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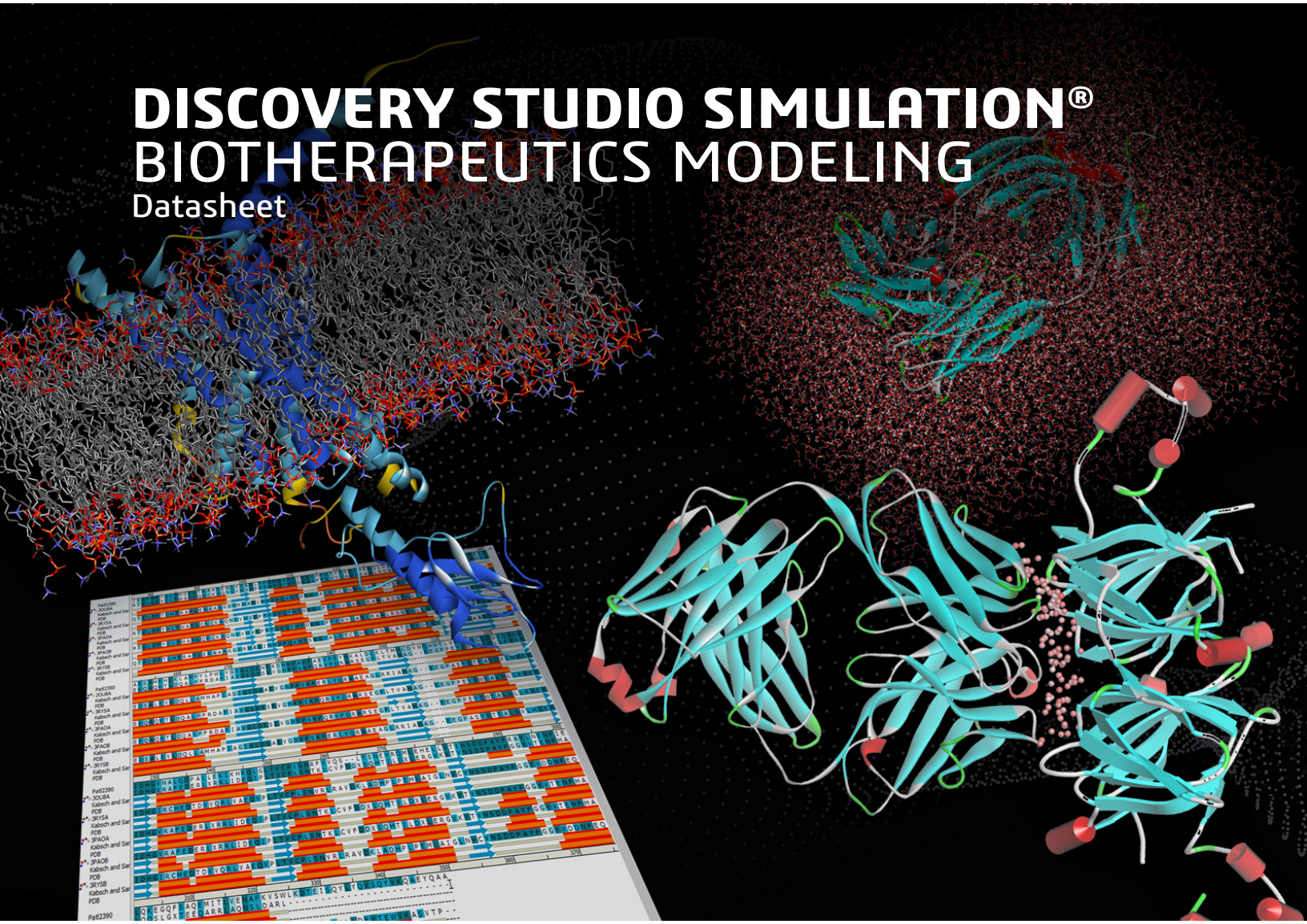
DISCOVERY STUDIO SIMULATION®
BIOTHERAPEUTICS MODELING
Datasheet



