BIOVIA

3DEXPERIENCE®

BIOVIA DISCOVERY STUDIO®
OVERVIEW

Datasheet

Built on BIOVIA Pipeline Pilot™, Discovery Studio® is uniquely positioned as the most comprehensive 3D modeling and simulation application for the Life Sciences discovery research. BIOVIA Discovery Studio® brings together over 30 years of peer-reviewed research with world-class *in silico* techniques in a single interface, delivering a comprehensive science suite to support early-stage discovery of biotherapeutics and small molecule drugs.

WHAT IS IN BIOVIA DISCOVERY STUDIO®?

- **Comprehensive research portfolio** addressing the needs of drug discovery processes from early-stage target identification, lead identification and optimization to preclinical formulations development
- **Mature science** based on proven and validated methods developed by academic leaders at Harvard, MIT, and UCSF and leveraged by scientists worldwide across industry and academia
- **Collaborative science** partnering with sophisticated modeling software such as CHARMm, NAMD, MODELER, ZDOCK , GOLD, and more

COMPREHENSIVE RESEARCH PORTFOLIO

Protein modeling and development:

- Perform sequence similarity searches using BLAST and PSI-BLAST against local or NCBI databases
- Perform a range of feature and motif predictions and biophysical property calculations on protein sequences
- Predict sites prone to post-translational modifications (PTM)
- Generate high-quality 3D models of target proteins from their sequences with the market leading MODELER homology modeling algorithm
- Systematically sample and refine loop conformations using the CHARMm-based LOOPER algorithm
- Optimize amino acid side-chain positions using the ChiRotor CHARMm-based algorithm

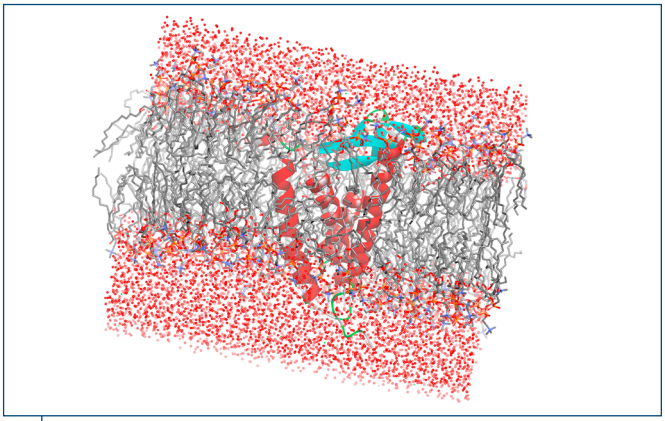


Figure 1: Solvated membrane protein within an explicit membrane.

- Prepare protein structures for molecular dynamics and docking studies using a comprehensive set of automatic protein preparation tools
  - Removes disorder and extraneous water molecules
  - Detects and adds missing atoms and residues with additional refinement
  - Predicts pKas of titratable amino acids and protonates at the desired pH for optimal interactions
- Calculate protein ionization, isoelectric point and other protein properties quickly and accurately
- Carry out protein-protein docking studies with ZDOCK and refine poses to examine binding partner interactions
- Perform combinatorial amino acid mutagenesis to evaluate the effects of mutations on protein stability and binding affinity, considering pH dependency and thermal effects
  - Mutations can be to a single residue such as in alanine-scanning or in selected, complex combinations
  - Clear output about the predicted effect of the mutation and how it is composed
- Calculate protein features and sequence descriptors for use in machine learning applications

Antibody design and modeling:

- Identify and annotate domains and Complementarity Determining Regions (CDRs) of antibody sequences based on custom or widely used numbering schemes – including IMGT, Kabat, Chothia and Honegger

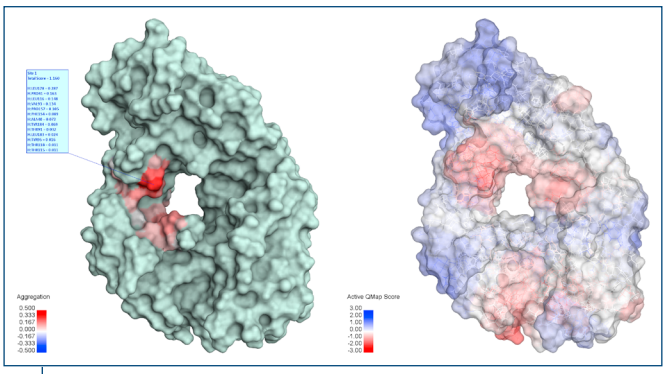


Figure 2: Aggregation Scores (left), with residue details, and Charge QMap (right) surfaces on an antibody structure.

