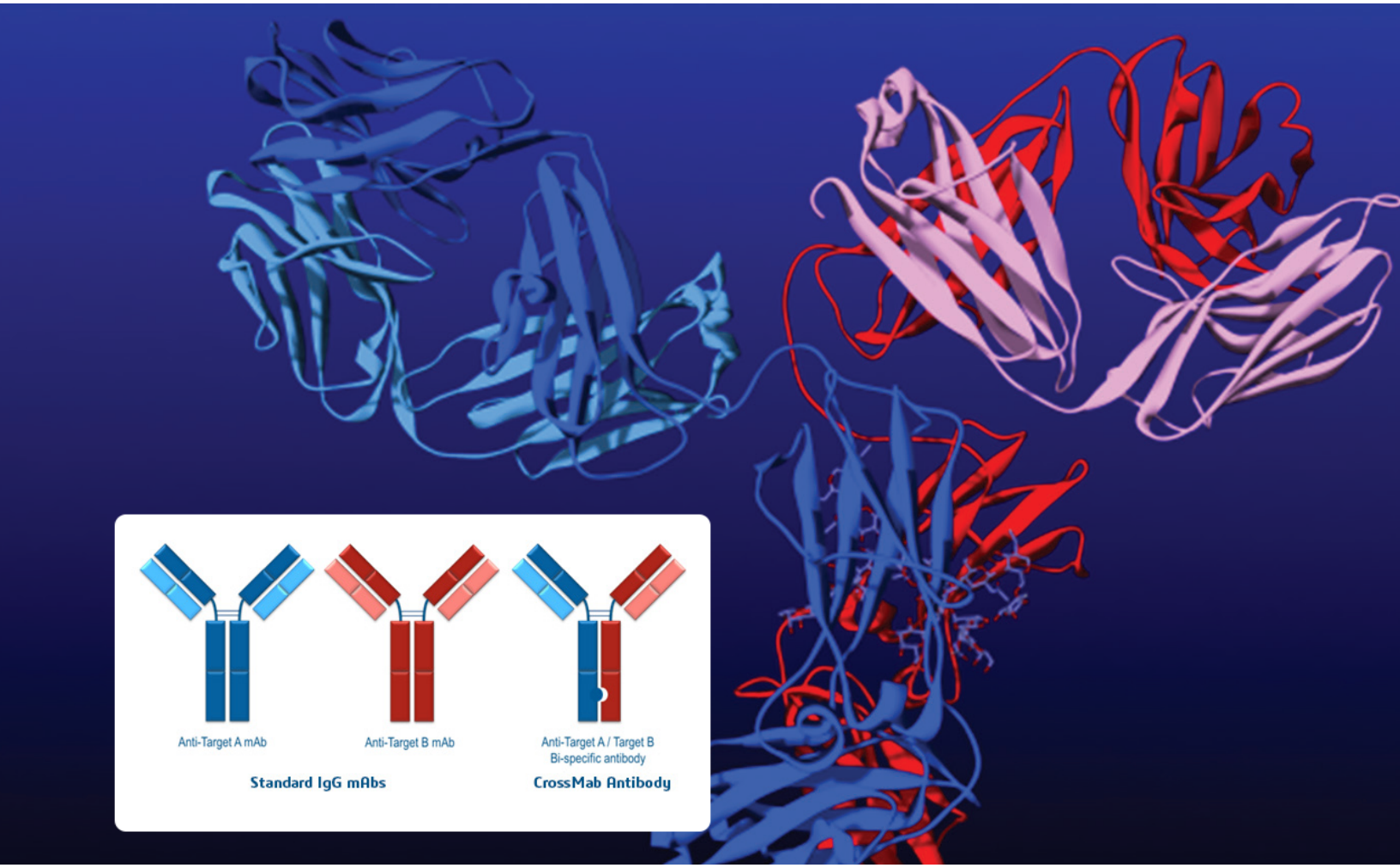
DASSAULT SYSTEMES

BIOVIA

# BIOVIA DISCOVERY STUDIO® 2017 R2

## COMPREHENSIVE MODELING AND SIMULATIONS FOR LIFE SCIENCESE




## ACCURATELY PREDICT LIGAND BINDING ENERGIES

**Drug discovery is a multi-objective optimization.** Scientists have to optimize both biochemical potency and characteristics such as ADME and toxicity. The latest release of BIOVIA's predictive science application, Discovery Studio®, continues the evolution of new science in its market-leading CHARMm[1] molecular simulations engine. Built on BIOVIA Foundation™, Discovery Studio® is uniquely positioned as the most comprehensive, collaborative modeling and simulation application for Life Sciences discovery research.

## DISCOVERY STUDIO 2017 R2

Part of the 2017 R2 BIOVIA product release series, Discovery Studio 2017 R2 continues to deliver key new Antibody and CHARMm-based molecular simulations enhancements.

## NEW AND ENHANCED SCIENCE

- **New!** Model full-length bispecific antibody (BsMAb) structures:
  - Separate light and heavy chains can be supplied for each half of the full-length antibody template
