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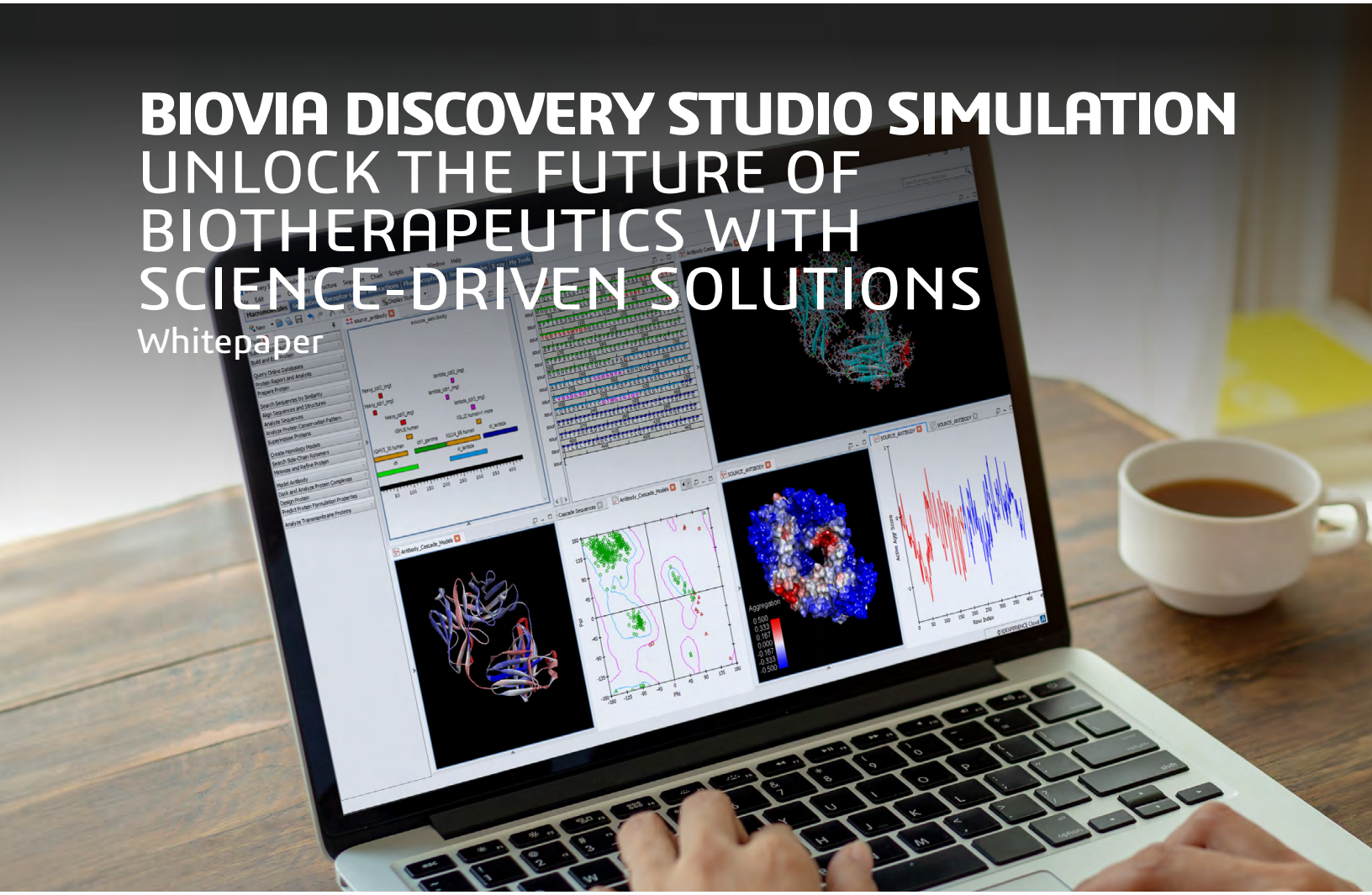
BIOVIA DISCOVERY STUDIO SIMULATION

UNLOCK THE FUTURE OF BIOTHERAPEUTICS WITH SCIENCE-DRIVEN SOLUTIONS

Whitepaper



In silico tools streamline biotherapeutics development by helping quickly identify high-quality novel candidates with desirable efficacy and safety profiles. Computational methods, such as homology modeling, molecular docking, molecular dynamics simulations, and mutation energy predictions, allow researchers to design and optimize candidates i*n silico* before moving on to expensive lab testing. Incorporation of these tools into existing workflows is crucial for modern drug discovery projects and saves countless hours of research and thousands of dollars in R&D costs.

