The Development of Computational Methods for the Design and Identification of Therapeutic Proteins

4:00 P.M. on Tuesday, November 5, 2019

Robert Pantazes is an assistant professor in the department of chemical engineering at Auburn University. He is currently developing and experimentally verifying computational methods to design and identify therapeutic proteins. He completed his PhD at Penn State University in 2014 under the supervision of Costas Maranas, where he developed computational methods for designing antibodies. From 2014 to 2016, he did an experimental postdoc at the University of California – Santa Barbara, where he worked with Patrick Daugherty on identifying biomarkers for autoimmune diseases. After the postdoc, he was briefly a Scientist at Serimmune, Inc. before joining Auburn University in August, 2016.

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Proteins have a broad range of applications, with uses in diverse fields such as medicine, materials and chemical production. Recent years have seen an ever-growing number of computationally designed proteins with experimentally verified structures. Some of the results are extraordinarily stable, remaining folded at 95 °C and 7 M guanidine hydrochloride, thus demonstrating a rapidly increasing understanding of the rules governing protein structures. Although these successes are significant, limitations remain. Exceedingly few proteins designed entirely with computational methods have functions that are comparable to naturally occurring proteins. In addition, the computational algorithms used to design proteins require access to high-performance computing resources, long run times, and an expert-level understanding of the relevant techniques. Although the computational design of proteins continues to improve, these factors have limited its effectiveness.

Antibodies and other binding proteins are promising candidates to target for the development of design methods that achieve native levels of function and reduce the computational burden of design. Their structures are well-understood and their functions are governed by modular loops that are known to be interchangeable with one another. This allows for the development of curated databases that can design such proteins in a combinatorial manner. Recently, our group has demonstrated that binding energies in these proteins are dominated by relatively few amino acids; on average, 5-6 residues contribute 70-80% of the binding energy. In light of this finding, we have developed algorithms that design binding proteins by 1) positioning amino acids around an epitope so that they have energetically optimal interactions and then 2) identifying binding loops and scaffolds that are compatible with the optimal positions. Using this workflow, we have *de novo* designed numerous binding proteins in as littles as a few minutes on personal computers. This talk will describe the rationale behind these algorithms, the details of their implementation, the computational benchmarking of the designs, and our plans for ongoing experimental validation.