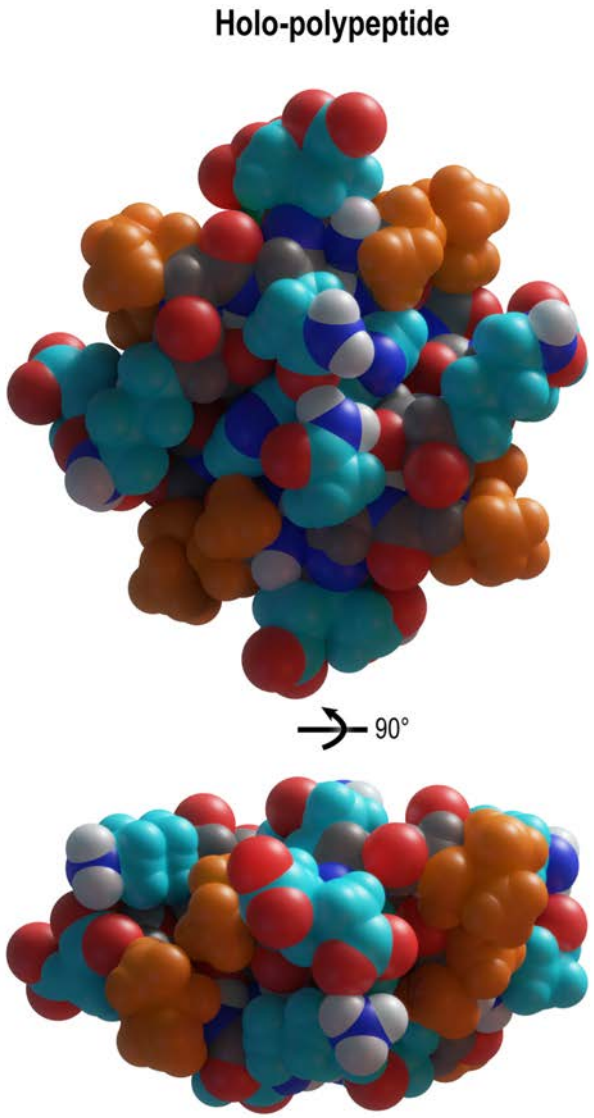
Crystal structure



In collaboration with Michael Sawaya, Inna Pashkov, and Todd Yeates.