- Generate high quality 3D full-length antibody, Fab or Fv structures from a set of light and heavy chain sequences
  - Automated modeling cascade easily and rapidly generates antibody models with refined loops
  - Templates are based on a curated PDB antibody template database
- Build bispecific and single chain variable fragment (scFv) antibody models using dedicated tools
- Calculate biophysical properties important for protein formulation, including solubility, viscosity and Developability Index (DI) for rapid, early stage assessment of suitability for development
  - Relative viscosity scores are estimated using the surface charge method (SCM)
  - The DI ranks the aggregation propensity of the antibodies and is calculated from the aggregation propensity score (AggMap) and total charge properties

- Predict preferential interaction of common excipients (Sorbitol, Sucrose, Trehalose, Proline, Arginine·HCl, and NaCl) with machine learning models to improve antibody formulation
- Predict the paratope residues in the antibody CDR regions to guide antibody-antigen binding studies

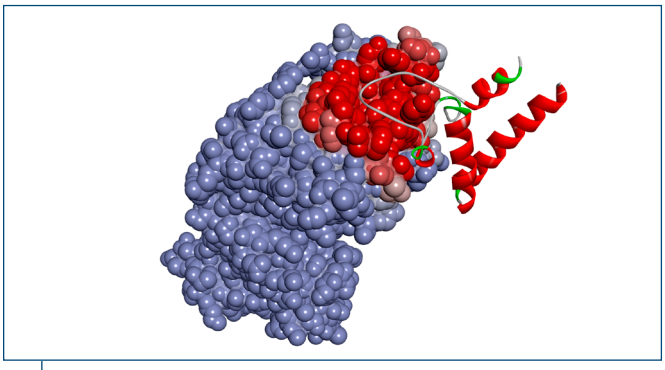


Figure 3: Predict paratope residues (colored in red).

- Create antibody-antigen complexes and perform affinity maturation studies to investigate binding improvements
- Reduce immunogenicity by predicting humanizing mutations without compromising antibody stability or efficacy
  - Residues to be mutated are suggested based on human germline gene sequences and frequency statistics from the NCBI
  - Humanized structures can be automatically generated for further analysis

Simulations:

- Perform minimization and Molecular Dynamics (MD) simulations on GPU and CPU with best-in-class simulation programs, CHARMm and NAMD
  - Support for a broad range of force fields, including CGenFF, charmm36 and CHARMm
- Apply hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) methods with DMol^3 and CHARMm to investigate electronic properties
- Visualize and analyze MD trajectories to understand conformational behavior and study structural properties
- Calculate relative binding free energies for an entire combinatorial library in a single GPU simulation using the efficient Multi-Site Lambda Dynamics (MSLD) workflow
  - Up to 20 times more efficient than free energy perturbation
  - Large scale validation of the science to explore large congeneric chemistry space in early lead optimization
- Perform Free Energy Perturbation (FEP) simulations to calculate the relative free energy of binding to between multiple pairs of ligands with NAMD or CHARMm (GPU)
  - Calculation of Forward and Reverse estimates of free energy
  - Custom lambda schedule with narrower windows near the end states to improve accuracy
- Create solvated explicit membrane-protein systems for MD simulations
  - Solvate with pre-equilibrated homogenous lipid bilayers or customized lipid boxes, including complex heterogeneous lipid compositions
- Detect and analyze transient and static binding pockets from molecular simulation trajectories

Structure and fragment-based design:

