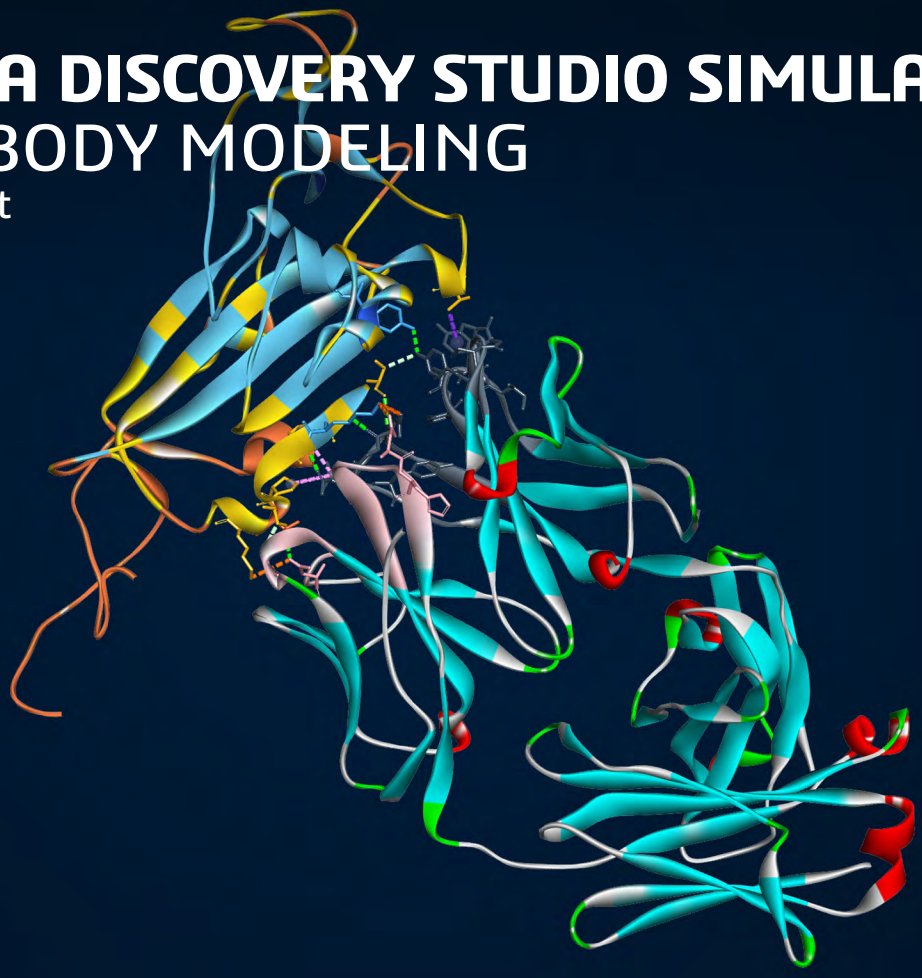
BIOVIA DISCOVERY STUDIO SIMULATION
ANTIBODY MODELING
Datasheet



COMPREHENSIVE ANTIBODY SUITE

Antibodies, renowned for their specificity and potency, are remarkably effective biological therapies for treating complex diseases, including cancer, infectious diseases, and chronic inflammatory, cardiovascular, and immune disorders. Similar to the challenges faced in designing small molecule drugs, optimizing therapeutic antibodies requires careful consideration of efficacy, safety, and developability. **BIOVIA Discovery Studio Simulation** on the **3D**EXPERIENCE® platform offers a wealth of advanced tools for modeling and simulating antibody structures and studying how these structures interact with their targets. This comprehensive antibody suite helps researchers confidently optimize the efficacy and pharmaceutical developability of antibodies as biotherapeutic agents, by delivering the essential science in an easy-to-use environment.