BIOVIA Discovery Studio Simulation is a market-leading, cloud-native solution for biotherapeutics design and optimization that combines an extensive suite of advanced, state-of-the-art physics-based methods with cutting-edge AI and machine learning models in a single environment. With **BIOVIA Discovery Studio Simulation**, researchers can focus on candidates most likely to succeed in clinical trials, reducing time to market and saving valuable resources in laborious biotherapeutics discovery research.

DASSAULT SYSTEMES

With refinement, the CDRs can be annotated using IMGT, Chothia, Kabat, or Honegger nomenclature conventions. Discovery Studio Simulation also includes a disulfide bond prediction algorithm that can be used to refine and improve the stability of a structure. (Figure 3)

Figure 3. Annotated aligned sequences are colored by light and heavy chain domains and CDR regions.

SIMULATIONS

After assembling an initial 3D model, MD simulations can help refine the overall structure generated by AI or homology modeling. They can help predict the behavior of a protein in various environments, such as in explicit solvents and lipid membranes (Figure 4), or in the presence of other molecules. Simulations can help predict the effects of perturbations to biological systems, such as mutations or changes to the pH of the solutions they are in. Simulations can also improve other processes such as antibody-antigen docking outputs.

In **Discovery Studio Simulation**, various MD tools are available depending on the desired insights. Researchers can perform implicit or explicit membrane or solvent-based simulations using CHARMm and explicit solvent MD simulations with NAMD. They can apply the Gaussian accelerated Molecular Dynamics (GaMD) to accelerate the sampling of protein conformations. In addition to the MD simulations, users can perform a hybrid of quantum and classical molecular mechanics (QM-MM) simulations to examine electronic effects in protein-ligand complexes.

PROTEIN-PROTEIN DOCKING

After building the 3D model of a protein, researchers can study if and how it will interact with their target protein of interest. **Discovery Studio Simulation** uses ZDOCK, a rigid-body docking program designed for sampling the conformational space of a protein-protein complex (eg, an antibody-antigen complex).[13] (Figure 5) Because ZDOCK does not depend on knowledge of the binding site, it is a powerful docking tool for initial screening, demonstrating a 70% docking success rate in a validation set of 1,000 protein-protein interactions.[13]

Discovery Studio Simulation incorporates additional scoring tools like ZRANK to augment protein docking and further increase predictive accuracy. Users can also input experimental information that can limit the search space, such as residues that should or should not be a part of the binding interface. The highest-scoring poses can be selected for refinement with the RDOCK workflow, identifying the most energetically favorable candidate complexes. MD simulations can further refine the docking results.