A metal-induced conformational switch





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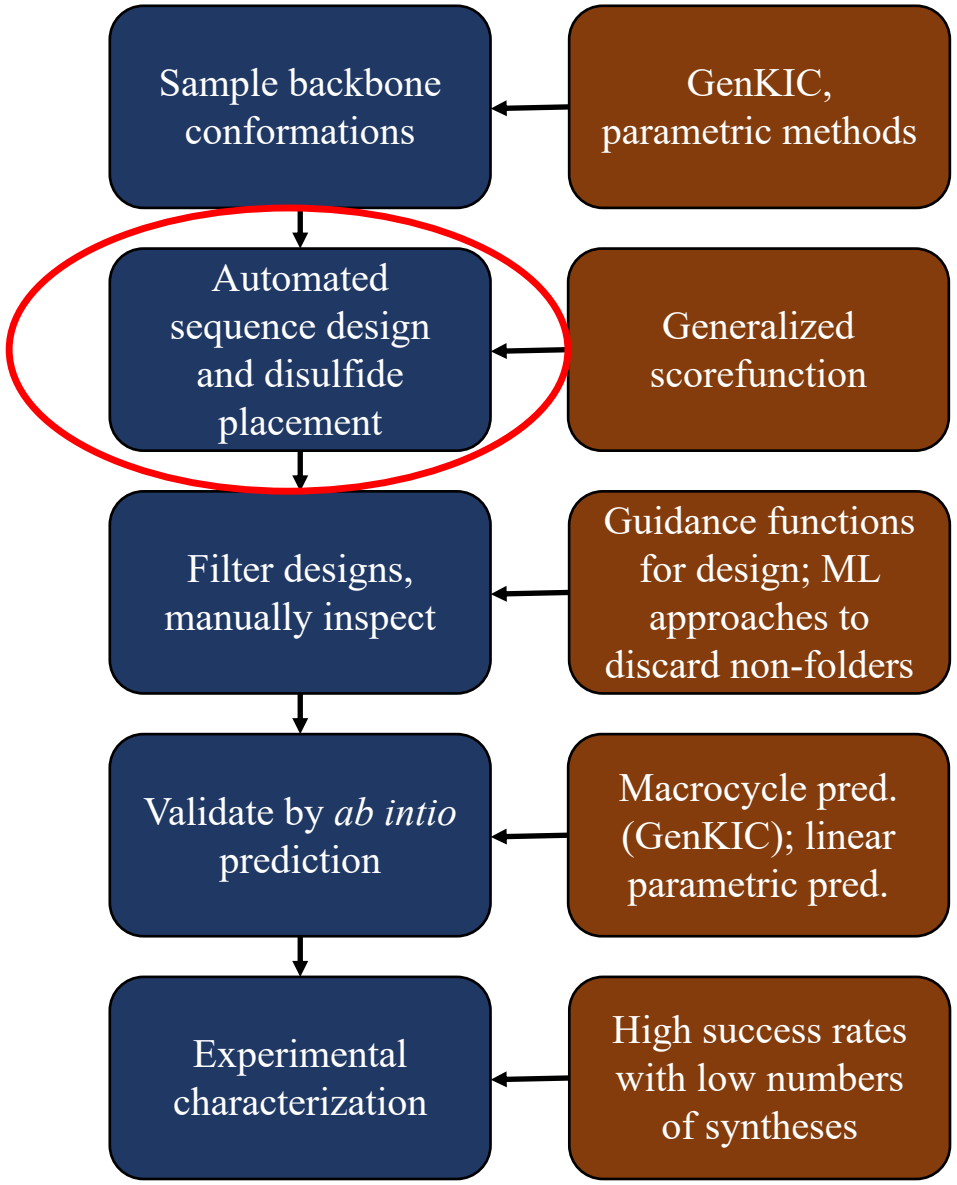
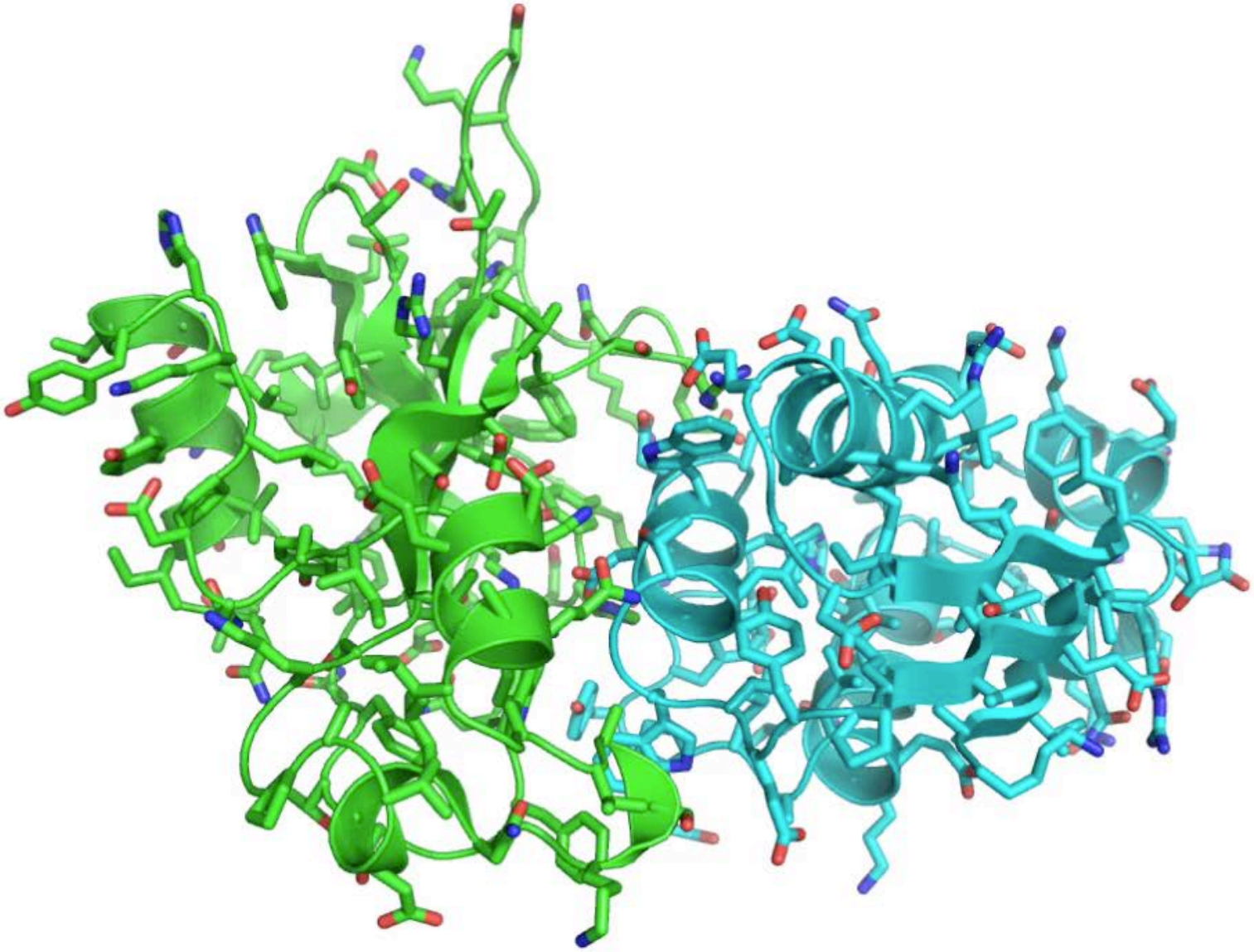
The generalized pipeline for *de novo* design of synthetic heteropolymers

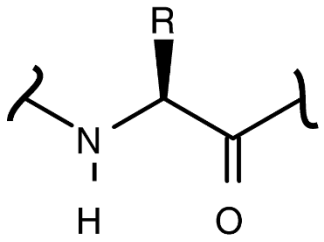


Designing an amino acid sequence to stabilize a given backbone conformation: The classical Rosetta packer

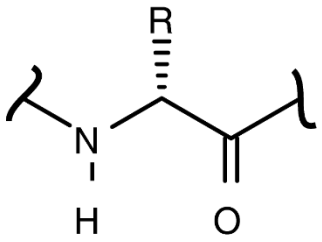


- Packing and design problems come in a very broad range of sizes.
- Symmetry can simplify a packing or design problem.
- Synthetic molecules are often smaller (fewer positions), but have more possibilities for the rotamer at each position.