  - 3D structure models of BsMAbs can speed up rational antibody design by predicting: expression, sequence liabilities, stability, and developability

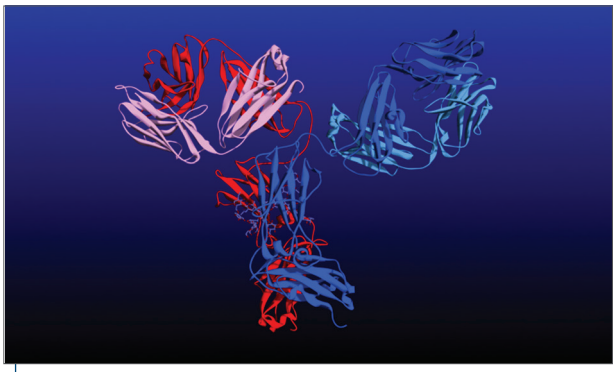


Figure 1: Example homology model of a BsMAb, comprising four unique heavy and light chains. Additionally, the model includes two different Fab templates, one for each distinct domain of the BsMAb.

- **New!** Graft Fab structure onto antibody models for either full-length modeling or in the automated model building cascade:
  - Full length antibody homology modeling: Graft a Fab structure onto full-length template prior to homology modelling
  - Antibody cascade modeling workflow: Produce full length antibody models by grafting the predicted Fab onto a provided full length antibody structure

- **Enhanced** *de novo* Loop prediction: Includes a new four-stage algorithm, allowing Looper to run in one of two modes:
  - Fast Mode: Equivalent to the original Looper approach
  - Precision Mode: Enhanced sampling of the backbone φ and ψ angles. Additionally, includes new filtering of the generated variants and additional backbone entropy term in the final scoring function

