DASSAULT SYSTEMES

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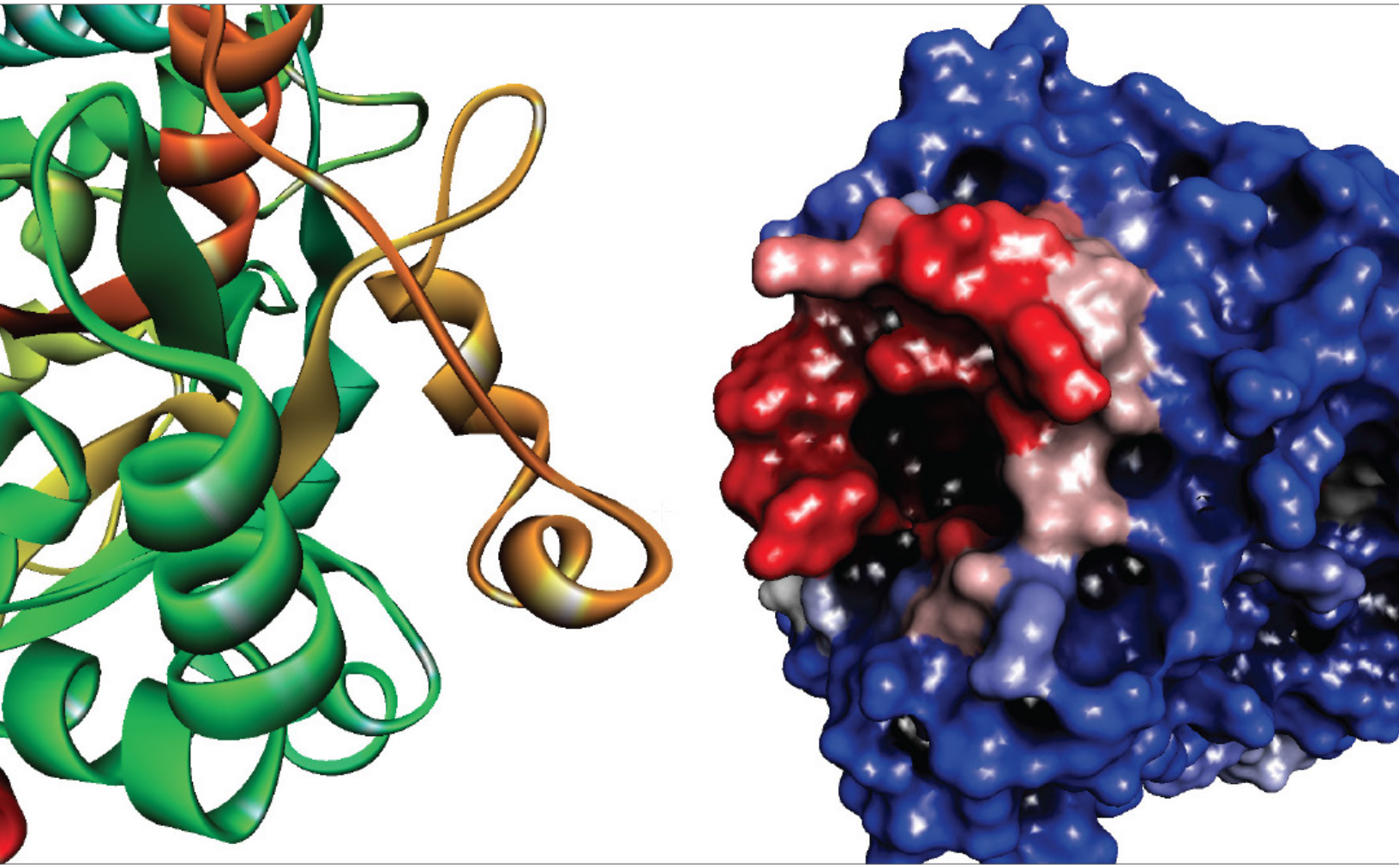
# ANTIBODY DEVELOPMENT WITH BIOVIA DISCOVERY STUDIO®

DATASHEET



## COMPREHENSIVE ANTIBODY SUITE

Antibodies have proven to be an effective treatment in a number of key diseases, including cancer, chronic inflammatory diseases, cardiovascular diseases, immune disorders, as well as infectious diseases[1]. Because of this potential, antibodies now represent one of the fastest growing classes of human therapeutic drugs[2,3]. With BIOVIA Discovery Studio, not only do you have the tools necessary to model antibody structures in an easy to use environment, but it also delivers the essential science to optimize their efficacy and pharmaceutical developability as therapeutic agents.

