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NEXT GENERATION CHEMISTRY SOFTWARE

Pipeline Pilot Cresset Package User Guide

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Contents

About Cresset Package for Pipeline Pilot

The Cresset Package incorporates key Cresset applications into Pipeline Pilot. Each component wraps the corresponding command line binary making it available within Pipeline Pilot.

The Cresset Package uses our proprietary XED molecular mechanics force field and gives realistic, low energy conformations and accurate molecular fields. However, the XED force field is optimized for small drug like molecules and hence is sub-optimal for tasks that lie away from the study of bioactivity. In particular, support for non-organic elements is limited and transition states are not supported.

Forge

Forge is Cresset's powerful computational suite to aid in SAR understanding and molecule design. It is available with both a graphical user interface and as a series of command line binaries which are incorporated into Pipeline Pilot components in this package.

The Forge components can be found under **Components > Chemistry > Cresset > Forge** and examples on how to use the components can be found under **Protocols > Examples > Chemistry > Cresset > Forge**.

Forge Align is a tool to align multiple molecules to a reference molecule in a predefined conformation. Molecules for alignment are not limited by 2D similarity to the reference molecule. When used on a congeneric series the tool can help in library design and give a rationale for the prioritization of compounds for synthesis. Using Forge Align on a diverse set of active molecules can help define the requirements of the protein of interest, aiding the synthetic chemist in the design of new actives. Forge Align will read molecules from the input stream either as a series of conformations (such as the output of the XedeX component) or as flat representations that require conformational analysis. For each molecule in the input stream the best alignment to the reference molecule is output. Optionally the Forge Align component can load a protein structure that can be used as an excluded volume for the alignment.

Activity Miner is designed to compare a dataset of compounds and output a matrix of similarities, distances or disparities for the molecules. In contrast to other similar methods the Activity Miner component can operate using either 2D or 3D metrics in calculating the matrix enabling the detection of activity cliffs in a biological context. Using Activity Miner highlights both the activity cliff and the reason for the observed change in activity. For more information see http://cresset-group.com/activityminer.

Forge Build is a tool for generating a 3D QSAR model for activity from a set of aligned molecules. It determines a set of "sample positions" around the molecules based on their field points, and then calculates the value of the molecular fields at those positions. The data matrix derived from this is then processed by partial least squares (PLS) to generate a linear model for activity. Optionally the data matrix can be exported for use with alternative data analysis methods.

Forge Score is a tool for calculating predicted activities for molecules against a 3D QSAR model. The molecules must be pre-aligned before scoring against the model.

Forge Model Viewer (on Client) component is used to view the model generated by the Forge Build component. Forge or Torch needs to be installed and licensed on the client machine for this component to work.

FieldTemplater is a tool for comparing molecules using their electrostatic and hydrophobic fields in order to find common patterns. When applied to several structurally-distinct molecules with a common activity, FieldTemplater can determine the bioactive conformations and relative alignments of these molecules in the absence of protein information. For more information see http://www.cresset-group.com/products/forge/fieldtemplater.

Spark

Spark is a bioisostere replacement tool. Given a 'starter molecule', the user selects a section to replace. Spark then searches a fragment database for replacement fragments with similar electrostatic and steric properties. Each replacement is merged into the starter molecule and energy minimized before scoring. Spark is supplied with databases of fragments derived from commercially-available compounds, literature compounds, and theoretical studies. An optional database generator module enables the creation of custom fragment databases.

The Spark components can be found under **Components > Chemistry > Cresset > Spark** and examples on how to use the components can be found under **Protocols > Examples > Chemistry > Cresset > Spark**.

Spark Database Search is used to search for bioisosteric replacements for part of a molecule. The section of the molecule to be replaced is specified using either a tag on the starter molecule or by a parameter on the component. In either case the section can be specified as a set of atom indices or as bonds to be broken where the first atom on a bond is retained and the second removed. The fragment databases to search can be specified using either a tag on the starter molecule or by a parameter on the component. Available databases are detailed using the Spark Database List Viewer.

Spark Database Search (on Client) is the same as the Spark Database Search component except the section of the molecule to be replaced and the databases to search do not need to be specified. Instead the component will temporarily stop the running protocol and will ask the user to select the section of the molecule to be replaced using a 2D image of the molecule. It will also ask which databases should be searched. Spark needs to be installed and licensed on the client machine for this component to work.

Spark Database List Viewer displays a report on which Spark databases have been installed on the Pipeline Pilot Server.