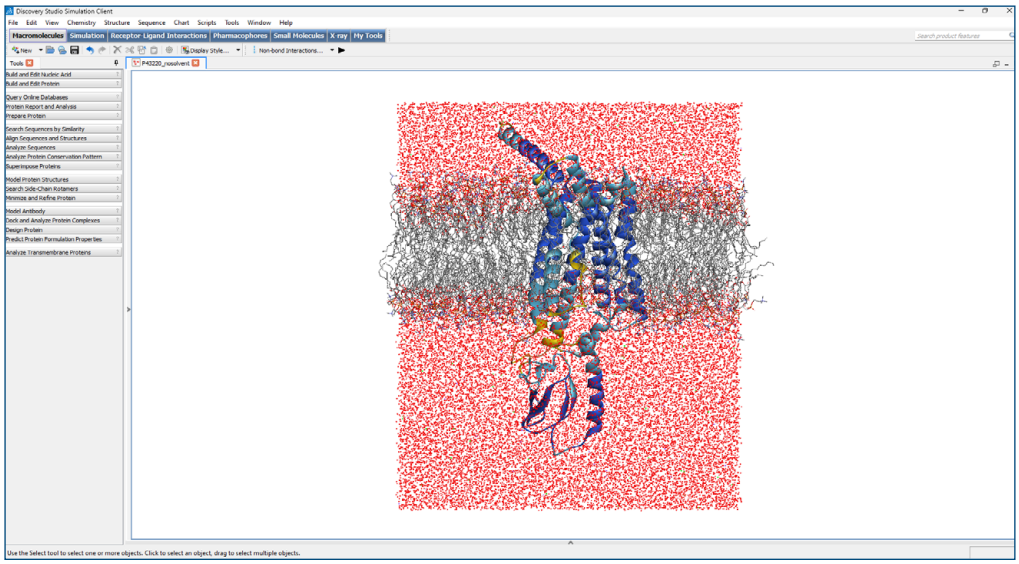


Figure 4. 3D structures derived from OpenFold/AlphaFold2 can be refined with MD simulations. Energy estimations can be calculated communicating the biophysical constraints and forces governing protein folding more realistically.

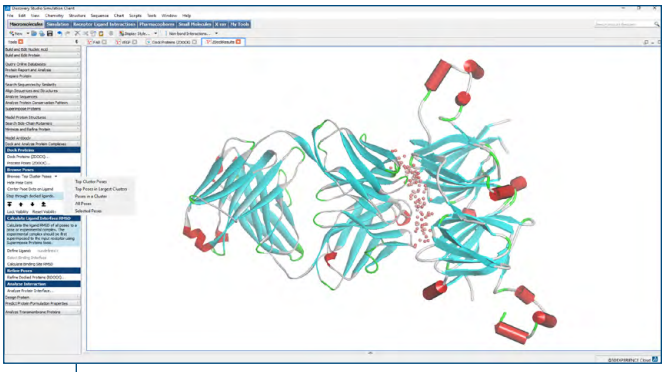


Figure 5. Users can comprehensively and effectively search protein-protein interaction patterns and output possible docking poses with ZDOCK and increase the accuracy of docked poses using the ZRANK scoring function.

MUTATION ENERGY PREDICTION

After identifying a promising candidate, the next step involves exploring how changes to the candidate molecule could impact and possibly improve its properties, including affinity and stability. Stability can affect the formulation, storage, and therefore shelf life of biotherapeutics. **Discovery Studio Simulation** allows researchers to perform *in silico* single- or multi-site mutagenesis experiments while taking into consideration the potential impacts of protein ionization, solution pH, ionic strength, and temperature-dependent effects.

Mutation energy prediction, as one of the most powerful tools in the **Discovery Studio Simulation** arsenal, allows researchers to simulate directed evolution rather than relying on empirical, wet lab methods. It helps select which candidates move forward in the pipeline, reducing the time and resources required to identify an effective biotherapeutic.

HUMANIZATION

Even for a candidate antibody with favorable biophysical properties, the immune system is a substantial barrier to efficacy. Most antibodies are produced from mice or other animal sources and can be recognized by the human immune system as foreign, triggering an immune response. The development of anti-drug antibodies (ADAs) is a clinically significant problem that is associated with loss of efficacy in patients receiving biotherapeutics.

The goal of humanization is to engineer an antibody variable domain such that the resulting antibody has lower human immunogenicity, but retains the stability and the antigen binding specificity and affinity of the original non-human antibody.[14] A 2005 analysis of monoclonal antibody clinical trials found that 84% of mouse antibodies elicited a marked anti-antibody response compared to only 9% of humanized antibodies.[15] Humanization thus increases success rates in clinical development and can be guided by computational tools.

