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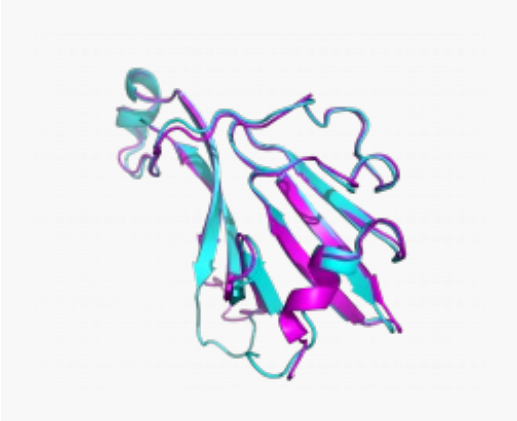
Consortium Led by IBBR Fellow John Moult Fosters Advances in Protein Structure Prediction

January 19, 2021 - Reports from the recent 14th Critical Assessment of Structure Prediction (CASP) community experiment show substantial progress in computing the structure of protein molecules. The three-dimensional structure of proteins provides key insights into understanding many aspects of their function, including disease mechanisms, the effect of genetic mutations, and facilitates the development of new therapeutics and vaccines. IBBR Fellow. Dr. John Moult is CASP Co-Founder and Organizing Committee Chair for this large community experiment.



Part of a plant virus glycoprotein. Computed structure blue, experiment magenta

Building upon prior CASP challenges where deep learning methods enhanced protein structure predictions relative to experimental findings, results reported at the winter CASP conference show that Artificial Intelligence (AI) methods predict protein structures with accuracy rivaling those determined experimentally. Understanding of protein function and interactions with other biological molecules is greatly enriched by knowledge of protein structure. Each protein is composed of a sequence of amino acids. In many cases, the amino acid sequence is known, but the three-dimensional structure, including how the protein folds and composition of binding surfaces for other molecules is unknown. The sequence contains the information determining the structure, so that in principle the structure can be computed, but this has been challenging in practice over a 50-year history of work on the problem.

CASP is a community experiment formed with the goal of accelerating progress in solving the problem of protein structure prediction by maximizing collaboration, communication, rigor, and transparency. The experiment addresses critical challenges in protein modeling, including determining the structure of single proteins and multi-

protein assemblies, residue contacts between amino acids in the 3D-structure, and the accuracy of the computed structures. CASP has seen a series of breakthroughs leading to progressively more accurate methods for calculating single protein structures. About 100 research groups across the world participated in the 14th CASP challenge. Participants submit computationally-derived structure models from amino acid sequences for cases where the experimental structures are not yet available. Independent assessors then compare models with new experimental data for those proteins. The assessment determined that the company DeepMind has developed methods that yield structures of similar accuracy to the experimental methods in many cases.

These new findings will aid in providing a means of generating higher accuracy models for proteins, and be applied to enhancing the speed of experimental structure determinations. In the future this could advance understanding of protein-protein interactions, development of new drugs as well as repurposing old ones, and improve methods for designing new proteins.
