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High-Resolution *in silico* Protein Structure Prediction and Docking

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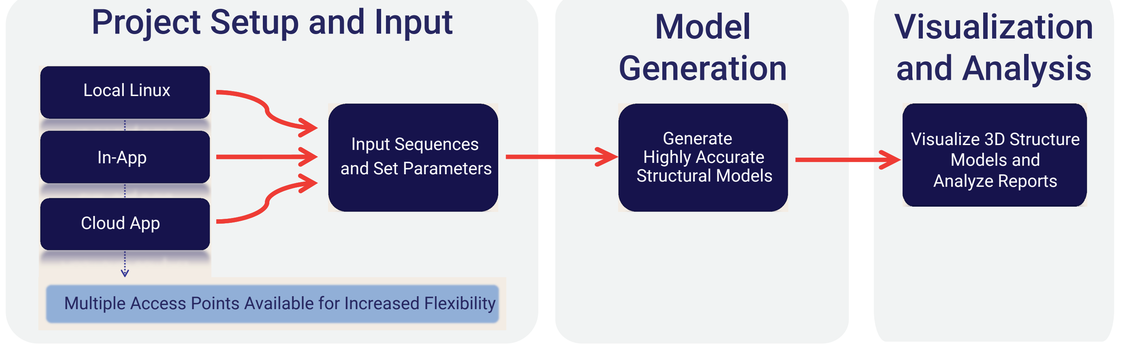
Abstract

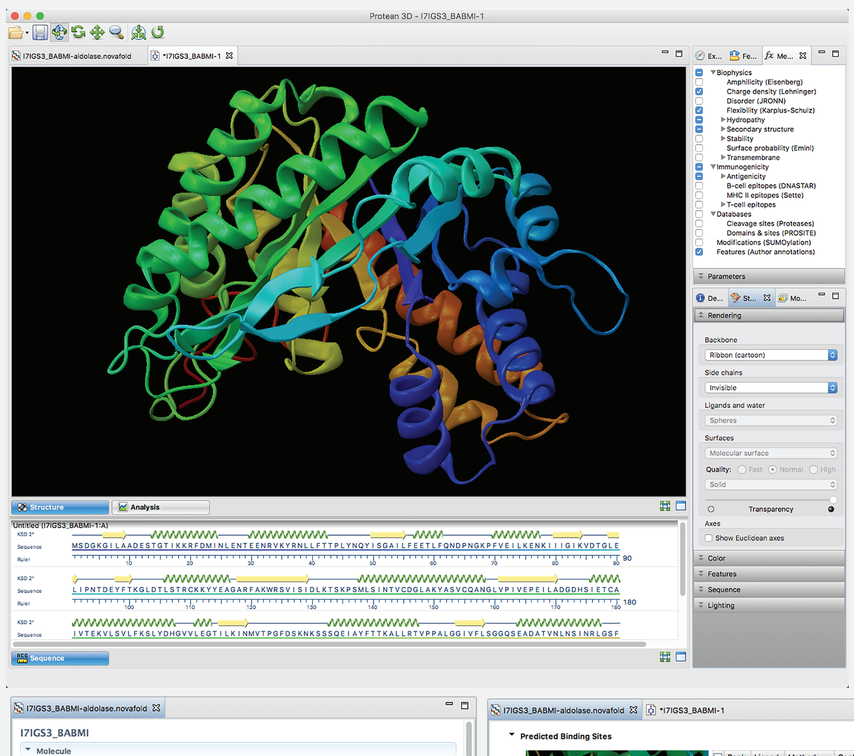
DNASTAR's new Nova applications allow researchers to generate highly accurate structural models of both proteins and protein-protein complexes that are unattainable through standard modeling methodologies. (1) NovaFold is a protein structure prediction program that utilizes the award-winning I-TASSER algorithm, which combines threading and ab initio techniques to build accurate, full 3D atomic models of proteins with previously unknown structures. (2) NovaFold Antibody is specifically designed to generate models of antibodies and antibody fragments by combining homology modeling for frameworks and ab initio loop prediction. (3) NovaDock is a high-resolution protein-protein docking application that explores flexibility during the modeling process through a particle swarm optimization process encoded by the SwarmDock algorithm. The Nova applications are integrated into the DNASTAR Lasergene Suite, which provides access to a 3D viewer to analyze the resulting models and reports in Protean 3D.