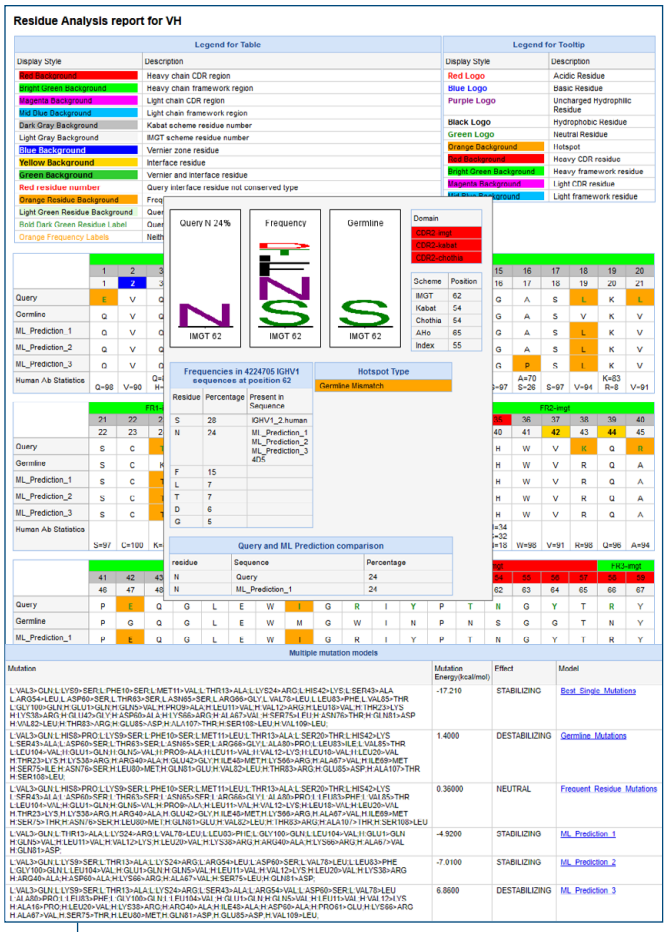


Figure 6. Users can generate an interactive humanization report that allows detailed examination of the residues and possible substitutions at each sequence position. Mutations are suggested based on the germline and/or frequent residue type, or based on a published machine learning method that uses a large-scale antibody sequence database to build classifiers that can distinguish between human and murine sequences.

Discovery Studio Simulation offers several methods for humanization. One method involves comparing the sequence of the candidate antibody to human antibodies and identifying "hotspots" — residue positions where the query sequence does not correspond to a known human residue and building models with the suggested mutations. The other humanization method is a published, validated machine learning method that uses an antibody database to build classifiers distinguishing human from mouse sequences.[16]

This method recommends substitutions that would effectively humanize a candidate antibody using a "humanization score." This process iteratively substitutes mouse residues for human until the candidate reaches a defined humanization score threshold. It can also recommend residue substitutions to enhance structural stability aligned with humanization. (Figure 6)

FORMULATION

Formulation prediction is another strong capability **Discovery Studio Simulation** offers, where users can predict how a biotherapeutic candidate will behave in a bulk solution. Successful development of novel biological therapies requires optimizing several biophysical properties. For instance an ideal candidate should have high solubility and stability, and low viscosity and aggregation propensity. Optimizing formulation properties reduces the risk of failure, allows flexible manufacturing processes, provides additional drug delivery options (such as subcutaneous injection instead of infusion only), extends drug product shelf life, and minimizes toxicity and immunogenicity.

Aggregation is a particularly salient concern, potentially limiting a biotherapeutic agent's integrity and shelf life and stimulating an immune response in the recipient. A protein's tendency to aggregate is related to the size and abundance of its surface-exposed hydrophobic patches. Proteins that are less likely to form aggregates have a lower **Developability Index.**[17,18] Users of **Discovery Studio Simulation** can calculate the **Developability Index** of a biotherapeutic candidate from the aggregation propensity score (AggMap) and total charge properties.[17] (Figure 7)

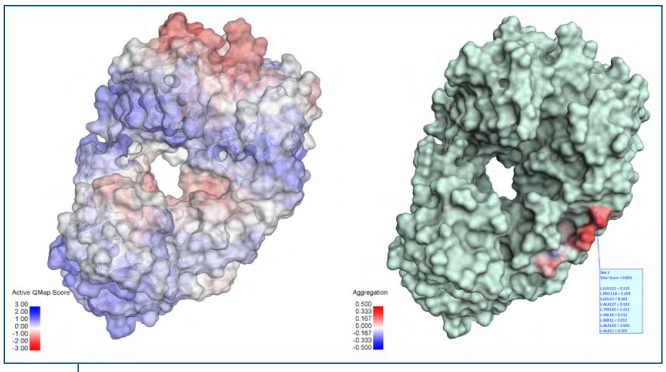


Figure 7. Aggregation scores can be calculated and viewed and analyzed via surface maps showing the details of a selected aggregation site.