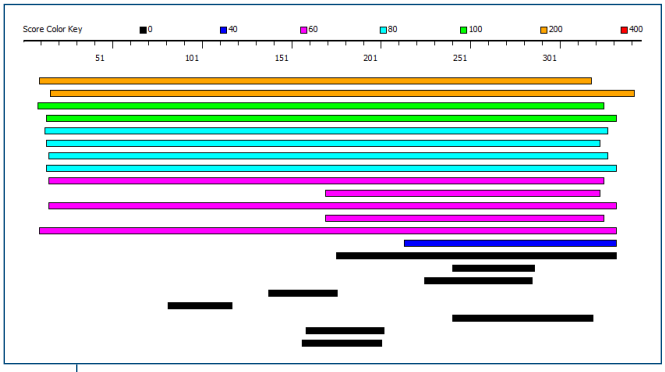
COMPREHENSIVE PROTEIN MODELING

Determining the three-dimensional structure and properties of a macromolecule such as enzymes, receptors, antibodies, DNA, or RNA is a fundamental component to a wide range of research activities. For example, predicting the location and characteristics of binding sites or optimizing the stability and selectivity of thera-peutic biologics all require access to precise, accurate molecular models. BIOVIA Discovery Studio Simulation delivers a comprehensive portfolio of market leading, validated scientific tools able to assist in every aspect of macromolecule-based research, allowing teams to optimize the performance of the candidates *in silico* and streamline their lab work. This datasheet outlines the capabilities of Discovery Studio Simulation for biotherapeutics modeling.

DASSAULT SYSTEMES

SEQUENCE ANALYSIS

- 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
- Align sequences quickly and accurately using multiple sequence-alignment algorithms
- Determine relationships between sequences and structural conservation of amino acids with phylogenetic and Evolutionary Trace analysis tools



	Title/Description	Accession	Identity	Sequence	Alignment	Bit Score	E-value	Positive	Resolution	SCOP	Ligand	Organism
1	Adenosine deami...	3pao_A	44	313	310	266.929	9.04392e-88	63	2.493		A:ADE328,...	Pseudomonas aer...
2	Adenosine deami...	3rys_A	40	335	328	252.677	7.34169e-82	61	2.601	c.1.9.0	A:ADE345,...	Paenarthrobacter...
3	Adenosine deami...	4gxw_A	24	369	334	106.686	6.15386e-26	46	1.3		A:ZN401	Burkholderia ambi...
4	Adenosine deami...	1vfl_A	24	349	338	102.449	1.85456e-24	47	1.8	c.1.9.1	A:ZN501	Bos taurus
5	Adenosine deami...	6n91_B	24	334	326	99.3673	2.04024e-23	44	2.05	c.1.9.0	B:CXS403,...	Vibrio cholerae O...
6	Adenosine deami...	3mvi_A	25	349	331	98.5969	4.14232e-23	46	1.6	c.1.9.1	A:GOL902,...	Mus musculus
7	Adenosine deami...	6n9m_A	25	331	324	93.2041	2.5217e-21	44	1.449	c.1.9.0	A:CA404,A...	Salmonella enteri...
8	Adenosine deami...	3lar_A	23	360	339	91.6633	1.25973e-20	45	1.52	c.1.9.1	A:3D1501,...	Homo sapiens
9	adenosine deami...	2amx_A	25	364	328	78.9518	3.32681e-16	47	2.02	c.1.9.1	A:CO1000,...	Plasmodium yoelii
10	Adenosine deami...	3ewd_A	29	364	159	76.2554	2.46066e-15	54	1.9	c.1.9.1	A:MCF372,...	Plasmodium vivax
11	Adenosine deami...	6ki7_A	23	355	335	73.1738	3.12261e-14	44	2.48	c.1.9.1	A:HPA402,...	Plasmodium falcip...
12	adenosine deami...	2pgf_A	29	359	165	72.4034	5.58789e-14	52	1.89	c.1.9.1	A:ADN501,...	Plasmodium vivax
13	Adenosine/AMP d...	6ijn_A	24	341	337	71.2478	1.03391e-13	43	1.66	c.1.9.0		Arabidopsis thalia...
14	Adenosine deami...	3lgd_B	29	482	126	41.9726	0.00051262	50	2		B:NAG750,...	Homo sapiens
15	AMP deaminase 2...	6hu6_A	22	614	171	40.0466	0.00255754	40	2.33		A:ZN901	Homo sapiens
16	Yeast Guanine De...	6oh9_A	40	452	47	32.7278	0.497529	59	1.75		A:ZN501	Saccharomyces c...
17	AMP deaminase | ...	2a3l_A	30	616	60	32.3426	0.589859	46	3.34	c.1.9.1	A:CF5841,...	Arabidopsis thalia...
18	GUANINE PHOSP...	1dqn_A	32	230	46	31.187	0.919487	54	1.75	c.61.1.1	A:IMU300,...	Giardia intestinalis
19	Dihydrolipoyllysin...	6zzn_A	37	224	35	31.187	1.10893	48	1.5			Mycobacterium tu...
20	GENERAL ODORA...	2wcj_A	28	141	78	29.6462	2.13762	51	1.4	a.39.2.0	A:M21114...	Bombyx mori
21	O-acetyl-ADP-rib...	4j5r_A	39	141	43	28.4906	4.52546	58	1.25		A:A1R201	Homo sapiens
22	TRNA ENDONUCL...	1a79_A	31	171	45	28.8758	4.77243	62	2.28	c.52.2.1...	A:AU4	Methanocaldococ...