## MODELING ANTIBODIES

BIOVIA Discovery Studio delivers a comprehensive portfolio of specialized tools for modeling antibody structures, including predicting the conformations of the CDR loops.

### Annotate antibody domains and CDR loops

- Automatically identify the variable and constant domains 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

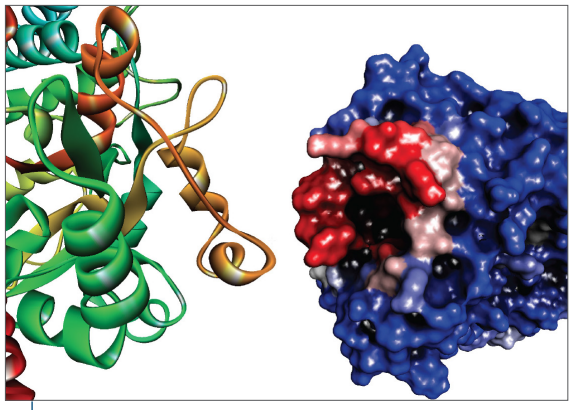


**Figure 1:** Solvent exposed surface on the fAb domain of an antibody, colored to show the predicted binding site 'hot-spot' (red) as calculated by the spatial aggregation propensity algorithm, Aggmap. The accompanying antigen is also shown in the figure [PDB: 3PGF]

### Template identification

- Search curated PDB antibody database to identify optimal templates for each chain or domain
- Refine template selection, by filtering for particular species, resolution, with or without CDR residues.

### Sequence alignment

- Quickly and accurately align model sequence with templates using multiple structure alignment and multiple sequence alignment algorithms
- Easily align multiple antibody sequences based on the residue numbering defined by the commonly adopted schemes: Chothia, Kabat, IMGT, and Honegger
- Simultaneously, but independently perform alignments on either light or heavy chains

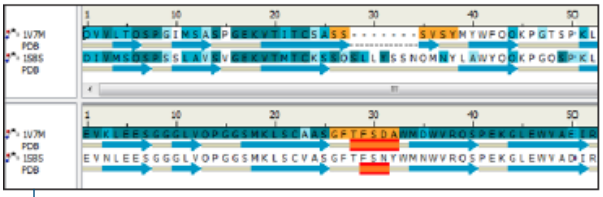


**Figure 2:** Example of light and heavy chain sequence alignments of antibody Fab domains [PDB: 1V7M and 1SBS]

### Build homology models

Use the industry-standard MODELER[4,5,6] to build homology models of antibodies automatically in BIOVIA Discovery Studio:

- Antibody Framework modeling: Specify different templates for heavy chain and light chain respectively, allowing you to easily build a chimeric model. Use a framework template structure to determine the relative spatial orientation of the two chains
- Model Full-length Antibody: Build models from full-length sequences of Immunoglobulin gamma isotype (IgG), based on IgG1 and IgG2 template structures

### Identification and refinement of CDR loops

- Automatically identify the CDR loops of an antibody structure using HMM. Search a database of known antibodies to find the best templates for each loop region. Optionally, build loops based on the templates
- Manual Loop Grafting: Copy the loop conformation from a template structure onto the target antibody model
- Ab Initio Loop Refinement: Use the LOOPER algorithm7 to systematically search the loop conformations that are then optimized and ranked using the CHARMm force field[8,9].

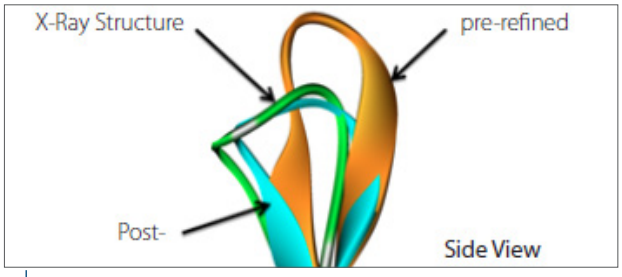



**Figure 3:** Loop refinement in antibody structure [PDB: 2AAB]

### Model analysis

BIOVIA Discovery Studio provides protocols to help perform a detailed analysis of the quality of antibody models.

- Verify Protein (Profiles 3D) calculates the likelihood of each residue to be found in its specific local 3D environment. Expected Verify Scores create indicators of the quality of the model
- Verify Protein (MODELER) scores the model conformation using a statistical potential
- Ramachandran plots/reports to verify the distribution of Phi and Psi angles of amino acids
- Capabilities to look at main-chain angular conformation, sidechain deviations from a known rotamer library, and more

## FORCEFIELD-BASED PROTEIN MODELING

Perform a range of model refinements including amino acid side chain optimization, Minimization and Molecular Dynamics.