Viscosity is another important factor with implications in biotherapeutics formulation based on the total charge of the antibody variable domain.[19, 20] **Discovery Studio Simulation** includes a viscosity prediction model that is reproduced from the work in Trout lab which included commercial datasets from Pfizer, AstraZeneca, and Novartis.[19]

EXCIPIENT INTERACTION PREDICTION

Excipient components, including agents like sodium chloride, sorbitol, sucrose, and other sugars, or amino acids, are added to formulations to provide stability. Excipients mitigate undesirable physical properties in the active biotherapeutic, such as reducing viscosity or aggregation propensity, but unfavorable excipient interactions may adversely impact bioavailability. **Discovery Studio Simulation** uses validated machine learning algorithms that can predict excipient interactions in silico to guide formulation design.[21] (Figure 8)

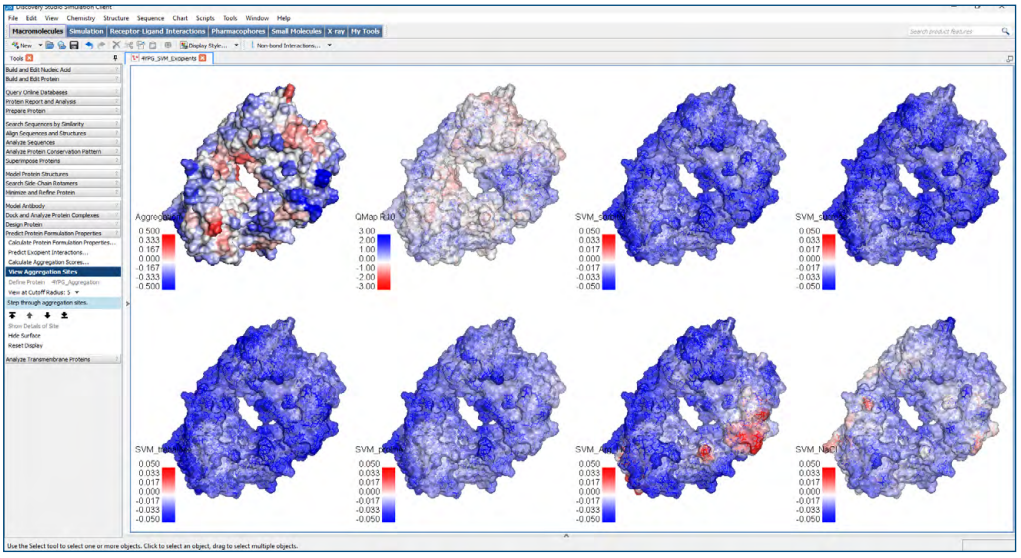


Figure 8. Surface maps colored by the excipient predictions can be generated, showing areas of inclusion and exclusion

Measuring formulation properties experimentally is challenging because of the high cost of obtaining sufficient sample with the necessary purity. Distinct experiments are needed to measure and quantify the formulation properties, making this step among the most challenging and labor-intensive when developing a candidate. Predicting these formulation properties *in silico* is a powerful capability that **Discovery Studio Simulation** offers to its users.

CONCLUSION

BIOVIA Discovery Studio Simulation is the most comprehensive solution in the market for biotherapeutics design and optimization. It integrates long-validated physics-based methods with AI and machine learning models, helping researchers tackle complex computational tasks in a single interface. It allows discovery teams to focus on the most promising candidates, accelerating life-changing therapies to market, while significantly reducing the time and resources needed for testing.

LEARN MORE

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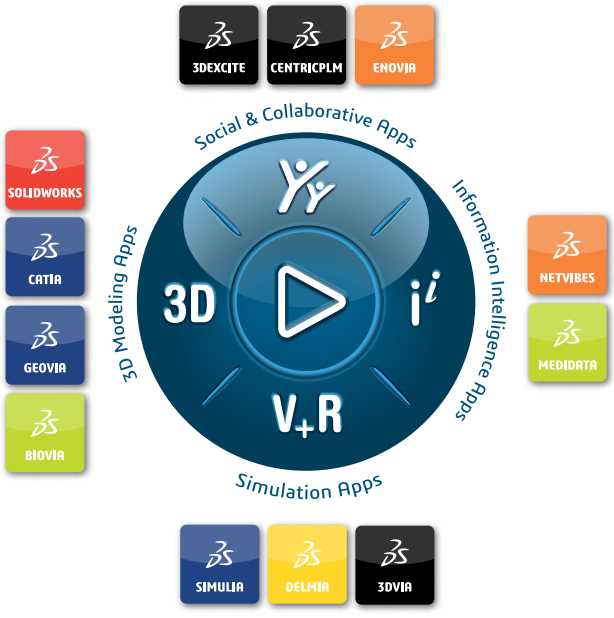

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