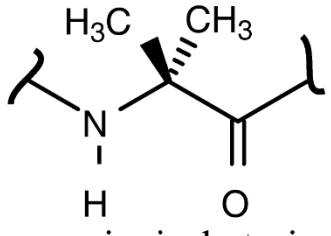
Additional building blocks from which heteropolymers may be synthesized



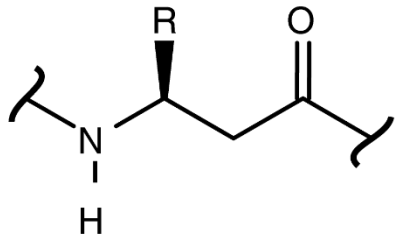
L-α-amino acid



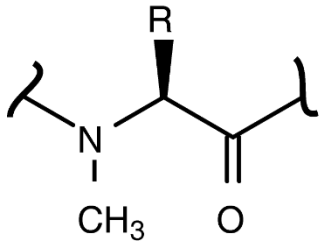
D-α-amino acid



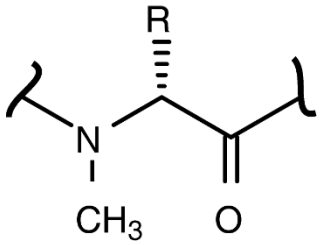
α-aminoisobutyric acid (AIB)



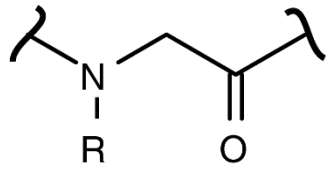
β-3-amino acid



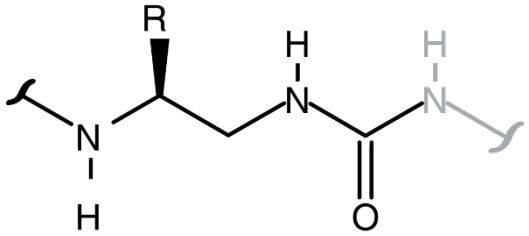
L-α-N-methyl-amino acid



D-α-N-methyl-amino acid



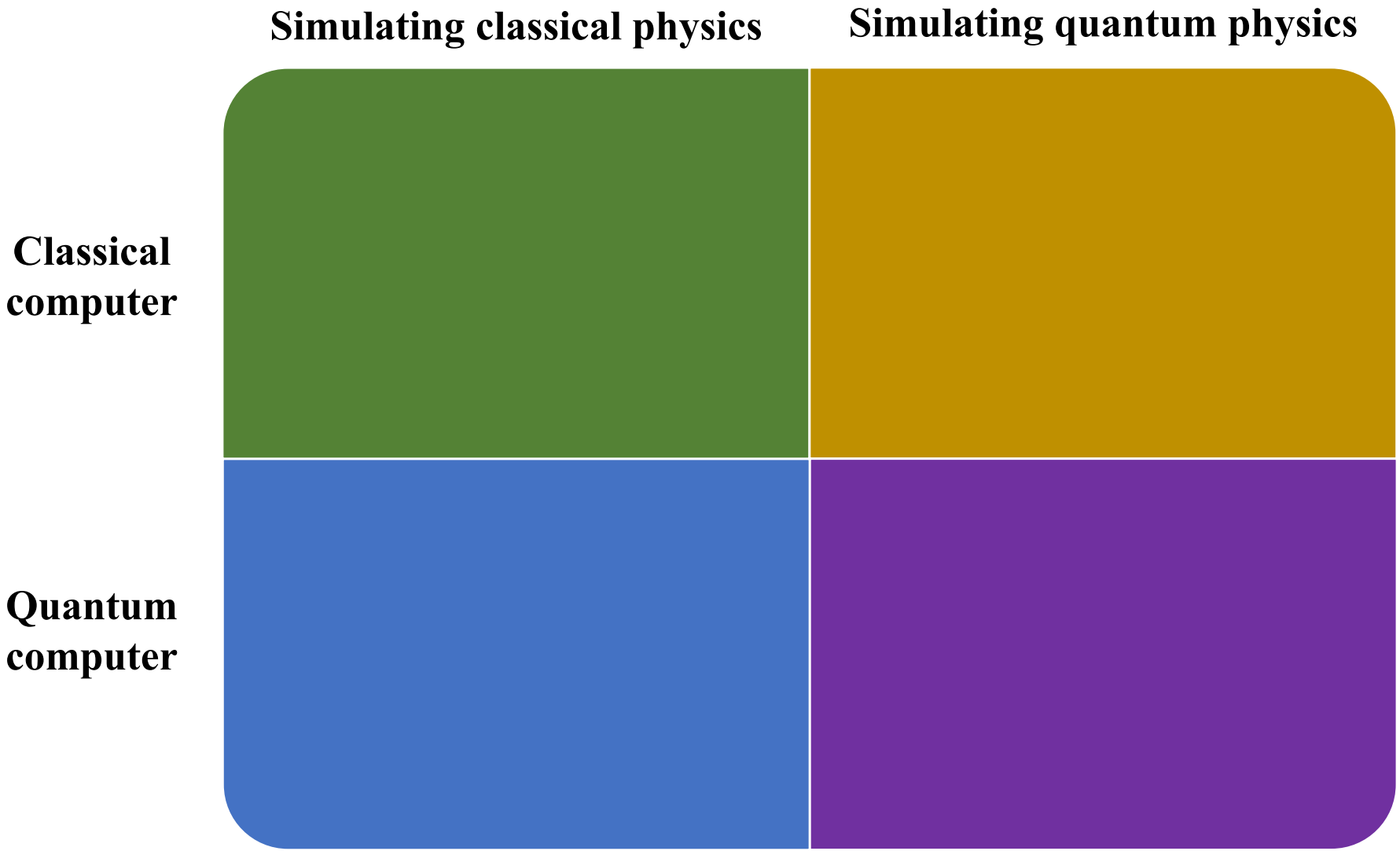
peptoid



oligourea

With Paramjit Arora, Haley Irene Merritt, James Eastwood, Kent Kirschenbaum, and Hans Melo.