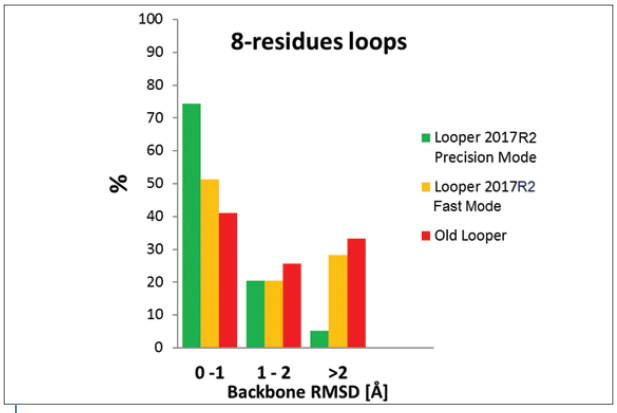
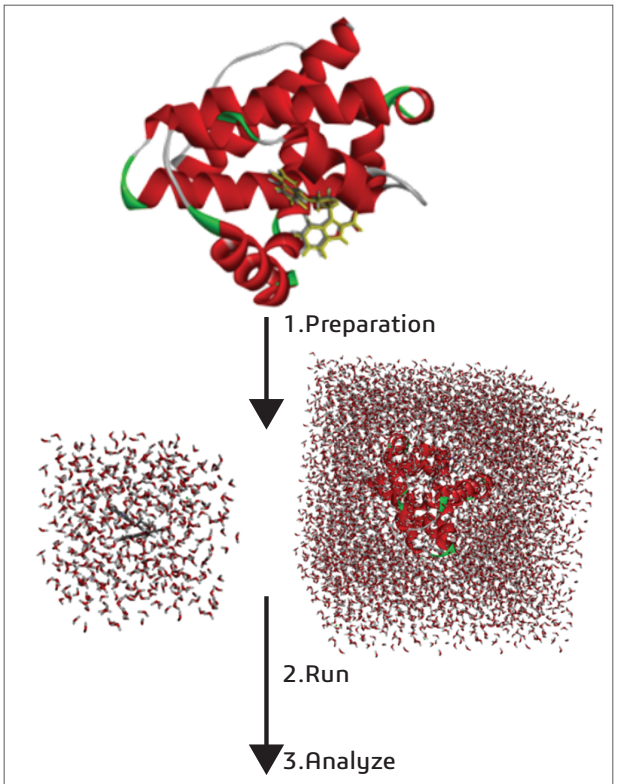



Figure 2: New 'precision mode' in Looper uses enhanced sampling of the backbone φ and ψ angles to yield significant improvements in prediction accuracy.

- **New (Prototype)!** Accurately predict relative ligand binding energy between a pair of molecules using the new prototype free energy perturbation (FEP) protocol:
  1. Preparation: 'Set Up Relative FEP' protocol takes a set of aligned pair of input ligand conformers (e.g., see 'Generate Analog Conformations' protocol) and the input receptor and generates two outputs: a solvated ligand pair and the solvated protein ligand-pair complex




ΔG from Lambda 0.000 to 1.000 = -9.094± 0.082 kcal/mol

| Lambda Window | Lambda0 | Lambda1 | Window Free Energy | Std. Dev. | Cumulative Free Energy |
|---|---|---|---|---|---|
| 1 | 0 | 0.0625 | -4.274 | 0.039 | -4.274 |
| 2 | 0.0625 | 0.125 | -3.123 | 0.024 | -7.397 |
| 3 | 0.125 | 0.1875 | -2.273 | 0.018 | -9.670 |
| 4 | 0.1875 | 0.25 | -1.715 | 0.011 | -11.385 |
| 5 | 0.25 | 0.3125 | -1.270 | 0.010 | -12.655 |
| 6 | 0.3125 | 0.375 | -1.075 | 0.006 | -13.730 |
| 7 | 0.375 | 0.4375 | -0.923 | 0.005 | -14.653 |
| 8 | 0.4375 | 0.5 | -0.812 | 0.006 | -15.465 |
| 9 | 0.5 | 0.5625 | -0.303 | 0.019 | -15.768 |
| 10 | 0.5625 | 0.625 | -0.190 | 0.018 | -15.958 |
| 11 | 0.625 | 0.6875 | -0.065 | 0.017 | -16.023 |
| 12 | 0.6875 | 0.75 | 0.178 | 0.016 | -15.845 |
| 13 | 0.75 | 0.8125 | 0.525 | 0.017 | -15.320 |
| 14 | 0.8125 | 0.875 | 1.064 | 0.019 | -14.256 |
| 15 | 0.875 | 0.9375 | 1.914 | 0.028 | -12.343 |
| 16 | 0.9375 | 1 | 3.249 | 0.036 | -9.094 |

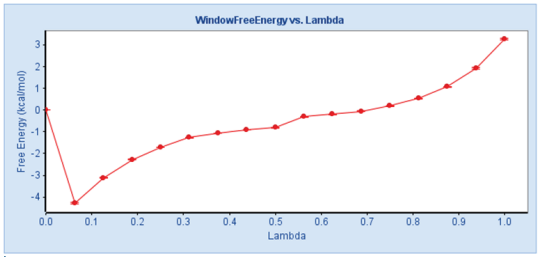



Figure 3: Example chart and tabular output detailing the calculated free energy per Lambda window.