Figures 1 & 2: BLAST hits in a map and table view

PROTEIN STRUCTURE DETERMINATION

- Predict protein structures from their sequences with the novel AI/ML algorithms OpenFold and AlphaFold[1]
- Generate high-quality 3D models of target proteins from their sequences with the market leading MODELER[2] homology modeling algorithm
- Assess the model quality with tools, including model confidence, scoring functions, energies and sequence-structure compatibility
- 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[3]

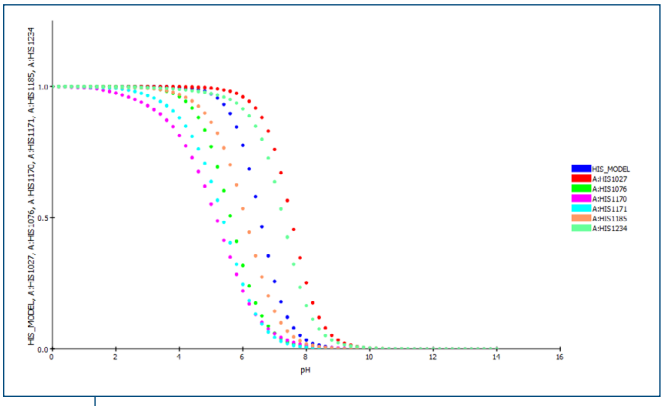


Figure 3: Titration curves of prepared residues can be analyzed

REFINEMENT AND SIMULATION

- Systematically sample and refine loop conformations using the CHARMm-based LOOPER[4] algorithm
- Graft loop conformations from a template structure onto a target model
- Optimize amino acid side-chain positions using the CHARMm-based ChiRotor[5] algorithm
- Prepare proteins in an explicit membrane with solvation for Molecular Dynamics (MD) simulations
- Perform implicit or explicit solvent-based MD simulations using CHARMm[6] (GPU) to model macromolecular motion, conformational change and interactions
- Perform GPU-enabled explicit solvent MD simulations with NAMD[7]
- Apply the Gaussian accelerated Molecular Dynamics (GaMD)[8] enhanced sampling method to accelerate sampling of protein conformations
- Examine electronic effects in protein-ligand complexes using a hybrid of quantum and classical molecular mechanics (QM-MM)

PROTEIN-PROTEIN DOCKING

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

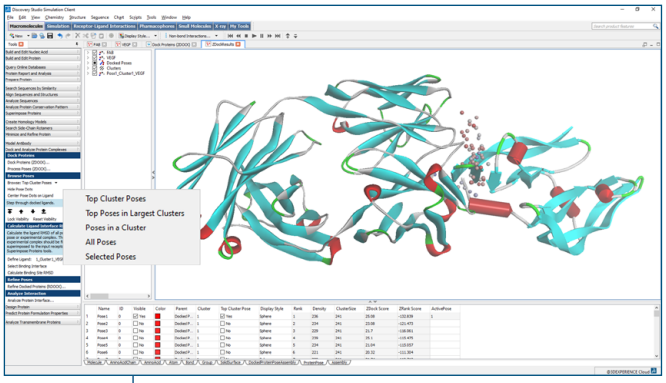


Figure 4: Analyze docked protein poses

PROTEIN DESIGN AND ENGINEERING

- Perform combinatorial amino acid mutagenesis to evaluate the effects of mutations on protein 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 in selected, complex combinations
  - Perform multi-site mutations to identify the optimal mutation combination for protein binding or stability
  - Provides clear analysis about the predicted effect of the mutation and how it is composed
- Identify mutation sites for disulfide bridge creation to improve protein stability

PROPERTY PREDICTION

- Calculate biophysical properties, such as solubility, isoelectric point, dipole moment, molecular charge, molar extinction coefficient, hydropathy and antigenic sites
- Calculate protein features and sequence descriptors for use in machine learning applications

FUNDAMENTAL MODELING TOOLS

- Rapidly build peptide molecules in defined secondary structure conformations
- Easily create RNA and DNA molecules in single or multi-stranded conformations according to standard A, B and Z forms.