STRUCTURE PREDICTION

Annotation and Alignment

- Automatically identify the variable and constant domains and complementarity determining region (CDR) loops of an antibody sequence or structure using HMM (Hidden Markov Model)
- For variable domains, report the CDR loops and number the residues based on several commonly adopted definitions, including Chothia, Kabat, IMGT, and Honegger
- Quickly and accurately align model sequences based on the annotation scheme

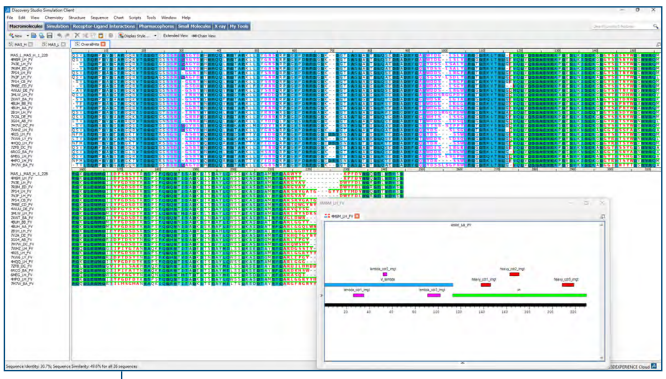


Figure 1: Annotated aligned sequences colored by light and heavy chain domains and CDR regions

Building Structural Models

BIOVIA Discovery Studio Simulation includes MODELER[1], the industry standard for homology modeling, and OpenFold[2]/ AlphaFold[3] AI/ML algorithms to build 3D structures of antibodies and antigens.

- Generate high-quality 3D full-length (bispecific) antibody, Fab, Fv, and single chain variable fragment (scFv) structures from a set of light and heavy chain sequences
- Rapidly generate antibody models of multiple input sequences with refined CDR loops using an automated modeling cascade workflow
  - Automatically search a curated PDB antibody database to identify optimal templates for each chain, domain, and loop
  - Refine template selection, by filtering for particular species, resolution, with or without CDR residues
- Alternatively, identify templates and build the framework models individually
  - Choose to have greater control over individual cascade steps
  - Build from a chimeric template based on different light and heavy chain templates
- Generate high-quality 3D models of antigen target proteins from their sequences with prediction from the novel OpenFold/AlphaFold AI/ML algorithms or the MODELER homology modeling algorithm
- Alternatively, build an antibody-antigen complex together with the AlphaFold multimer algorithm

Model Refinement

- Search a database of known antibodies to find the best templates for each loop region and build the loops based on the templates
- Determine and refine individual loop conformations
  - Graft a loop conformation from a template structure onto the target antibody model
  - Perform *ab initio* loop refinement by systematically sampling and refining loop conformations using the CHARMm-based LOOPER[4] algorithm
- Optimize amino acid side-chain positions using the CHARMm-based ChiRotor[5] algorithm
- Perform implicit or explicit solvent-based GPU MD simulations using CHARMm[6] to model antibody motion, conformational change and interactions
- Perform GPU-enabled explicit solvent MD simulations with NAMD[7]
- Perform Gaussian accelerated Molecular Dynamics[8] simulations to quickly explore conformational space

AFFINITY AND SELECTIVITY

BIOVIA Discovery Studio Simulation includes a suite of tools to optimize antibody-antigen binding.

Antigen-Antibody Docking

- Predict the structures of antibody-antigen complexes quickly and accurately with ZDOCK[9]
  - Cluster poses based on their spatial proximity and filter poses based on known interface (CDR) residues
- Refine docked poses with RDOCK to optimize binding interactions
- Analyze epitope and paratope binding interfaces and generate reports for different types of interactions

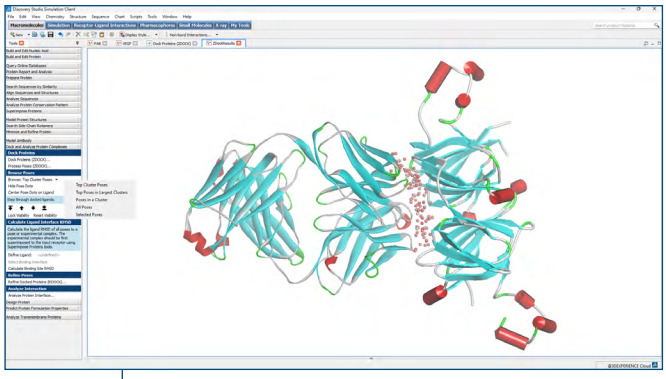


Figure 2: Analyze antibody-antigen docked poses.

