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Title: Integrative Structure Modeling in the Age of Deep Learning: Overcoming Challenges in Modeling Antibody-Antigen Complexes and Large Complex Assemblies

Abstract:
Integrative structure modeling is often used to characterize structures and dynamics of large macromolecular assemblies by combining various types of input information. To construct the assemblies, individual proteins or domains are represented by either atomic structures or low-resolution sphere models. This information is combined with data from sources such as cross-linking mass spectrometry, cryo-electron microscopy, and small-angle x-ray scattering. Recent progress in protein folding enabled by deep learning by AlphaFold2 and RosettaFold have improved structural coverage for domains, and even protein-protein interactions, which are essential inputs for integrative structure modeling. However, these methods depend on multiple sequence alignment (MSA), that is not available for immune response complexes, such as antibody-antigen interactions. Another challenge is the size limit of modeled assemblies. Our research addresses these limitations by developing deep learning models that accurately model immune response complexes, including antibody-antigen and peptide-MHC interactions, without the need for MSA. Additionally, we are working on algorithms for integrative modeling of large complex assemblies, incorporating cross-linking mass spectrometry data, subunit models, and pairwise subunit-subunit interaction models predicted by AlphaFold2.