2. Run: 'Free Energy Perturbation (NAMD)' protocol performs a dual-topology relative FEP calculation for the ligand-pair or protein-ligand complex across 16 Lambda intermediate states.
3. Analyze: 'Analyze FEP Results' protocol generates a detailed report of the dual-topology relative FEP results

- **New!** 'Generate Analog Conformations' protocol uses maximal common substructure mapping between lead and analogs to identify unique fragments, efficiently enumerates conformers and applies MM-GBSA scoring to elucidate optimized ligand structures and rank order them by affinity. Can be used to prepare ligand structures, and shortlist them in support of FEP calculations
- **Enhanced** support for CHARMm forcefield patching and improper Definition support
- **Enhanced** antibody modeling components: Significantly improved compatibility and portability for use in custom Pipeline Pilot protocols
- **New!** Export files for 3D printing and virtual reality visualizations: Added the COLLADA (COLLAborative Design Activity) export format, an interchange format suitable for a wide range of 3D applications, such as 3D printers, or VR applications.
- **Update!** TopKat® QMRF Reports[2]: the following TopKat Toxicity Models QSAR Model Report Format (QMRF) reports have been accepted and published on the European Commission Joint Research Center (JRC)

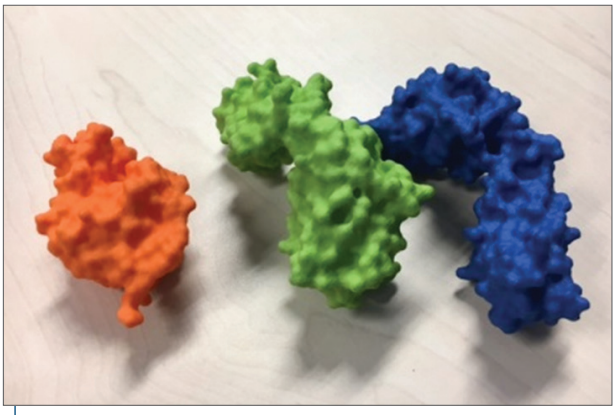


Figure 4: 3D printed models of the antigen (orange) and the Fab light and heavy chains of an antibody generated in Discovery Studio 2017 R2.

| QMRF # | Title |
|---|---|
| Q50-54-55-508 | BIOVIA toxicity prediction model – prenatal developmental toxicity |
| Q50-54-55-510 | BIOVIA toxicity prediction model – weak vs strong sensitiser |
| Q50-54-55-509 | BIOVIA toxicity prediction model – skin sensitiser vs non sensitiser |
| Q51-54-55-514 | BIOVIA toxicity prediction model – acute toxicity to Daphnia |
| Q50-54-55-507 | BIOVIA toxicity prediction model – weight of evidence rodent carcinogenicity |
| Q50-54-55-504 | BIOVIA toxicity prediction model – NTP carcinogenicity call (female mouse) |
| Q50-54-55-512 | BIOVIA toxicity prediction model – moderate vs severe eye irritant |
| Q50-54-55-511 | BIOVIA toxicity prediction model – mild vs moderate eye irritant |
| Q50-54-55-513 | BIOVIA toxicity prediction model – eye irritant vs non-irritant |
| Q51-54-55-515 | BIOVIA toxicity prediction model – acute fish toxicity |
| Q50-54-55-503 | BIOVIA toxicity prediction model – NTP carcinogenicity call (male rat) |
| Q50-54-55-505 | BIOVIA toxicity prediction model – NTP carcinogenicity call (female rat) |
| Q50-54-55-506 | BIOVIA toxicity prediction model – NTP carcinogenicity call (male mouse) |
| Q51-54-55-502 | BIOVIA toxicity prediction model – rat oral LD50 |
| Q50-54-55-501 | BIOVIA toxicity prediction model – Ames Mutagenicity |
| Q53-55-56-522 | Artificial Intelligence Expert Predictive System (AIEPS) model for aqueous solubility |
| Q52-55-56-517 | Artificial Intelligence Expert Predictive System (AIEPS) model for algal (*Pseudokirchneriella subcapitata*) toxicity |
| Q52-55-56-521 | Artificial Intelligence Expert Predictive System (AIEPS) model for acute fish (fathead minnow) toxicity |
| Q52-55-56-520 | Artificial Intelligence Expert Predictive System (AIEPS) model for acute toxicity to Daphnia magna |
| Q52-55-56-519 | Artificial Intelligence Expert Predictive System (AIEPS) model for biodegradation |

