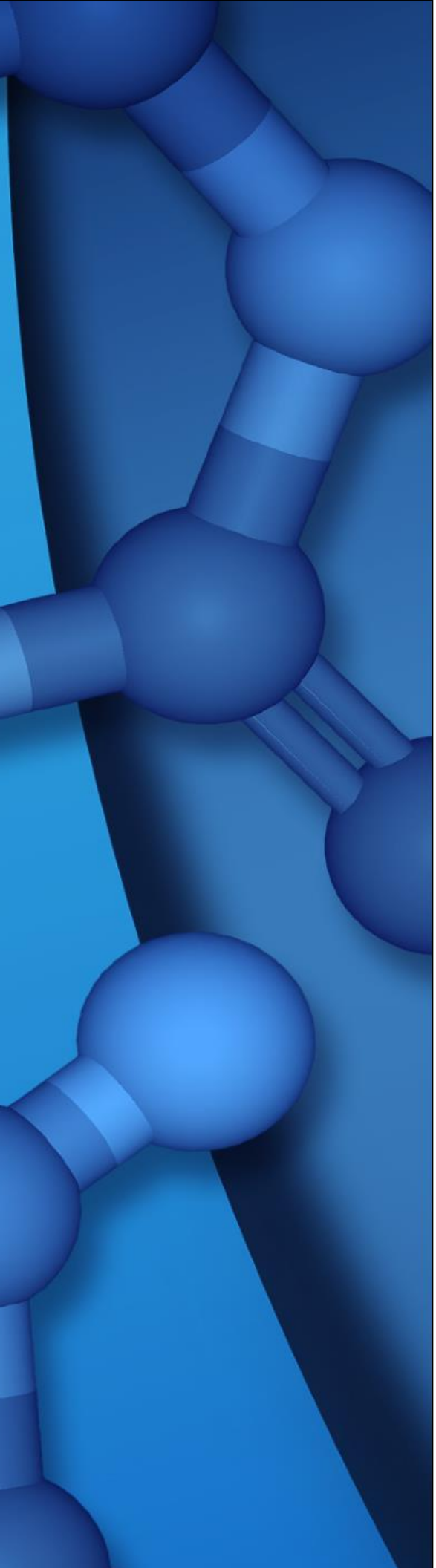

ACCELRYS DISCOVERY STUDIO 4.0

PRODUCT RELEASE DOCUMENT

Applies to: 4.0

Last Updated: Sep. 20, 2013

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Contents

About this Document

This document contains the following release information for Discovery Studio 4.0. This release includes defect fixes and known issues for the current release of Discovery Studio 4.0.

Customer Release Details

Release of Discovery Studio 4.0

September 2013

Accelrys is pleased to announce the release of **Accelrys Discovery Studio 4.0**. This release is now available for download at the Accelrys Community at http://community.accelrys.com/. Note that you must log in to your Accelrys Community account and click the blue Download Center arrow at the top of the page to view software products available for download.

The latest release of Discovery Studio (DS) includes the following new science and updates. For a full list of the new functionality available in this release, see What's New.

Key Technical Points

- **New and Enhanced Protein Design Tools:**
  - *New! Predict and create disulfide bridges:* Identify compatible residue pairs that are suitable for creating new stabilizing bridges.
  - *New! Calculate mutation energy:* New features for improving protein stability and calculating mutation energy for multiple simultaneous mutations.
  - *Enhanced Workflow:* The Identify Framework Templates, Model Antibody Framework, and Build Homology Models protocols are simpler and easier to use.
- **Simulations**
  - *Updated! CHARMm 37b2*: The new release of CHARMm contains performance improvements to both scalability and performance on long duration (nanoseconds) simulations. Also includes support for the charmm36 forcefield (including CGenFF)
  - *Enhanced MD*: Improved support for longer duration nanosecond scale molecular dynamics simulations including RMSD and RMSF analysis and reporting, file processing, concatenation, frame selection and temperature and energy (versus time) plots.
  - *Explicit water solvation:* Performance improvements mean that full length antibody structures can be quickly solvated for simulations with explicit waters and counter ions
  - *Enhanced NAMD support:* A new protocol leveraging the high-performance simulation program NAMD is now part of the Discovery Studio installation, adding faster, more scalable, production dynamics with zero configuration.
- **Structure-based Design**
  - *New!* Powerful New non-bond Interactions Tool: Rapidly detect a host of new key non-bonded interactions and analyze important favorable and unfavorable interactions in a simple one-click interface and tool panel that is easy to use for new and expert users alike.
  - *Updated: Analyze ligand poses* now uses the new non-bond interaction monitors to aid analysis and refinement of virtual screening results