Index	Mutation	Mutation Energy (kcal/mol)	Effect
1	I:GLY29>LYS	-2.72	STABILIZING
2	I:GLY29>HIS	-1.29	STABILIZING
3	I:GLY29>ARG	-1.05	STABILIZING
4	I:CYS3>LYS	-0.93	STABILIZING
5	I:ARG1>HIS	-0.64	STABILIZING
23	I:PRO4>LYS	2.20	DESTABILIZING
24	I:ARG5>LYS	2.61	DESTABILIZING
25	I:ILE6>LYS	2.94	DESTABILIZING
26	I:PRO4>ARG	3.39	DESTABILIZING
27	I:ARG5>HIS	3.78	DESTABILIZING

The table reports up to 5 lowest energy and up to 5 highest energy mutations. For the full list of results click the links in the Results section.

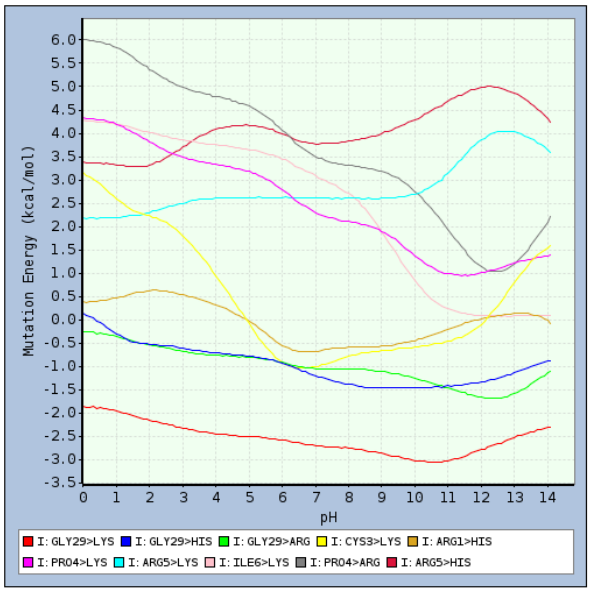


Figure 5: A summary of the lowest and highest energy mutations and the corresponding effect of the mutation. A line plot of mutation energy against pH is also available for these mutations.

- Quickly assess structures from the RCSB with detailed reporting and analysis tools
- Specify the preparation of a protein, including standardize atom names, select alternate conformations, insert missing main-chain or side-chain atoms, adjust terminal residues, and more
- Examine backbone conformations of residues graphically with interactive Ramachandran plots for structure validation
- Align and superimpose protein structures based on structural or sequence similarity
  - Detailed RMSD analysis available at the residue level
- Perform simple x-ray structure determination and model structure refinement with CNX (Crystallography and NMR Explorer)

LEARN MORE

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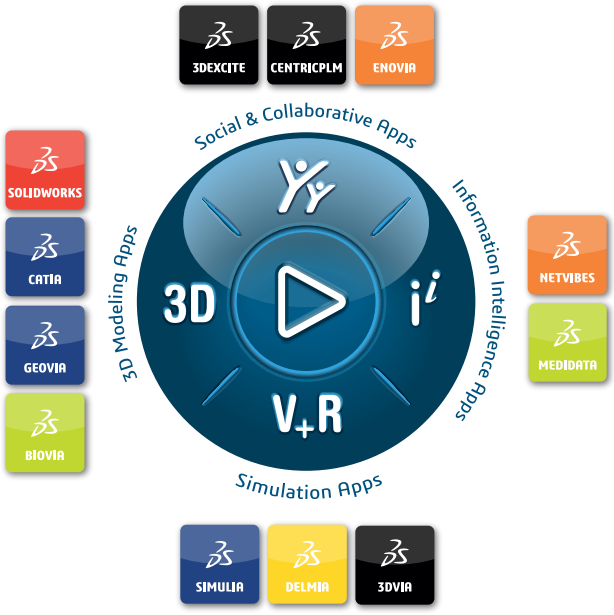

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