Prediction and Optimization of Binding Affinity

- Perform combinatorial amino acid mutagenesis to evaluate the effects of mutations on antibody stability and binding affinity, considering pH dependency and thermal effects[10,11]
  - Mutations can be to a single residue such as in alanine scanning or multi-site, complex combinations such as for *in silico* affinity maturation
  - Provides clear analysis of the predicted effect of the mutation and how it is composed
- Identify mutations that change the pH-dependent binding profile of the antibodies to the receptors to optimize effector function and serum half-life

DEVELOPMENT AND FORMULATION

BIOVIA Discovery Studio Simulation allows users to apply validated algorithms, including those licensed from the Massachusetts Institute of Technology and developed at Prof. Trout's laboratory, to help assess the early-stage developability of antibody candidates, increasing chances of success during late-stage development.

Candidates can be ranked and evaluated to identify modifications to improve formulation, long-term stability, and developability.

- Predict aggregation propensity with the Spatial Aggregation Propensity[12] (SAP) score
  - Identify the size and location of regions on antibodies prone to aggregation
- Predict the Developability Index[13] (DI) for rapid, early-stage assessment of suitability for development, incorporating aggregation propensity score and total charge properties
- Calculate relative viscosity scores using the surface charge method[14] (SCM), considering the exposed negative charge
  - Visualize charge surface maps to identify regions correlating with higher viscosity
- Calculate additional biophysical properties including, solubility, isoelectric point, pH of maximum stability, net charge, dipole moment
- Identify post-translational modification sites (e.g. deamidation, oxidation) using default or user-specified definitions

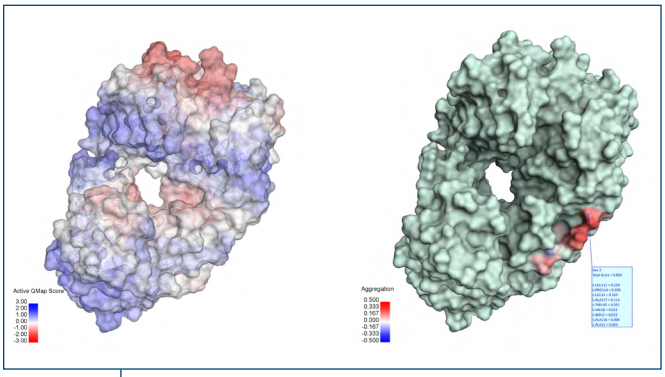


Figure 3: Surfaces showing the aggregation scores and the details of a selected aggregation site

Excipient Formulation

- Predict preferential interaction of common excipients (Sorbitol, Sucrose, Trehalose, Proline, Arginine·HCl, and NaCl) with machine learning (ML) models[15] to improve antibody formulation
  - Visualize excipient interactions at sites with high aggregation or surface charge

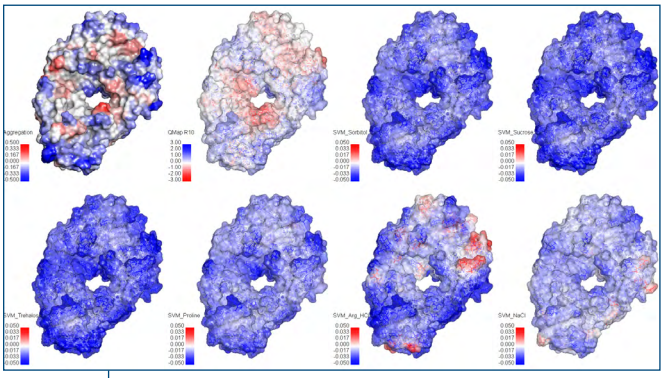


Figure 4: Surfaces colored by the excipient predictions, showing areas of inclusion and exclusion.