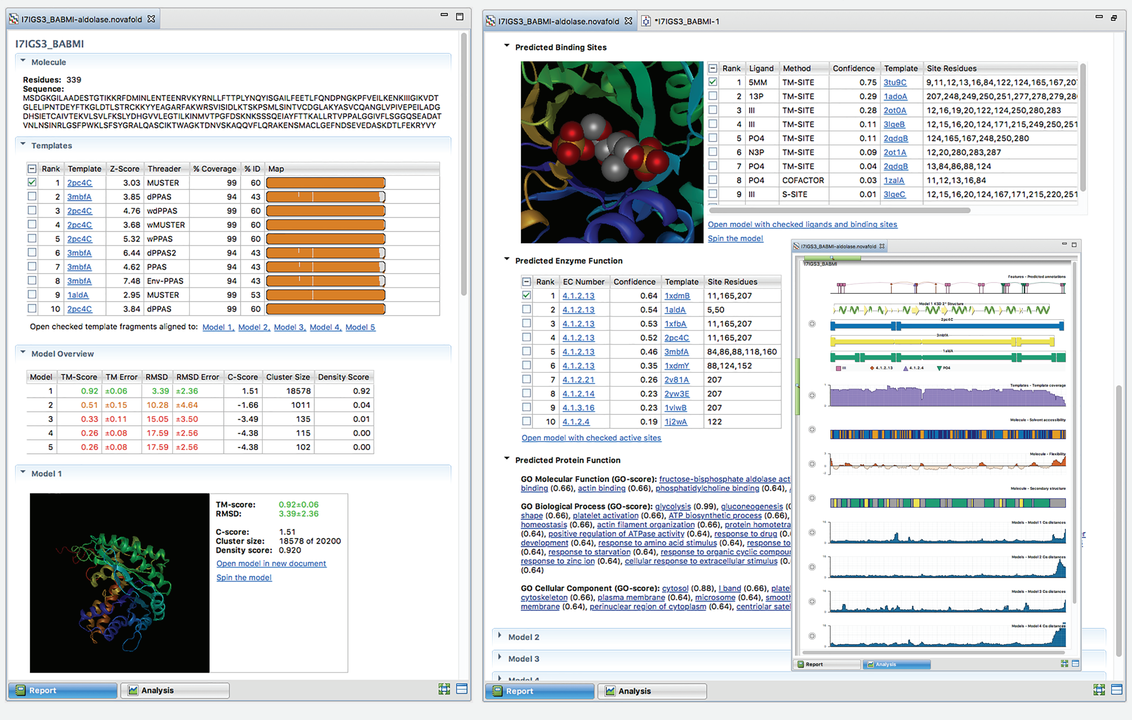
Lasergene Structural Biology Suite allows users to access the Nova applications locally on a Linux workstation, on the Amazon Cloud as an add-on to Protean 3D, or on the Cloud through a web application. Following model generation, the protein structures and reports can be viewed and analyzed in the Protean 3D molecular viewer.

Accurate Protein Structure Prediction

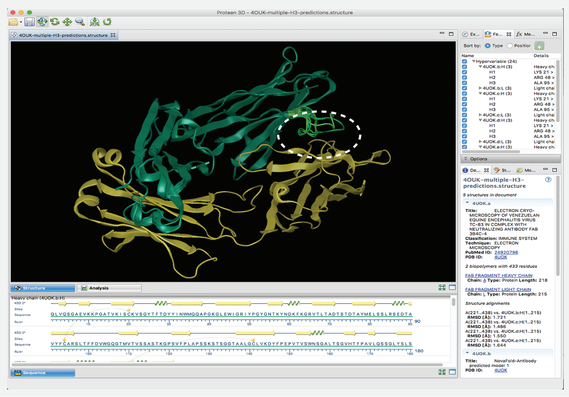
The foundation of NovaFold is the I-TASSER hybrid prediction algorithm, which yields the most accurate protein structural models (up to 2,000 residues). Predictive methods are also applied during NovaFold's automated process that identify potential ligand binding sites and protein functions. From the final report, users can assess model quality through global and local confidence scores, structural and sequence alignments, and apply analysis methods to explore the biophysical properties of the structure.



