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Spark™ V10.5.6 Release Notes

About Spark.....	2
Supplied Binaries.....	2
Supported Platforms.....	3
Installation.....	3
Supplied Databases	5
Start Spark.....	5
Licensing	6
Changes in 10.5.6.....	6
Changes in 10.5.5.....	6
Changes in 10.5.0.....	6
Changes in 10.4.0.....	8
Changes in 10.3.0.....	9
Changes in 10.2.0.....	10
Changes in 10.0.1.....	11
Version 10.0.0	11
Uninstalling Spark.....	11
Known Issues and Bugs	12
Support.....	12

About Spark

Spark suggests biologically relevant replacements (bioisosteres) for key fragments of known active molecules. You load an active molecule into Spark, preferably in the bioactive conformation, circle the part of the active that you wish to replace and specify which databases to search. Spark will present a list of biologically relevant replacements ranked using Cresset's unique molecular field technology (<http://www.cresset-group.com/science/>). As well as replacing central parts of a molecule, Spark can suggest replacements for terminal groups. It can be used to grow ligands and fragments into unoccupied pockets of the target protein, carry out ligand joining and macrocyclization experiment, and to find a fragment which displaces a crystallographic water molecule near your ligand.

To create the results, Spark uses a set of databases that contain conformationally explored fragments. These databases are stored on a file system that must be accessible to the main application. Usually this means the local disk but can be network disks or removable drives as well.

Supplied Binaries

Spark functionality is available through a graphical user interface with two interlinked binaries (Spark, FieldEngine) and as command line binaries (sparkcl, sparkdb, sparkdbupdate and FieldEngine):

Spark.exe	The main graphical interface for Spark.
FieldEngine.exe	<p>The calculation engine for Spark and command line binaries. FieldEngine is started directly by the primary interface to perform specific calculation tasks. By default, one FieldEngine binary is started for each CPU core on the host machine (but this can be reconfigured in the application preferences or by command line switches). The applications communicate with the FieldEngine using a TCP/IP protocol that can cause network access warnings in some situations.</p> <p>The FieldEngine process can be run on a remote machine with communication managed through a variety of methods including Cresset's Engine Broker.</p>
sparkcl.exe	This is the command-line equivalent to the main Spark GUI. It is used to search a database of fragments for bioisosteres of the section of the molecule that you specify on the command line. At the completion of the calculation the 'sparkcl' application collates the results and outputs these in the format specified by command line options (e.g. SDF file).
sparkdb.exe	This is the command-line version of the database generator functionality in Spark. It is used to create a database of fragments for use with Spark by fragmenting existing molecules or by importing existing fragments. At regular intervals during the calculation the 'sparkdb' application collates the results and saves these to the specified database.
sparkdbupdate.exe	This binary can be used to install and update all or selected Spark fragment databases, as an alternative to the Spark Database Updater available within the Spark GUI.

Supported Platforms

Minimum specifications

Hardware	Specifications
RAM	1GB
Processor	Intel i5 processor or equivalent
Disk space	6GB (for 4 Common DBs)

When using a machine close to these specifications, then Cresset recommend that only three databases are installed and searched - contact [Cresset support](#) for a detailed discussion.

Recommended specifications

Hardware	Specifications
RAM	2GB
Processor	Intel i5 processor or equivalent
Disk space	40GB

Supported Operating Systems

Spark is supplied as 64bit binaries for Windows®, macOS® and Linux®.

Windows®	macOS®	Linux®
Windows 7	macOS 10.12	Red Hat Enterprise Linux 6.10+ CentOS 6.10+
Windows 10	macOS 10.13	Red Hat Enterprise Linux 7

Installation

Platform based installation instructions are given below and at <http://cresset-group.com/installing-desktop-applications>.

Installing the Spark application

Windows

1. Browse to the Windows folder of the Spark distribution media (or locate the installer in your Downloads folder) and double click the executable installer file.
2. Follow the on-screen instructions.
3. If you have a previous version of Spark installed, then this will be removed before installing the new version.