### Side-chain refinement

- Systematically optimize amino acid side-chain conformation using ChiRotor CHARMm simulations[10]

### Predict protein ionization and residue pKs

Using a novel in-house computational method[11], quickly and accurately calculate protein ionization using a Generalized-Born solvent model in CHARMm[12,13,14], incorporating an iterative mobile clustering approach[15] to the equilibria of proton binding.

- Predict the pK and titration curves for each of the titratable amino acid residues
- Calculate the total protein charge as a function of pH and predict the isoelectric point (pI)
- Calculate the electrostatic contribution to the free energy of folding as a function of pH
- Protonate the acidic and basic residues and optimize the hydrogen network at a given pH

### Perform simulations on antibody structures

- Perform either implicit solvent or explicit solvent Molecular Dynamics (MD) simulations using the latest version of CHARMm 37b2
- Alternatively perform the MD simulations using the (fast) NAMD16 program*

## OPTIMIZING AFFINITY AND SELECTIVITY

BIOVIA Discovery Studio includes a suite of tools to help identify antigen binding sites and predict Fab domain binding affinity:

### Antigen-Antibody docking

- Use ZDOCK[17,18] to comprehensively search antigen epitope sites and output putative docking poses
- Increase the rank order accuracy of docked poses using the ZRANK scoring function[19].
- Analyze protein binding interfaces and generate reports for favourable, unfavourable and unsatisfied interactions

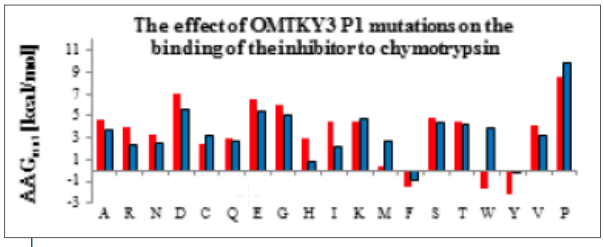



**Figure 4:** Calculated (blue) vs. experimental (red) mutation energies in the binding of turkey ovomucoid inhibitor to chymotrypsin for residue Leu18. to 18 other amino acid types[21,20].

### Predict binding affinity

- Perform combinatorial amino acid scanning mutagenesis on a set of selected residues to evaluate the effect of single-point or multiple mutations on the binding affinity of molecular partners
- Help in the affinity maturation process by identifying mutations that optimize binding affinity

### Optimizing Effector function and serum half life

- Identify mutations that change the pH dependent binding profile of the antibodies to the receptors[21]

## OPTIMIZING STABILITY

Apply validated algorithms to help speed up the optimization of protein characteristics associated with good developability.

### Optimize protein stability[21]

Calculate the effect of a single-point or multiple mutation on protein stability at a given temperature or as a function of pH

- Perform a search for most stabilizing double or triple mutations in a protein structure, among a list of specified amino acid substitutions
- Perform combinatorial scanning mutagenesis on a set of selected residues to evaluate the effect on the protein stability for all combinations of single, double or multiple mutation sites and specified amino acid substitutions

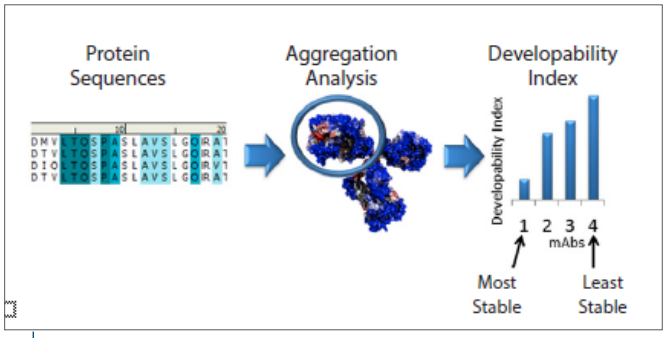



**Figure 5:** Based on aggregation propensity and molecular charge, calculate the Developability Index (DI) of IgG1 antibodies graphics card.

### Spatial Aggregation Propensity and Developability

Use the experimentally validated Spatial Aggregation Propensity and Developability algorithms, licensed from the Massachusetts Institute of Technology and developed at Prof. Trout's laboratory[22,23,24]

- Identify the size and location of regions on antibodies prone to aggregation
- Predict mutations leading to improved stability
- Based on aggregation propensity and molecular charge calculated using our pK prediction method, rank proteins for their long term stability and developability
- Additionally, predict other protein-protein recognition sites, including the paratope, Fc receptor, protein A, and protein G binding regions[25]

To learn more about BIOVIA Discovery Studio, go to **accelrys.com/discovery-studio**.

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