- *Updated: Scaffold hop:* Now uses the new non-bond interaction monitors to aid analysis. Also includes optional ligand constraints to keep the core constrained during minimization
- *Updated* In situ *ligand enumeration:* Now uses the new non-bond interaction monitors to aid analysis. Also includes exhaustive torsion sampling, and optional ligand constraints to keep the core fixed or harmonically constrained during minimization

- **Upgraded Performance:**
  - A *large number of performance improvements have been made throughout the product. Expect to see gains in productivity with improved performance when opening and saving files, running quick protocols, running simulations, analyzing poses, and more.*
  - *Improved Stability: A large number of stability improvements have been made, including a new undo mechanism that reduces the memory requirement for longer workflows and running scripts to a fraction of before.*
- **Updated Scientific Servers:**
  - CHARMm 37b2
  - Modeler 9v12
  - DMOL3 6.1 sp2
  - VAMP 10.0
- **New tutorials and examples:**
  - Visualizing non-bond interactions and evaluating interactions from screening results (new tutorial)
  - Analyzing non-bond interactions screening results with the Analyze Ligand Poses protocol (new tutorial)
  - Preparing and analyzing an explicit solvation molecular dynamics simulation (new tutorial)
  - Creating a 3D model of an antibody Fv domain from a sequence (new tutorial)
  - Annotate Sequence Motifs (new example protocol)
  - Correct Rotated Atom Properties (new example protocol)
  - Update Antibody Database (enhanced example protocol)
- **Improved Welcome Page:** Keep track of various recently used items in the application.

Note: We remind you of our plans to move support for Windows XP, Internet Explorer 6, and Office 2003 SP2 into our Legacy support status. See "(July 2010): Notice of change in support status for Microsoft Windows XP, Internet Explorer 6.0 and Office 2003." at https://community.accelrys.com/docs/DOC-2848 for full details.

Note: Accelrys, as previously announced, has been discontinued support for Windows XP, Internet Explorer 6, Office 2003, Red Hat Linux 4, and Windows Server 2003 for our Pipeline Pilot, Accord, Materials Studio, and Discovery Studio product lines.

For complete details, see (June 2011): Notice of changes in platform support matrix for Materials Studio, Discovery Studio, Accord products and Pipeline Pilot.

Note: With Discovery Studio 4.0, Accelrys is announcing or reiterating the dates at which various versions of Discovery Studio move into their legacy and unsupported phases:

Version	Legacy support begins	Unsupported as of
2.0	30-Sep-2009	30-Sep-2009

Version	Legacy support begins	Unsupported as of
3.0 and 3.0 SP1	21-Nov-2013	21-Nov-2014
3.1	26-Jun-2014	26-Jun-2015
3.1 SP1	31-Aug-2012*/ 31 Aug-2014**	31-Aug-2013*/ 31-Aug-2015**
3.5	20-Jun-2015	20-Jun-2016
3.5.1	20-Jun-2015	20-Jun-2016
4.0	30-Sep-2016	30-Sep-2017

* For applications deployed in unregulated environments (for example, Discovery).

** For applications deployed in regulated environments, where the installation must be validated for regulatory authorities.

For full details of these support phases, see the "Product Support Guidelines" at https://community.accelrys.com/docs/DOC-2833

System Requirements

See System Requirements for Discovery Studio 4.0.

Getting Help

If you have any questions, contact Accelrys Customer Support at:

- Support for Accelrys Products is available at support@accelrys.com or support-japan@accelrys.com (for our customers in Japan).
- Accelrys Support on the Web: https://community.accelrys.com/index.jspa

A complete list of regional Accelrys Customer Support offices is available at:

- Accelrys Support Offices: http://accelrys.com/customer-support/contact.html

Release Notes

What's New

This release of Discovery Studio 4.0 includes the following new features and enhancements.