- Virtually screen ligands and fragments with a range of tools, depending on project and available data
  - Methods include the CHARMm-based CDOCKER workflow, hotspots-based LibDock, Ludi, Multiple Copy Simultaneous Search (MCSS) and pharmacophore-based methods

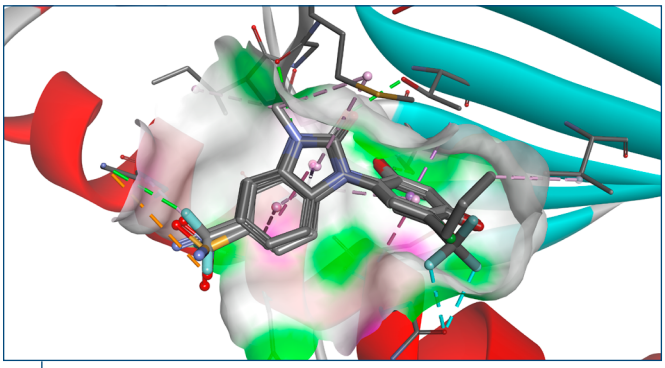


Figure 4: Combinatorial library defined with a core and two sites within the Hsp90 binding site for MSLD simulation.

- Interface with your GOLD installation from the Cambridge Crystallographic Data Centre to launch docking calculations
- Perform *in situ* lead optimization using classical medicinal chemistry reaction transformations and commercially-available reagents
- Develop new ideas with scaffold hopping or *in situ* R-group substitutions using molecular fragments derived from commercially-available compounds
- Calculate quick and accurate binding energies with CHARMm-based MM-PBSA or MM-GBSA methods

- Enrich screening results with the identification of critical interacting residues using a comprehensive set of favorable, unfavorable and unsatisfied non-bond monitors
  - Non-bond interaction criteria can be customized as desired
- Create advanced predictive models by combining empirical and energy-based scoring functions with classical QSAR, fingerprints, and quantum mechanics-based descriptors

Pharmacophore and ligand-based design:

- Automatically generate 3D pharmacophores with the market leading Catalyst pharmacophore engine from:
  - Active small-molecule ligands (qualitative, quantitative, with inactive data, small and large datasets)
  - Receptor binding sites
  - Receptor-ligand complexes
- Perform vigorous model validation with detailed metrics, confusion matrices and ROC plots for easy analysis

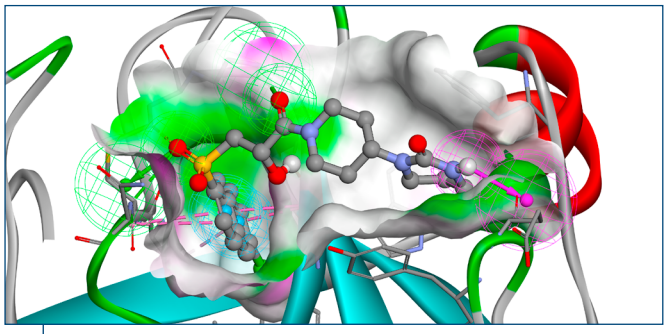


Figure 5: Interactions pharmacophore from a receptor-ligand complex harmonizes with non-bond feature perception.

- Conduct robust screening studies with powerful and flexible pharmacophore-ligand fitting methods
  - Study the multiple mappings of ligands to a pharmacophore
  - Screen ligand libraries with flexible feature combinations, focusing on the highest fitting pharmacophore for each molecule
  - Profile with multiple pharmacophores to map multiple ligands, determining the best fit of features or FitValue
- Build and search databases of pre-generated 3D ligand conformations
- Explore off-target activity and drug repurposing using the PharmaDB repository of diverse receptor-ligand pharmacophore models derived from the scPDB
- Enumerate reaction- or Markush-based combinatorial libraries
- Optimize library selection using Pareto optimization, clustering, diversity and similarity analysis

Pharmacokinetic properties and toxicity:

- Calculate hundreds of physicochemical, topological, electronic, geometric, fingerprint and Quantum Mechanics based descriptors, as well as physics-based energy properties
- Create predictive statistical models including Bayesian, Recursive Partitioning, Partial Least Squares, Genetic Functional Analysis, 3D Field-based QSAR and more
- Identify Matched Molecular Pairs transformations and study activity cliffs
- Assess ADMET safety profiles (absorption, distribution, metabolism, excretion and toxicity) with predictive models including blood-brain barrier penetration, human intestinal absorption, aqueous solubility, hepatotoxicity, CYP2D6, AMES, Rat Oral LD50, and many more
- Calculate assessments of small molecule toxicity and environmental effects such as Ames mutagenicity, rodent carcinogenicity, skin irritancy and sensitization, eye irritancy, aerobic biodegradability and many more

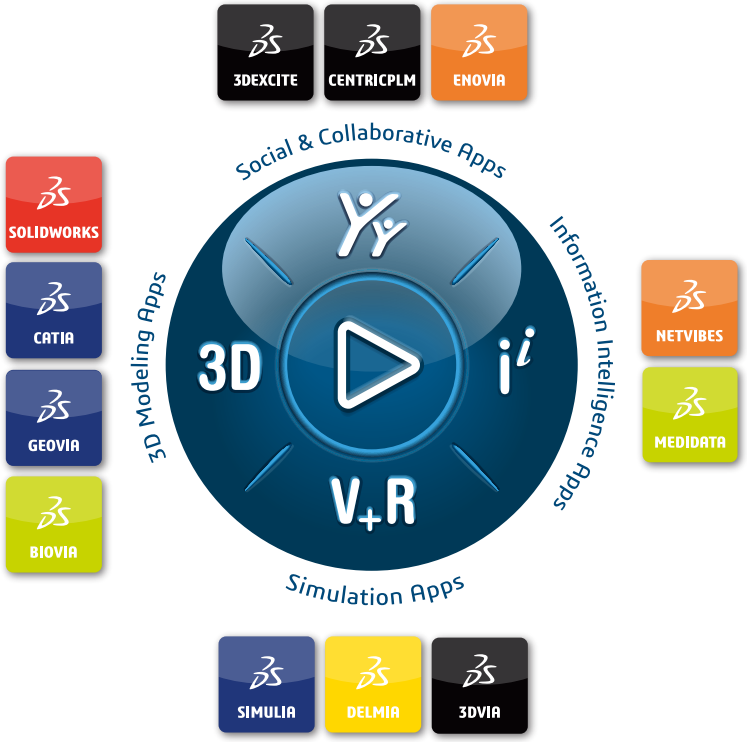
MATURE SCIENCE

BIOVIA Discovery Studio® is built on over 30 years of peer-reviewed scientific research and has been validated by scientists worldwide across industry and academia. Search through tens of thousands of indexed references on our database.

COLLABORATIVE SCIENCE

- **CHARMm** for force-field based simulations: Distributed with both CPU and GPU editions
- **NAMD** for force-field based simulations: Distributed with both CPU and GPU editions
- **MODELER** for protein homology modeling
- **BLAST+** for sequence searching
- **GOLD** for protein-ligand docking
- **ZDOCK** for protein-protein docking
- **Catalyst** for pharmacophore modelling
- **AggMap** and **SCM** for protein aggregation & viscosity prediction

LEARN MORE



Our **3D**EXPERIENCE® platform powers our brand applications, serving 11 industries, and provides a rich portfolio of industry solution experiences.

Dassault Systèmes, the **3D**EXPERIENCE Company, is a catalyst for human progress. We provide business and people with collaborative virtual environments to imagine sustainable innovations. By creating 'virtual experience twins' of the real world with our **3D**EXPERIENCE platform and applications, our customers push the boundaries of innovation, learning and production.

Dassault Systèmes' 20,000 employees are bringing value to more than 270,000 customers of all sizes, in all industries, in more than 140 countries. For more information, visit **www.3ds.com**.

Europe/Middle East/Africa
Dassault Systèmes
10, rue Marcel Dassault
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

DASSAULT SYSTEMES | The **3D**EXPERIENCE® Company