How we might use quantum computing for our purposes



Mapping the Rosetta packing algorithm to quantum hardware

$$E_{\vec{S}} = \sum_{i=1}^{N} O(S_i) + \sum_{j=1}^{N-1} \sum_{k=j+1}^{N} T(S_j, S_k)$$

One-body rotamer energies can be precomputed classically in O(N) time.

Two-body rotamer pair energies can be precomputed classically in $O(N^2)$ time (worst-case), and more commonly in O(N) time.

$$f(\vec{s}) = \sum_{i=1}^{n} o_i q_i + \sum_{j=1}^{n-1} \sum_{k=j+1}^{n} t_{j,k} q_j q_k$$

The packing problem can be solved using the quantum computer as a specialized co-processor *only* for annealing

- Handle complex molecular modelling
- Precompute pairwise interaction energies / other precomputed values

*The goal is **not** to show a speed advantage today.*

*The goal is to show that this problem **can** be solved on the quantum hardware without simplifying the problem, with the same accuracy as the classical annealer.*

The side benefit is the discovery of better-scaling classical algorithms for solving these problems!

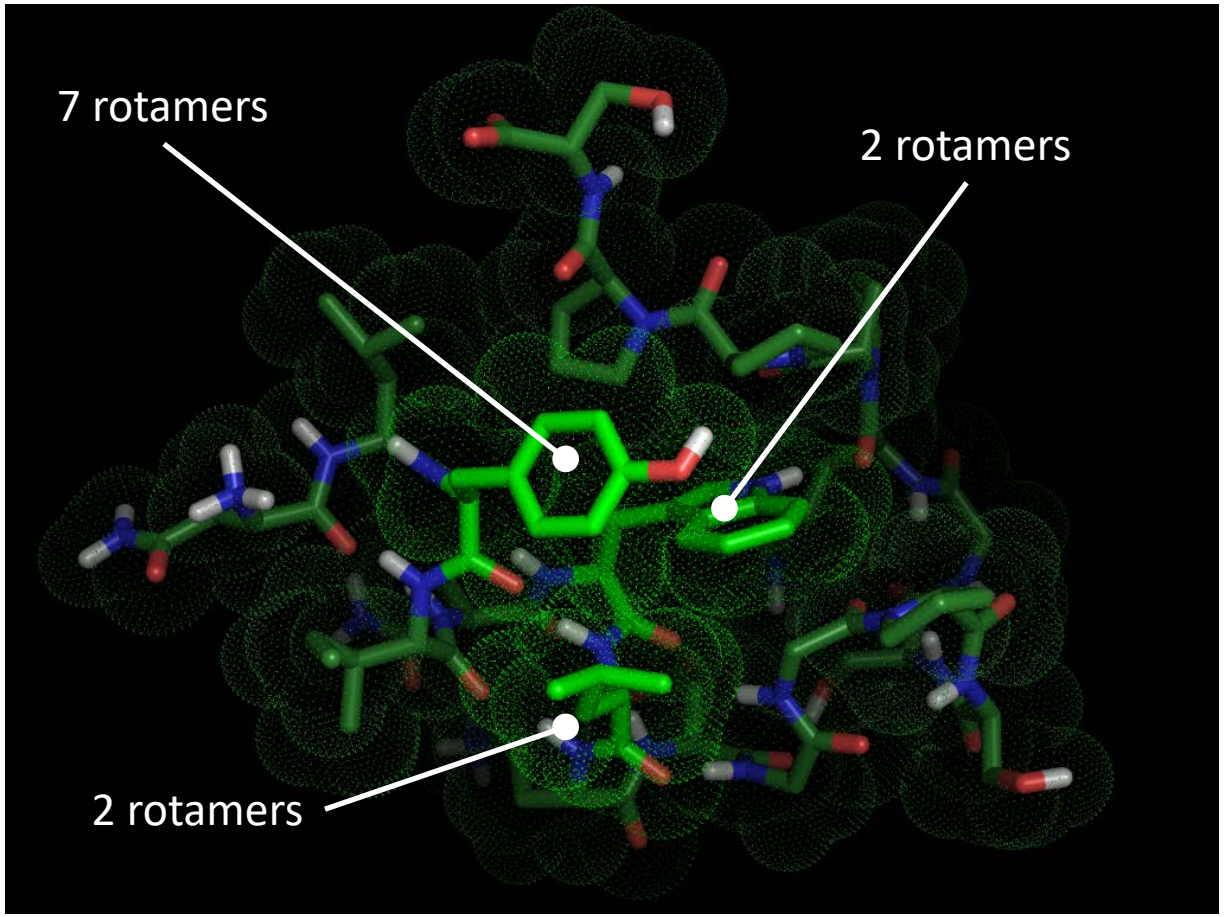
*Given a working quantum packing algorithm, the scaling is such that there **will** be a quantum performance advantage as the hardware grows.*