Enhancements for Discovery Studio 4.0

General

Description
Improved performance and memory usage for rendering in line mode.
The undo feature was updated to use no additional memory.
Opening a file from URL now supports automatic http gzip compression, which significantly improves the download performance from compatible servers, such as RCSB PDB site.
The Van der Waals radii have been modified to be closer to the standard definitions [Bondi, 1964]. Those changes may have a small effect on energy monitors, atom display, and surfaces, but Simulation calculations are not affected because they use radii defined by the forcefield.

Description
Two new templates have been added to the File Explorer preferences | URL Location subpage to facilitate the retrieval of ideal ligand coordinates from the Protein Databank in PDB or SD format: ■ PDB Ligands (PDB format): http://www.rcsb.org/pdb/files/ligand/@_ideal.pdb?download=true ■ PDB Ligands (SD format): http://www.rcsb.org/pdb/files/ligand/@_ideal.sdf?download=true
Improved error handling for parallel protocol runs. All errors are now included in the report page. You now have the option to retain partial output when you stop a protocol during a run.

Macromolecules

Description
Enhanced the Calculate Mutation Energy (Stability) and Calculate Mutation Energy (Binding) protocols with the ability to calculate mutation energy for multiple simultaneous mutations (e.g., single, double, triple, etc.) Additionally, the interface is more flexible, allowing you to specify which amino acid types to mutate into for each selected residue.
Added a set of tools to the Design Protein tools panel to predict sites that can form disulfide bridges by mutating pairs of residues to cysteine.
A new tool panel, Predict Protein Aggregation, provides access to the functionality for calculating developability indices and aggregation scores. Note that these tools were previously contained in the Design Protein tools panel.
Added the ability to run the Model Antibody Loops, Model Antibody Framework, and Model Full Length Antibody protocols using coarse grain parallelization.
Enhanced the Identify Framework Templates protocol: ■ The Input Sequence is divided into two parameters, Light Chain Sequence and Heavy Chain Sequence. Note that this affects backward compatibility. ■ Lists the organism of the identified templates. ■ Download the hit template structures from the antibody database and provide links to the templates in the report to allow easy access. ■ Generate corresponding alignments of light and heavy chain hits and overall framework hits based on the selected residue numbering scheme.
Enhanced the Model Antibody Framework protocol: ■ The model can be built based solely on the interface template. Light and heavy chain templates are now optional. ■ A new advanced parameter allows you to build a Single Chain Model. ■ Query and template sequences are aligned using residue numbers assigned by a specified residue numbering scheme.
Enhanced the Model Antibody Loops protocol: ■ Added a new parameter to preserve the residue numbering of the input protein molecule. ■ Modified the output alignment and template structures so that there is one copy of the template for each loop hit to makes it easier to select a subset of loop templates to remodel the specific CDR loops using the Build Homology Models protocol.
Improved the Update Antibody Database example protocol to create cleaned and superimposed antibody structures as part of the antibody database.
Upgraded the Annotate Antibody Sequence protocol and Find Antibody Domains component to use the new HMMER 3.0 based components in the Sequence Analysis collection.
Enhanced the Calculate Aggregation Scores protocols to allow you to preview the number of frames and other information when selecting a trajectory file (DCD).
Protein Report tools now include experimental pH if it is specified in the PDB file's REMARKs section.
Modified RCSB Structure Search protocol to use the new REST service.
Enhanced the NCBI Entrez Sequence Search and BLAST Search (NCBI Server) protocols to allow you to run the protocols using a proxy server that requires authentication.

Description
Enhanced the Verify Protein (MODELLER) protocol to report the Normalized DOPE score and residue DOPE profile.
The Build Mutant protocol has been modified to retain the water molecules present in the input structure.
The Scan Sequence Profiles protocol, Scan Profile component, and related ProfileHits result window are no longer available. Similar functionality can be achieved using BLAST or PSI-BLAST search.