## PARTNER SCIENCE

- **CHARMm:** Incorporates the latest release of the academic CHARMM, version c41b1[1]
- **GOLD Support:** Dock Ligands (GOLD) now includes support for the latest release of CCDC GOLD, version 5.5[3]
- **NAMD:** Distributed with the CPU edition, version 2.10[4]
- **MODELER:** Incorporates the latest release of the academic MODELLER, version 9.17[5]

## DATABASES

- **ANTIBODY** has been updated to include the latest antibody template structures from the PDB (based on PDB release Sept. 30th, 2016)
- **BLAST** databases updated for PDB_nr85, PDB, SwissProt, UniRef90 based on corresponding public databases on Sept 30th, 2016
- **The RCSB ligand database** was updated for the RCSB Structure Search protocol (October 2015; 20,861 entries)

## PLATFORM

**Compatibility**: Discovery Studio 2017 R2 is built on and supports the latest release of BIOVIA Pipeline Pilot, version 2017 R2

## REFERENCES


4. Brooks B. R., Brooks III C. L., Mackerell A. D., Karplus M., et al, *J. Comp. Chem.*, **2009**, 30, 1545-1615.
5. http://qsardb.jrc.it/qmrf/
6. GOLD is available from the Cambridge Crystallographic Data Centre: http://www.ccdc.cam.ac.uk/products/life_sciences/gold/
7. A valid GOLD license is required to run GOLD and GOLDscore.
8. Phillips J.C., Braun R., Wang W., Gumbart J., Tajkhorshid E., Villa E., Chipot C, Skeel C.D., Kale L., and Schulten K., J. *Comp. Chem.*, **2005**, 26, 1781-1802.
9. Eswar N., Marti-Renom M. A. Webb B., Madhusudhan M. S., Eramian D., Shen M., Pieper U., Sali A., *Current Protocols in Bioinformatics*, John Wiley & Sons, Inc., **2006**, Supplement 15, 5.6.1-5.6.30.

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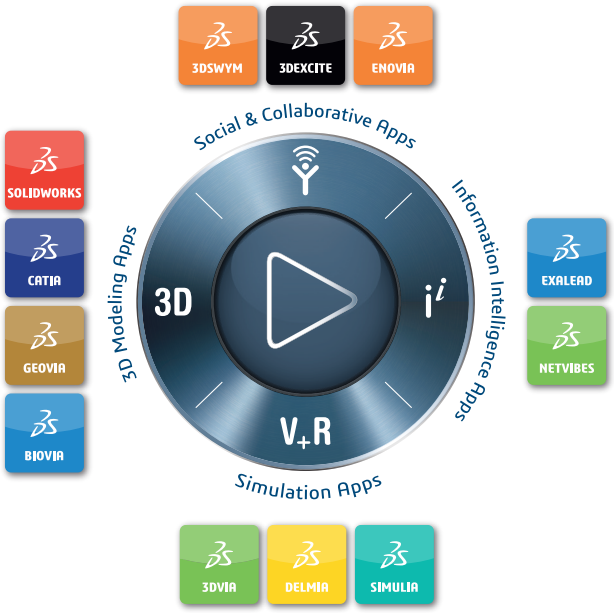


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