Classical computer

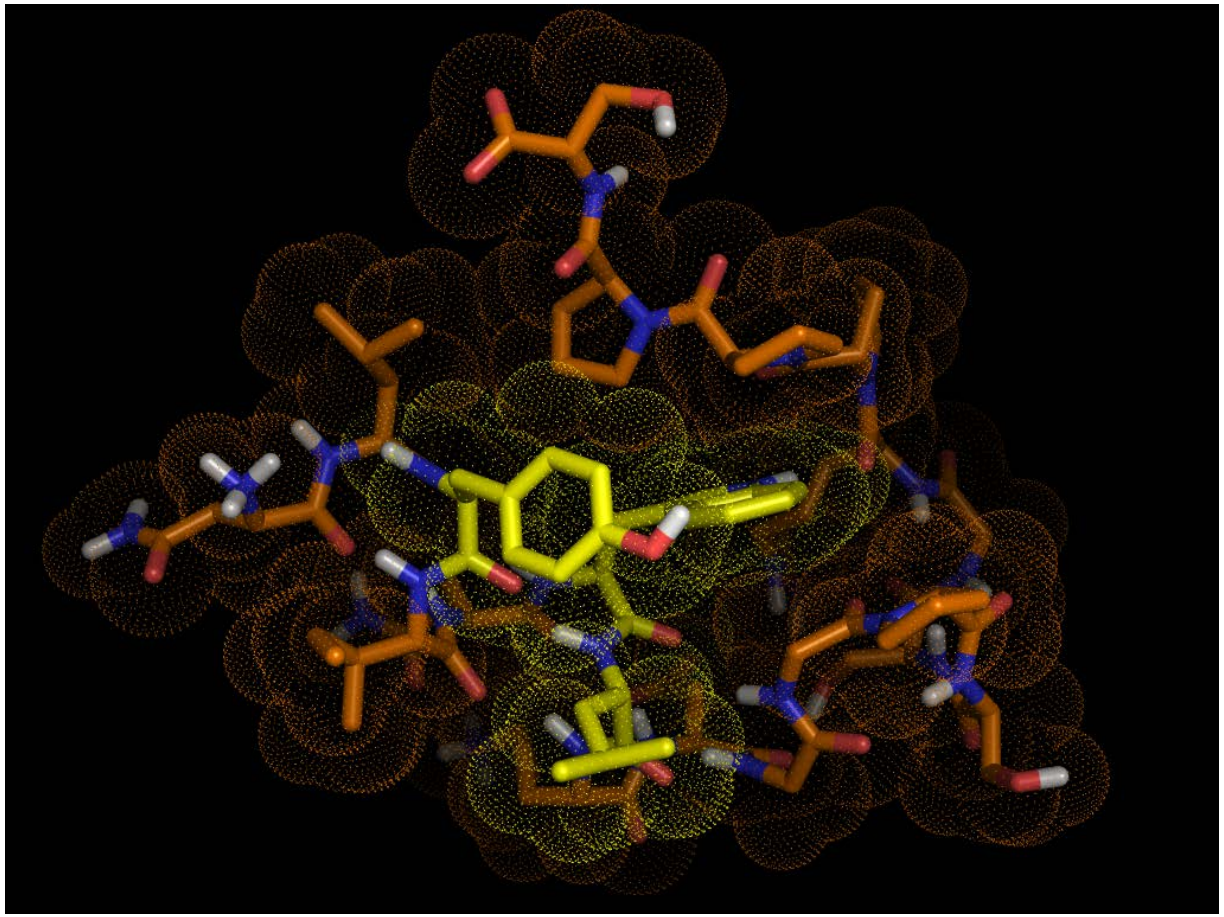
- Convert minimal output from quantum computer into full-atom solution structure
- Rank designs produced
- Visualize to select designs for synthesis and experimental validation

With Hans Melo.

Packing the Trp cage mini-protein with on the D-Wave hardware, using the Rosetta energy function