Generate Spark Database is used to create or update a Spark fragment database from the set of molecules. The database can then be used by Spark Database Search component.

Blaze

Blaze is Cresset's ligand based virtual screening technology. Given an active molecule in its bioactive conformation, Blaze is used to search through databases of millions of molecules to find those that have the most similar shape and electrostatic properties. Blaze has extensive compound management features that enable the control of compound collections and pre-population of conformations for all uploaded molecules. Blaze can be accessed using a web browser or using a REST API with the server located internally or in the cloud

Components to access Blaze's functionally through the REST API can be found under **Components > Chemistry > Blaze**. To use the Blaze components you will need an account for your internal Blaze server or for Cresset's software as a service offering of Blaze. To evaluate the Blaze functionality you can connect to our Blaze Demo server using a username and password from http://www.cresset-group.com/products/blaze/blaze-saas-demo-signup/.

New Blaze Search creates a new Blaze search.

Blaze Searches Viewer displays a brief overview of all your searches in Blaze.

Detailed Blaze Search Viewer displays a detailed report a Blaze search.

Download Blaze Search Results downloads the results of a Blaze search.

Blaze Collections Viewer displays a report on the Blaze collections which are available for searching.

Upload Molecules to Blaze Collection uploads molecules to a Blaze collection.

Blaze Status Viewer displays a report on the status of the Blaze server.

XedTools

The XedTools components wrap key functionality of the XED force field and can be found under **Components > Chemistry > Cresset > XedTools** and examples on how to use the components can be found under **Protocols > Examples > Chemistry > Cresset > XedTools**.

XedMin is a tool to minimize molecules using the XED force field from Cresset. XedMin uses a conjugate gradient to minimize the energy of a molecule using the XED molecular mechanics force field. All energies are calculated in vacuo. If the input structure is 2D or smiles then an initial conversion to 3D is undertaken before minimization with the conjugate gradient minimizer. Optionally XedMin can be used to minimize just one fragment in a multi-fragment complex. However, XedMin can only process molecules with a maximum of 10,000 atoms (including all hydrogen and XED atoms) which roughly equates to a maximum of 2,500 heavy atoms. Optionally the XedMin component can load a protein structure (in mol2 format) that can be used as a context for the ligand minimization. Note that the 10,000 atom limit includes any protein structure that is loaded.

XedeX component provides an interface to the XedeX command line conformation generator. XedeX is a program to read in one or more molecules in multiple formats, perform a conformational hunt using the XED force field, and write the results to standard output. The conformational hunt process is designed to generate a highly diverse set of conformations, all of which are minimized, in as short a space of time as possible. XedeX is designed to find a representative set of minimum vacuum energy structures using the features of the XED force field. It is not designed to find all local minima over a given energy range. Rather, it has been designed to collect as broad a range of conformationally diverse structures as possible above the global minimum. This strategy is implemented deliberately to feed the requirements of the field overlay protocols (e.g. Forge Align) which need wide sampling of conformational space.

Cresset Molecule Writer component converts molecules into Cresset's BXD file format. This can be used in Web Protocols to write out molecules to $(JobDir) directory as BXD files. Links to the molecules BXD files will then appear in the job result page, and when clicked the molecules will be opened in Forge or Torch.

Viewers

Viewer components can be found under **Components > Chemistry > Cresset > Viewers** and examples on how to use the components can be found under **Protocols > Examples > Chemistry > Cresset > Viewers**.

Cresset Molecule Viewer (on Client) is used to launch Forge or Torch (including TorchLite) for viewing molecules. These powerful molecular viewers, editors and sketchers show your molecules in 3D overlaid with field patterns together with 2D structure and physicochemical properties. Every molecule that is loaded into the viewing application is presented in 3D and in 2D in a molecule table that contains calculated physico-chemical properties such as logP and TPSA and any data that was present in the original file (e.g. sdf file tags). The molecule table can be filtered on any of the columns present to focus the view towards molecules with specific values. Molecules that are highlighted in the 2D table are also displayed in the 3D window enabling comparison of molecules in specific alignments either side by side or overlaid with each other. Any molecule can be marked as a “favorite” or as a “search molecule” enabling greater control over these entries. Forge or Torch needs to be installed and licensed on the client machine for this component to work.

The Cresset Support Team

Cresset
New Cambridge House
Bassingbourn Rd
Litlington
Cambridgeshire
SG8 0SS

www.cresset-group.com
support@cresset-group.com
skype: cressetgroup
@cressetgroup
Join Cresset group on Linkedin
+44 1223 85 88 90