HUMANIZATION

- Reduce immunogenicity by predicting humanizing mutations without compromising antibody stability or efficacy
  - Utilize an ML model[16] trained on human and murine antibody sequences
  - Explore suggestions based on frequency statistics compiled by extracting human antibody variable domain sequences from the Observed Antibody Space database and frequency statistics from the NCBI
  - Analyze interactive residue reports of predicted mutations
  - Generate humanized structures automatically for further analysis

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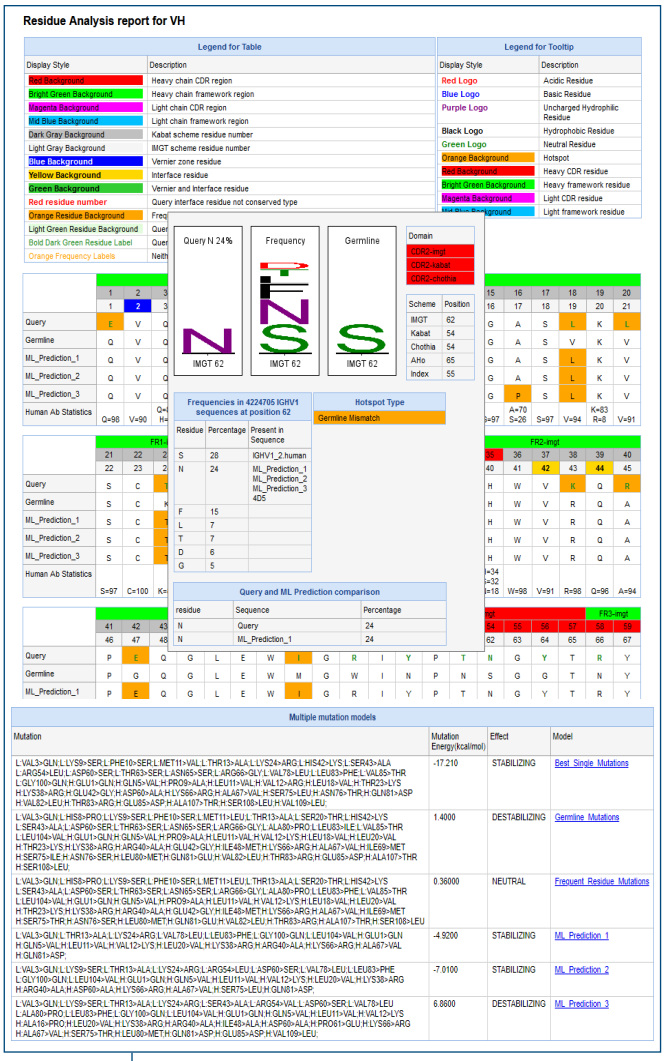

Figure 5: Humanization report and table of predicted ML models

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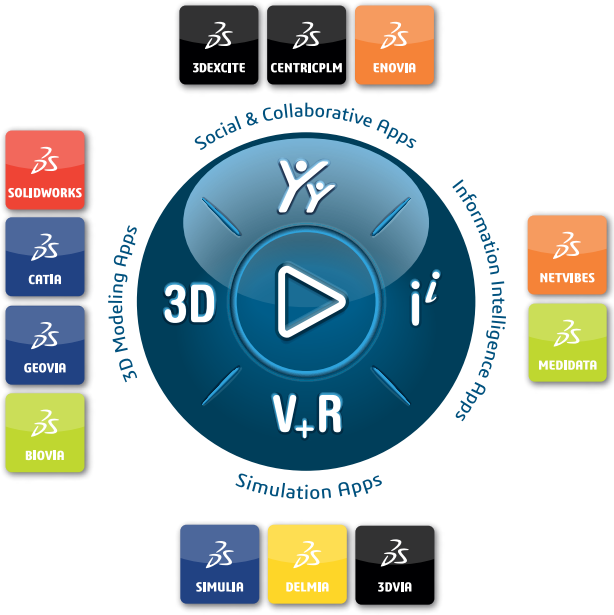

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Europe/Middle East/Africa
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CS 40501
78946 Vélizy-Villacoublay Cedex
France

Asia-Pacific
Dassault Systèmes K.K.
ThinkPark Tower
2-1-1 Osaki, Shinagawa-ku,
Tokyo 141-6020
Japan

Americas
Dassault Systèmes
175 Wyman Street
Waltham, Massachusetts
02451-1223
USA

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