Simulation

Description
Added initial support for the charmm36 forcefield. All protocols that support the charmm27 forcefield now support charmm36. The new forcefield is a revised version of charmm22/charmm27 forcefield, with improved backbone CMAP and side-chain torsion parameters, which improves protein simulation results.
Enhancements to the Dynamics (NAMD) protocol: ■ The protocol is now available from the Run Simulations tools panel, and no longer requires a separate download. ■ Includes the latest version of NAMD 2.9. ■ Updated and improved the user interface to make it easier to set up and run the protocol.
Added a new protocol, Process Trajectory Files, that concatenates multiple DCD files from consecutive dynamics simulation jobs, saves a subset of the frames or subset of atoms from one or more dynamics simulations, and converts a CHARMm ENE file into CSV format for plotting.
Enhanced the Analyze Trajectory protocol: ■ You can calculate RMSD against a specified molecule and report the average RMSD. ■ You can calculate side-chain, backbone, and whole residue RMS fluctuation (RMSF) of all or selected residues. ■ Improved the protocol interface to allow you to choose frames from the DCD file as reference. Note that this affects backward compatibility. ■ You can select frames to be analyzed from the input molecule. ■ You can preview the number of frames and other information when selecting a trajectory file (DCD). The same mechanism is also available the new protocol Process Trajectory Files.
Enhanced the Solvation protocol: ■ Improved performance and removed system size limitations. ■ Added an optional minimization stage so that the solvated system can be easily minimized before running other simulation jobs. ■ New capability to add counter ions for a sphere boundary.

Description
Improvements to the dynamics simulations protocols: ■ Added temperature and energy (versus time) plots in the report for Dynamics (Heating and Cooling) and Dynamics (Equilibration) protocols. ■ Added energy (versus time) plot to the reports for the production stage of Standard Dynamics Cascade and Dynamics (Production) protocols. ■ The SHAKE option is now on by default and the Time Step is 2fs by default. ■ Increased the minimization steps in Standard Dynamics Cascade protocol to better minimize the initial structure. ■ Modified the simulation time, save results interval, and time step parameters to use time units. Note that this change affects backward compatibility. ■ Reduced the memory requirements for the Standard Dynamics Cascade protocol when running large systems, such as fully solvated full length antibody. ■ Partial results are now retrieved for failed dynamics simulation jobs. ■ Solvent counter ions are now removed (in addition to solvent water) from *_nosolvent.dsv.
Added a new option, Automatic, for the Electrostatics parameter and made it the default in the following protocols: ■ Dynamics (Heating and Cooling) ■ Dynamics (Equilibration) ■ Dynamics (Production) ■ Standard Dynamics Cascade ■ Calculate Energy ■ Minimization
This automatically determines whether to use periodic boundary condition (PBC) and particle mesh ewald (PME) when calculating non-bond interactions and long range electrostatics based on whether the input contains an explicitly solvated water box.
The Trajectory Principal Component Analysis protocol can now analyze molecular systems with more than 4500 atoms on 64 bit system.
The B3LYP density function was added to all DMOL3 related protocols such as: ■ Calculate Molecular Properties ■ Calculate Energy (QM-MM) ■ Minimization (QM-MM) ■ Calculate Energy (DFT) Additionally, a new parameter, Add Dispersion Correction, was added to the DMOL3 settings.

Receptor-Ligand Interactions

Description
Enhanced the Dock Ligands (LibDock) protocol. Implicit Solvent Model is now set to Distance-Dependent Dielectrics by default to improve the in situ minimization results. Additionally, the default values for the Nonbond List Radius and Nonbond Lower Cutoff
Distances were standardized with other protocols.