Linux

1. Browse to the Linux folder of the Spark distribution media.
2. Install the Spark re-locatable rpm package using one of the command lines below (where <vers> is the version number, <arch> is the architecture and <path> is install location (/opt by default)):

```
yum install creset-spark-<vers>-1.<arch>.rpm
```

or

```
rpm -U [--prefix <path>] creset-spark-<vers>-1.<arch>.rpm
```

3. Alternatively, unpack the supplied tgz file to a suitable location (e.g. \$HOME or /usr/local or /opt).

macOS

1. Open the supplied disc image.
2. Drag the Spark icon onto the Applications icon to install the application in the Applications folder.

Installing Spark Databases

The database files contain conformationally explored fragments of known molecules. Creset recommend installing at least the databases 'ChEMBL_common', 'VeryCommon', 'Common' and 'LessCommon' as these cover most fragments that are convenient to synthesise.

Spark fragment databases can be installed as follows:

- By copying to the appropriate folder (see the default database locations table below).
- Using the built-in Spark Database Updater
- Using the sparkdbupdate.exe binary

If you have been supplied with the databases on a USB key then simply copy them to one of the default database locations listed below. Note that administrator privileges will be required to copy them to a system location.

Full installation details are available at <http://www.creset-group.com/products/installing-desktop-applications>.

Spark Database Updater

The Spark Database Updater (available from the Spark GUI) can be used to download and/or install and update databases from the internet. The updater will install or update system-wide databases if the user has permission to write to these locations, otherwise it will write to a user location or a custom location set in the Spark Preferences (Edit → Preferences menu). Please refer to the 'Database Updater' section of the Spark manual for a detailed explanation. To update system-wide databases either run the application as an administrator and set the database download location in the Preferences, or download the databases to a user directory then move them to the system location.

Default database locations for Spark

OS	System install	User level install
Windows	C:\Program Files\Creset-BMD\Spark\databases	%LOCALAPPDATA%\Creset-BMD\Spark\databases

Linux	/opt/cresset/Spark/databases	/path/to/install/directory/cresset/Spark/databases
macOS	/Library/Application Support/Cresset/Databases	\$HOME/Library/Application Support/Cresset/Databases
Preference Setting	The 'Databases' tab of the Spark Preferences enables the addition of multiple custom locations for databases.	
Environment Variable	The variable <code>SPARK_CRESSET_DB</code> is used as a path for databases. Setting this variable enables to search for the Spark databases in multiple locations.	

If you require help or advice regarding your installation, then please contact [Cresset support](#).

Supplied Databases

Cresset supply a range of fragment and reagent databases for use in Spark derived from commercially available and literature compounds. The fragments obtained are split into separate databases based on the frequency with which the fragments were observed.

Additional fragment databases derived from commercially available reagents and building blocks are available through the database updater.

Details of the current databases can be found at <http://cresset-group.com/current-spark-databases/>.

Start Spark

Windows

The install process places an entry in the 'Start menu' and a shortcut on your desktop. Double click this shortcut or navigate:

Windows 7

Start menu → Programs → Cresset → Spark

Windows 10

Choose **Start**, and type Spark (the search panel opens automatically as you type). In the search results, click Spark to start the application.

Linux

If the installation was from rpm then select the shortcut in the Applications menu.

Alternatively, in a terminal window type:

```
/path_to_installation/cresset/Spark/bin/Spark
```

where *path_to_installation* is the directory where the Spark distribution was unpacked. If Spark was installed from an rpm package with the default locations, then the installation will be in `/opt`.

macOS

Navigate to the Applications folder and double click the Spark icon.

Licensing

To run Spark, you will require a valid licence file, available from enquiries@cresset-group.com. To install a license, start the application and click on the 'Install license' button.

Changes in 10.5.6

- Windows only release, to fix an issue causing an incorrect update of the 3D window. This issue only affects systems with an Intel GPU and drivers version 24.* or later on the Windows operating system.