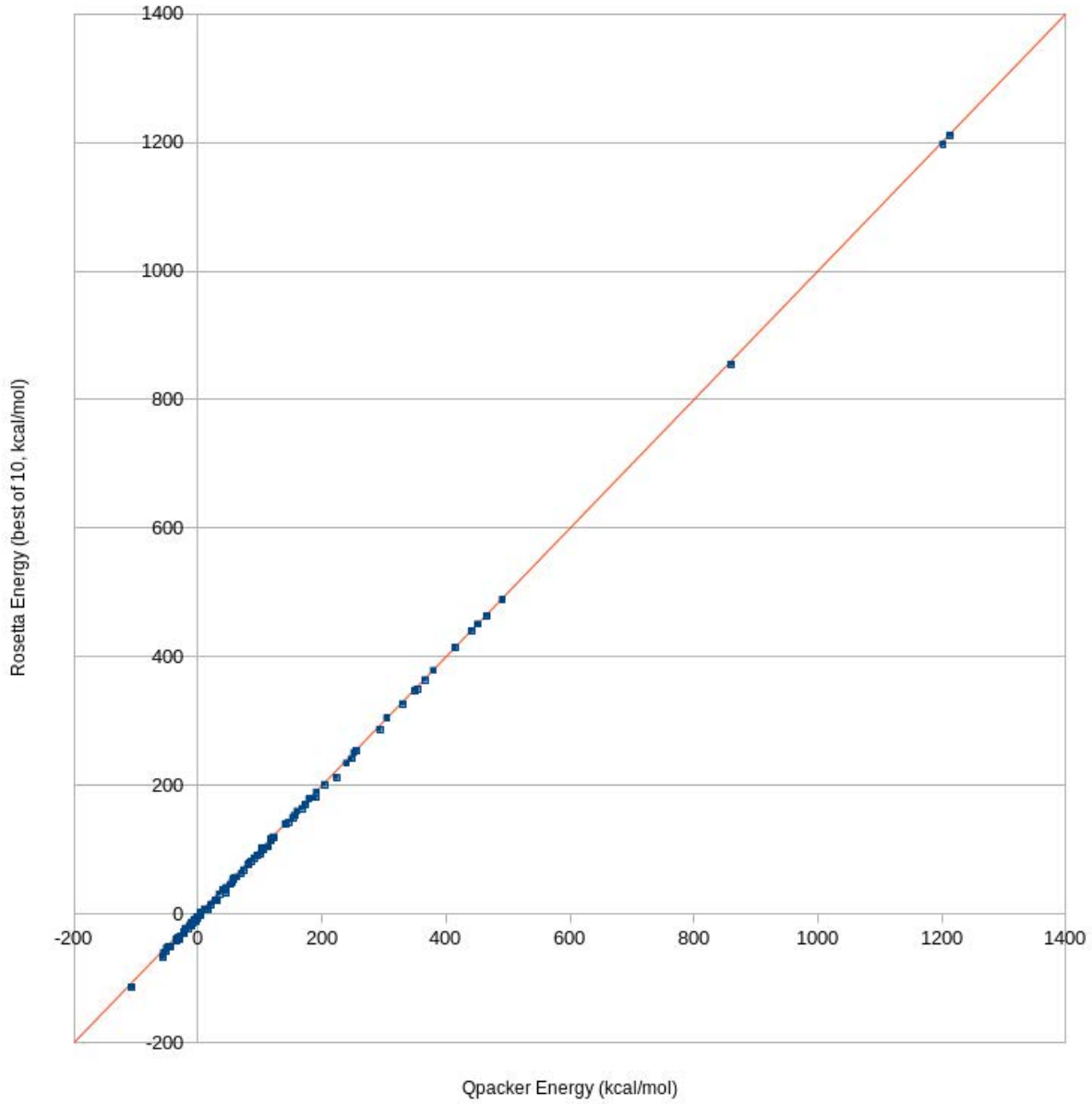
Trp cage mini-protein (PDB ID 1L2Y)
This simple 3-residue packing problem has 28 solutions.



Solution found by D-Wave.
(Note: exact native rotamers were not provided to the D-Wave. This solution is optimal, of the 28 possible.)

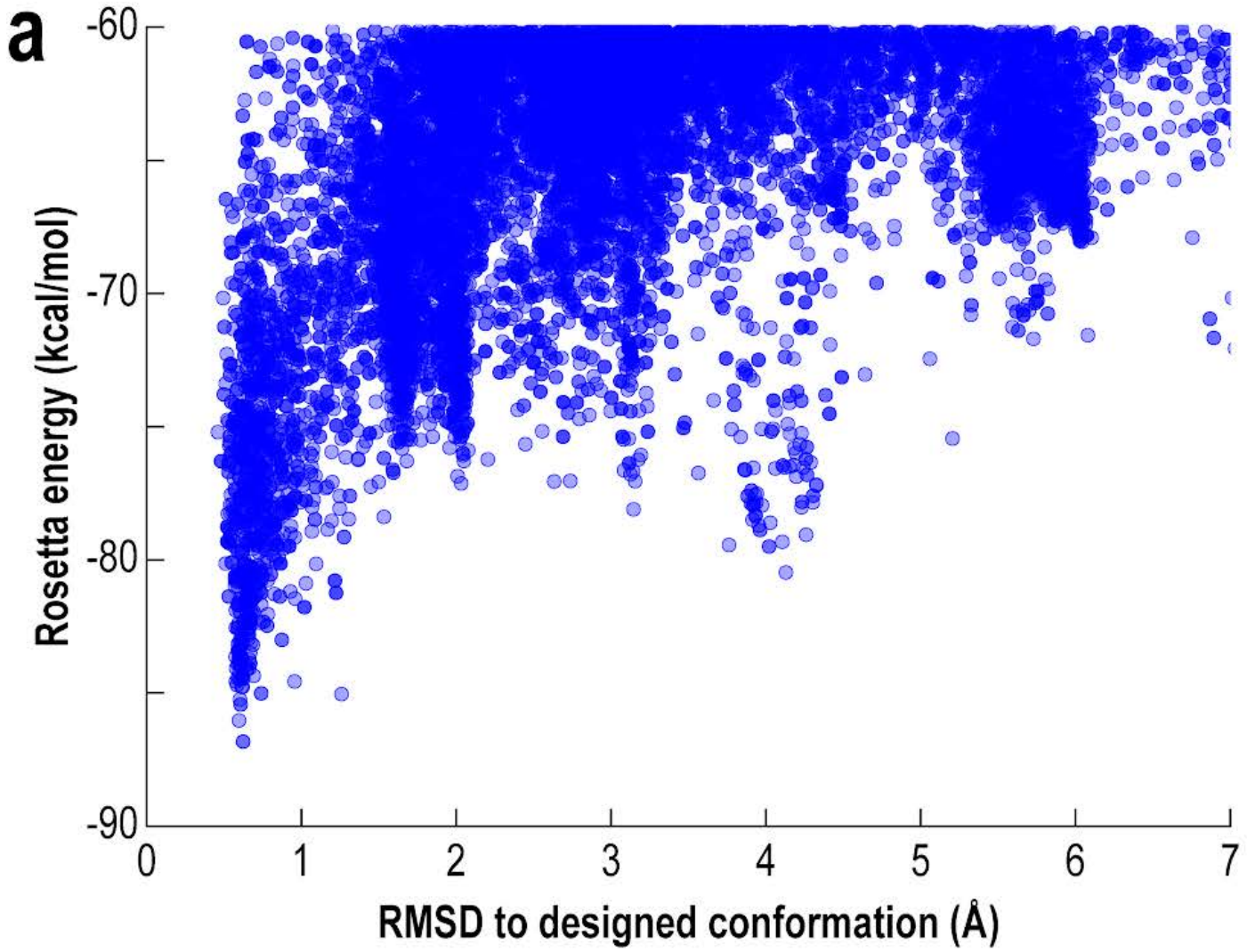
With Hans Melo.