Description
Enhanced the Dock Ligands (CDOCKER) protocol: ■ Hydrogens are added automatically and alternate amino acid conformations are removed from the receptor. ■ Missing hydrogens are added to the input ligands. ■ The default for the Pose Cluster Radius parameter is now set to 0.1 to ensure a more diverse set of top scoring poses. ■ Eliminated platform dependencies.
Enhanced the In Situ Ligand Minimization protocol: ■ A new parameter, Input Receptor Hydrogen Flexibility, allows for flexible receptor hydrogen atoms in the vicinity of the ligand during minimization. ■ Increased performance up to 100% when minimizing ligands with rotatable atoms. ■ Added a new parameter, Substructure Constraints | Input Substructure to specify a constrain substructure during minimization (Fixed or Harmonic).
Enhanced the Analyze Ligand Poses protocol: ■ Improved the interface. ■ Interaction types are split into several categories using non-bond perception. ■ The protocol creates an interactions summary, histogram, and a heat-map plot. ■ You can filter ligands for favorable receptor interactions. ■ Increased performance more than an order of magnitude when using ligands with rotatable (flexible) receptor atom properties generated by docking protocols such as Dock Ligands (GOLD) and In Situ Ligand Minimization.
Enhanced the Grow Scaffold protocol: ■ Uses the new non-bond interaction perception. ■ A new parameter, Torsion Sampling, allows for exhaustive torsion angle search. ■ A new property, RMSD scaffold, is now calculated for each ligand. This property quantifies the shift of the scaffold after the in situ minimization. ■ A new option, Ligand Constraint, allows you to keep the scaffold core fixed or allow restricted minimization during in-situ minimization.
Enhanced the Replace Fragment protocol: ■ Uses the new non-bond interaction perception. ■ Ligands can be minimized in the absence of a receptor. ■ Improved fragment placement and fragment minimization. ■ The input has been simplified by replacing the six custom library selection parameters with one parameter: Fragment Libraries | Custom. The protocol analyzes the files and assigns the libraries accordingly. ■ When a custom library is used, the report indicates the number of fragments used in each library. ■ A new option, Ligand Constraint, allows you to keep the scaffold core fixed or allow restricted minimization during in situ minimization.
Enhanced the performance of the Calculate Binding Energies protocol. Depending on the settings the protocol/component runs two to three times faster.

Small Molecules

Description
Enhanced the Align to Selected Substructure protocol: ■ The protocol now supports the SD file format. ■ Removed the Remove Molecules That Do Not Match protocol. All ligands that do not match the substructure search are now written to the fail file.
Enhanced the Analyze Activity Effects using MMP and Find Activity Cliffs using MMPs protocols by adding the following new parameters to improve control of the results: ■ Minimum Core Size ■ Maximum Fragment Size ■ Minimum Core Size ■ Maximum Core Size
Enhanced the Calculate RMSD protocol: ■ Included a table in the report with detailed information for pose cluster. ■ Included a link to the dendrogram scripts in the report.
Enhanced the Prepare Ligands protocol to include a property, Duplicate Name, for duplicate ligands that have been filtered.
Enhanced the Analyze Conformations protocol to use the new non-bond interactions perception.
The Build Fragment tools panel has a new category, PDB_Carbohydrates, which contains a selection of residues commonly found in glycosylated proteins with PDB nomenclature and some typical multi-residue glycan moieties.

Updates to Third Party Software

Description
CHARMm has been updated to version 37b2.
MODELER has been updated to version 9v12.
NAMD version 2.9 is now part of the Discovery Studio installation.

Component Collection Enhancements

Description
Create Free-Wilson Least Squares Model protocol: This example protocol was enhanced to return a virtual library with maximized activities.
DS Alignment Reader: A new option, Keep Features, allows for reading of sequence features and annotations from .bsml alignment files.
Annotate Antibody Sequence protocol and Find Antibody Domains component: Updated the Annotate Antibody Sequence protocol and Find
Antibody Domains component to use the new HMMER 3.0 based components in the Sequence Analysis collection. HMMER 3.0 is the most recent version of the Hidden Markov model based HMMER sequence analysis package.
Semi-empirical QM Descriptors component: Updated with VAMP version MS 6.1 SP2.

Database Updates

This release includes the following fixed defects:

Description
The Antibody database has been updated.
The BLAST database has been updated.
The PDB_Antibody sequence database was removed from supported BLAST databases. This database was used to identify antibody framework templates for building antibody framework models. The functionality is replaced by an improved algorithm in the Identify Framework Templates protocol.
The PharmaDB is updated with the 2012 version of the scPDB (an annotated database of druggable binding sites from the protein dataBank) This database was built in collaboration with Didier Rognan of the University of Strasbourg. An example subset is installed with Discovery Studio. The full PharmaDB must be installed separately.