NovaFold was used to generate accurate structural models of a putative drug target from Babesia microti, Aldolase. The example here demonstrates that predictions of high confidence are achievable using templates of low to moderate sequence identity.
Top: Highly accurate model (TM-score 0.92, RMSD: 3.4Å) of Aldolase displayed in Protean 3D. Lower Left: Sequence alignment of Aldolase to templates used for structure prediction and threader details.
Lower Middle: NovaFold predicted ligand binding sites and functions and connectivity to AmiGO site.
Lower Right: Synchronized view of several biophysical methods applied to the sequence.



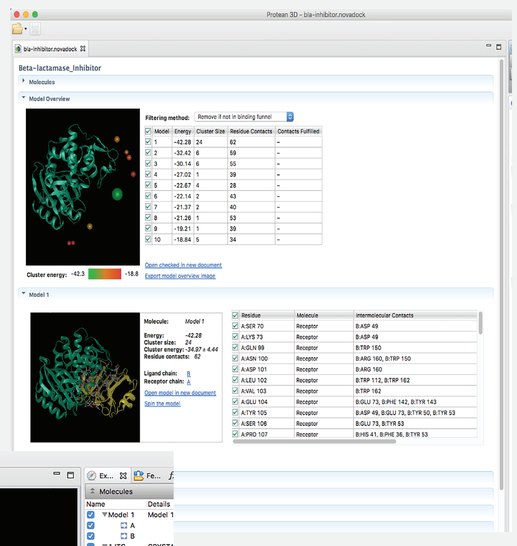
Antibody Models in Minutes

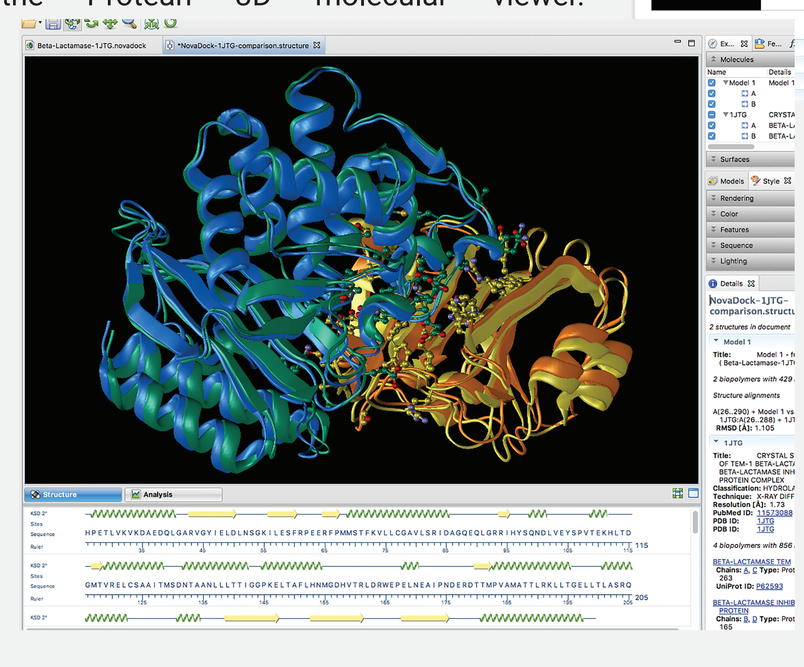


Using a curated library of antibody frameworks or your own custom templates, NovaFold Antibody builds structural models of antibodies and antibody fragments. Ab initio modeling is used for H3 hypervariable loops, and CDR regions are auto-annotated for user's convenience.
NovaFold Antibody was used to generate four distinct models of a human anti-VEEV antibody. The ensemble of hypervariable H3 loop conformations is highlighted.

High-Resolution Protein Docking

NovaDock accurately predicts the flexible binding interface of two binding partners, and generates an efficient report displaying potential binding poses. In the NovaDock report, users are able to evaluate energy scores, cluster sizes, observable ligand contacts, and alternate docking conformations for each model. From this interactive view, users can easily identify interfacial residues and create new documents to interrogate the model with the Protean 3D molecular viewer.





NovaDock was used to generate a near-perfect structural model (RMSD: 1.27Å) when compared to the co-crystal x-ray structure of the E. coli TEMP-1 beta lactamase and beta lactamase inhibitor protein II complex (PDB ID: 1JTG). No structural templates or prior knowledge were used in the docking simulations.
Top: The results overview with interfacial contact residues identified.
Bottom: Structural alignment of the model (green and yellow) against the 1JTG x-ray co-crystal structure (blue and orange).

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