Scaling to larger problems: Comparison of the accuracy of the QPacker



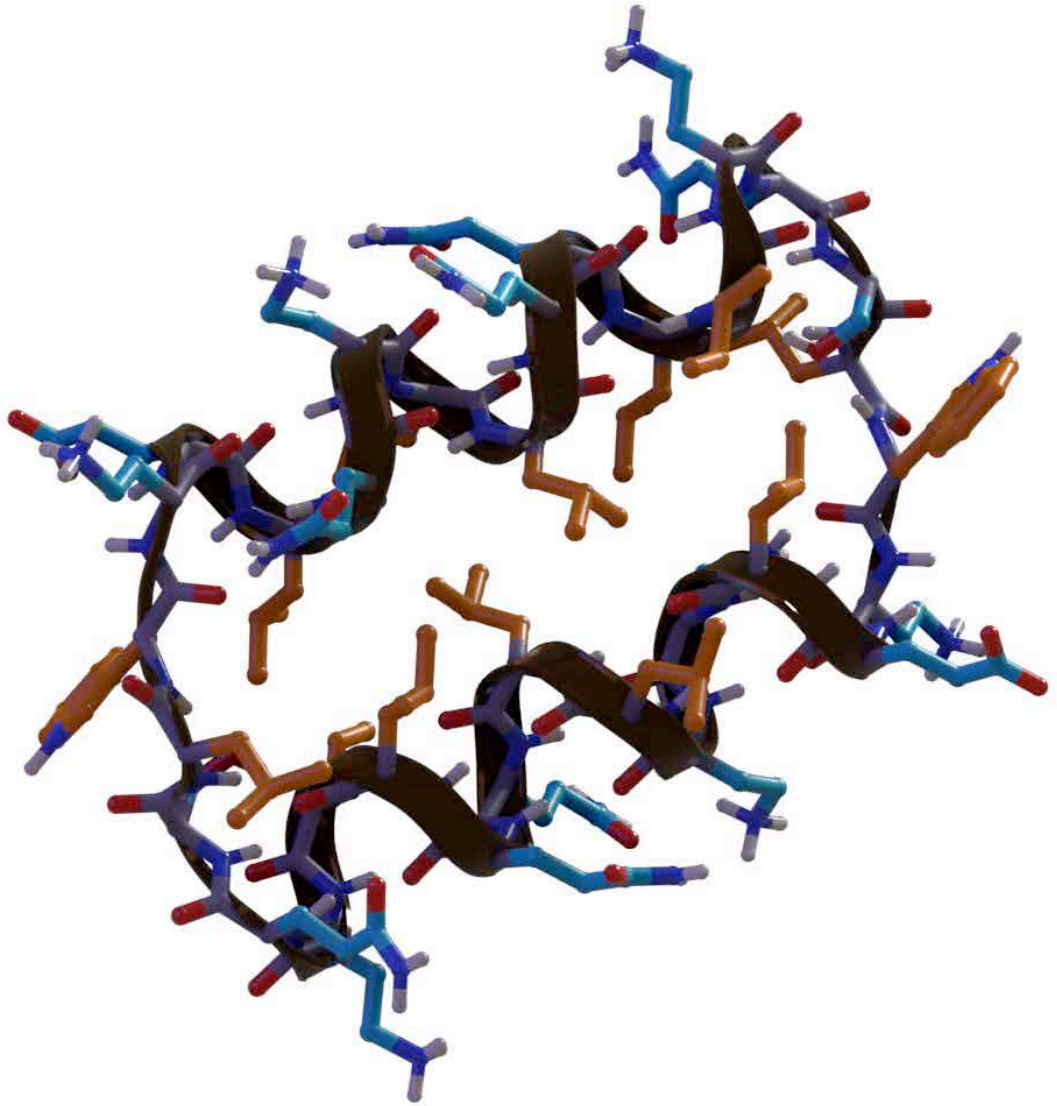
With Hans Melo.

