

**Title:**

A robust and versatile computational peptide design pipeline to inform wet-lab experiments

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**Abstract:**

Since Merrifield's development of solid-phase peptide synthesis, we have seen explosive growth in the number of synthetic building-blocks that can be incorporated into peptides. This has created a problem: the number of possible molecules that could be synthesized is many orders of magnitude greater than the largest conceivable combinatorial libraries. Computational design, based on combinatorial optimization algorithms, addresses this problem by proposing sequences likely to have desired folds and functions. These computational methods complement experiments by reducing astronomically large numbers of combinatorial possibilities to experimentally tractable shortlists. This presentation describes our robust, versatile methods, made available to peptide scientists in the Rosetta and Masala software suites, for designing peptides that fold into rigid conformations. Our physics-based methods generalize to exotic chemical building blocks poorly amenable to machine learning-based methods for want of training data. Our pipeline has produced experimentally-validated mixed-chirality peptides that bind to targets of therapeutic interest, and peptides that diffuse across cell membranes. Ongoing research is mapping the sequence optimization problem (which grows intractable even for supercomputers as the number of candidate chemical building blocks grows very large) to current and near-future quantum computers, allowing use of quantum algorithms in the context of the existing, widely-used design protocols.