Fixed Defects

This release includes the following fixed defects:

Description	Issue ID
The Prepare Protein protocol now preserves the bond order in ligands when the Build Loops option set to True.	DSC-15895
Reduced the memory requirement for loading the output loop models from the Loop Refinement protocol.	DSC-18798
Improved the RCSB Structure Search protocol so that models in NMR structures are no longer counted as unique hits and added option to download only the first model or all models.	DSC-18494
The Build Mutants protocol now retains the residue insertion codes.	DSC-17102
Fixed an issue with the Calculate Binding Energies protocols where when using in-situ minimization with flexible receptor atom minimization, they did not correctly identify the rotated receptor atoms.	DSC-19724
Fixed an issue in the Dock Ligands (LibDock) protocol that occurred when the protein name contained the letters .pdb	DSC-17737
Enhanced the Grow Scaffold protocol so that fragments with amide bonds are always in the trans conformation.	DSC-18172
Improved the performance of the In Situ Ligand Minimization protocol by 15% when specifying flexible residues.	DSC-18589
Fixed an issue with the Grow Scaffold protocol that caused it to fail due to scaffold hydrogen bonds, which resulted in bump check failures.	DSC-18551
A filter was added to Filter by SMARTS to avoid duplicate Names and SMARTS from being used. Additionally, existing duplicate SMARTS entries were removed.	DSC-19001
Reduced the number of symmetry operations in the Generate Conformations protocol clustering step when minimization is enabled.	DSC-18745
Fixed an issue with the Split Ligands into Multiple Files protocol that caused it to fail when a corrupted molecule was encountered.	DSC-18773

Description	Issue ID
Fixed an issue that caused an error to be flagged when running Prepare Protein on a Japanese language machine.	DSC-16711
Enhanced the Dock Ligands (LibDock) protocol. Implicit Solvent Model is now set to Distance-Dependent Dielectrics by default to improve the in situ minimization results.	DSC-16926
Fixed an issue with Generate RECAP Fragments where ligands with sulfonamide fragments were not correctly enumerated in some cases.	DSC-16935
Resolved an issue that caused the application to crash when loading CIF files with unspecified angles.	DSC-17013
Enhanced the Dock Ligands (CDOCKER) protocol. The default for the Pose Cluster Radius parameter is now set to 0.1 to avoid similar top scoring ligand poses. This ensures that the top scoring poses are diverse. Also eliminated platform dependencies.	DSC-17285, DSC-18632
Added theory documentation for the ADMET Developmental Toxicity Potential model.	DSC-17305
Fixed an issue in the Toxicity Prediction (Extensible) protocol that caused a problem with the detailed report when the number of fingerprint features was less than 3.	DSC-17313
Fixed a defect in the Hierarchy View where the incorrect object hierarchy would be displayed when running the conformations to molecules script from the Structure Editing submenu of the Scripts menu.	DSC-17393
The Catalyst Configuration File parameter of the Common Feature Pharmacophore Generation protocol is now correctly used when aligning the ligands to the generated pharmacophores.	DSC-17452
Resolved an issue that caused the client to take a long time to open when loading Jobs.xml files for protocols that generate a large number of files.	DSC-17573

Known Issues

This release of [Product Name] includes the following known issues:

Description	Issue ID
Discovery Studio cannot correctly perceive input files with incorrectly specified connectivity (e.g., a ligand in a PDB file with wrong/partially missing CONECT records). You can correct this by performing the following steps: 1. Select the affected part of the structure. 2. Choose Chemistry | Bond | Bond Order from 3D from the menu bar. 3. Check and fix any incorrectly perceived bonds. This will find bonds using a distance search before assigning bond orders based on the geometry.	DSC-18152
There are known graphics issues on Linux machines with NVIDIA card that are using drivers with versions 319 and 325. Also, there are reported shading issues when using the ATI driver version 12.104.2. See the system requirements for a list of supported drivers: System Requirements for Discovery Studio 4.0.	DSC-21457
The BLAST search programs can use a lot of memory and fail if the input is too large or if there are too many hits.	DSC-18464