Examining the energy *gap* between designed and alternative conformations



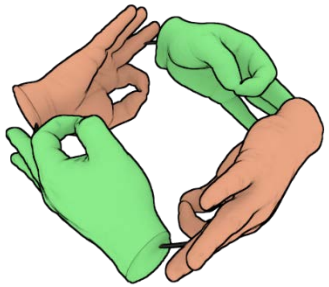
$$P_{near} = \frac{\sum_{i=1}^{N} e^{\frac{-RMSD_i^2}{\lambda^2}} e^{-\frac{E_i}{k_B T}}}{\sum_{j=1}^{N} e^{-\frac{E_j}{k_B T}}}$$

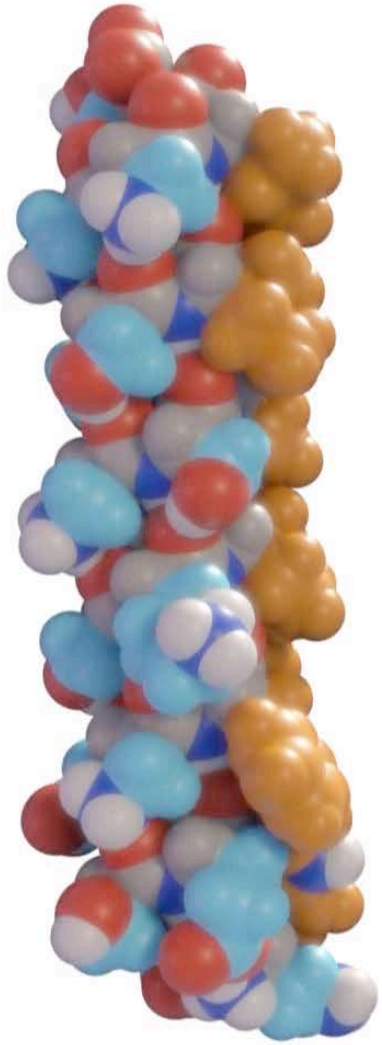
Designing polypeptide macrocycles with QBSolv and the D-Wave 2000Q



With Parmjit Arora, Haley Irene Merritt, and Hans Melo.

Designing heterochiral helical bundles with QBSolv and the D-Wave 2000Q





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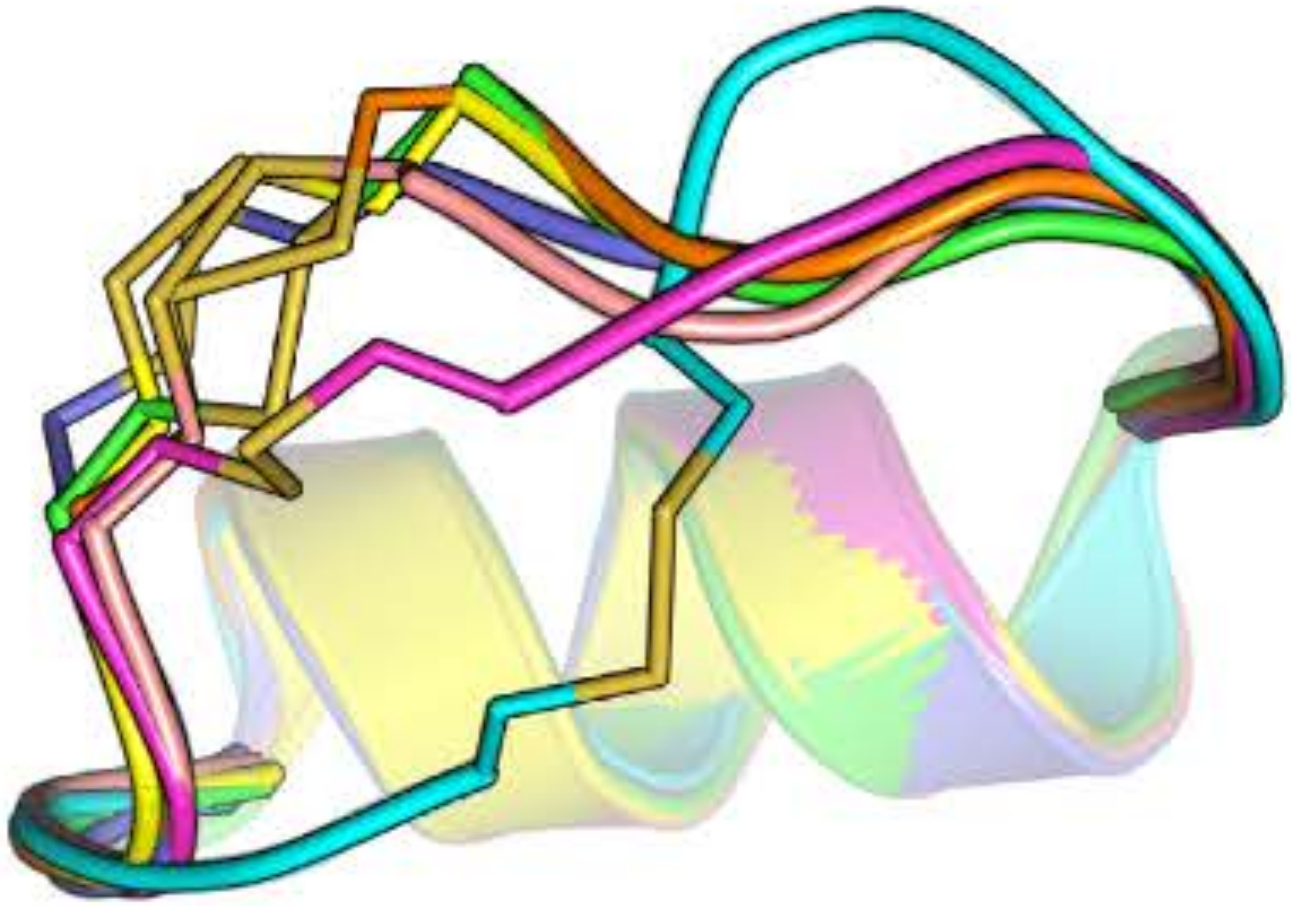
Long-range goals: The conformational problem



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Acknowledgements

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Innovative and Novel
Computational Impact on Theory
and Experiment (INCITE) program

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