Changes in 10.5.5

- Improved look & feel and performance of the 3D window graphics
- Improved support for the configuration of proxy servers
- Improved support for high-dpi displays
- Improved Spark start up times when using databases sitting in a remote location on a slow connection
- Fixed bug which caused the effect of the application of pharmacophore constraints to be overestimated in some circumstances
- Fixed bug on macOS which prevented to dock back in the desired position any dock window moved outside of the main Spark interface
- Fixed rare bug in the wizard where in some occasions the desired hydrogen atom could not be picked for replacement
- Functionality to show/hide the 3D border text now available from the View menu.

Changes in 10.5.0

- New 'Ligand Growing Experiment' wizard, to grow a starter molecule into new space, guided by existing ligands mapping a different region of the same active site
- New 'Join Two Ligands' wizard, to join together with a linker two ligands sitting in the same active site
- New 'Macrocyclization' wizard, to cyclize a molecule by joining two atoms with a linker
- New 'Water Replacement' wizard, to search for a replacement group which will displace a crystallographic water molecule near your ligand
- New 'Ligand Growing' and 'Ligand Joining / Macrocyclization' calculation methods to support ligand growing, ligand joining, macrocyclization and water replacement experiments
- New functionality to download a starter molecule directly from the RCSB clicking the 'Protein' button in the wizards
- New functionality to replace Hydrogen atoms in the starter molecule
- New 'merge' functionality to merge molecules in the wizards (when appropriate) and in the Manage/Edit References dialog
- New 'Commercial' databases derived from ZINC and eMolecules screening compounds
- New sparkdbupdate.exe binary to update all or selected Spark databases
- New 'Install or Update Displayed Databases' functionality in the Spark Database Updater, to install or update all the Spark databases in one go
- New 'database category' information now available in the Spark Database Updater, to organize the databases to be updated in a logical structure

- New functionality in the Spark search dialog to inform the user that updated versions of the Spark databases to be searched are available for download
- New Constraint and Field Point Editor window, enabling users to:
- Define pharmacophore constraints to bias Spark results to have a particular feature (for example, a H-bond acceptor) at a specific position, by introducing a penalty which down-scores results that do not satisfy the constraint
- Define field point constraints to specify that a particular type of field must be present in the Spark results, by introducing a penalty which down-scores results that do not satisfy the constraint
- Add customer-defined field points to be constrained
- Enable protein display to help you set up pharmacophore and field constraints appropriately
- New alternative similarity metrics (Tanimoto, Tversky) for scoring Spark results
- New individual field similarity weighting for scoring Spark results
- New 'Send to [Flare™](#)' functionality to send either all results, favorite results or selected results to Flare, including as appropriate the starter and reference molecule(s) and the protein
- New Storyboard window, to capture scenes recording all details from the 3D window that can be easily recalled when needed, including capability to annotate and rename scenes
- New button in Spark Appearance Preferences to swap color of fields (blue/red)
- New functionality to control 3D display font and font size separately from the Spark application font size
- New stereo view functionality
- New support for touch screen displays
- New HiDPI support
- New 'Generate Diagnostic Data' functionality available from the Help window to generate data which can be used by [Cresset support](#) to troubleshoot problems
- New Flexibility column in Spark Results tables
- New Flexibility filter which can be applied to the whole molecule when performing a Spark search, to limit the results to the desired physico-chemical space
- Improved performance of Spark database generation
- Improved Spark search algorithm now retaining multiple regioisomers for each Spark result (when applicable)
- Improved starter molecule region selector now including both 2D and 3D display
- Improved 'View Parent Structure for Selected Result' functionality now including both substructure and identity search
- Improved File menu functionality, now also showing a list of recently opened molecules files in addition to recently opened project files
- Improved 'Grid' button functionality, replacing the old 'Sep' and 'Grid' buttons
- Improved display of protein ribbons, offering a choice of different ribbon styles and capability to show ribbons for the active site only
- Improved export of CSV files, now including parent molecule SMILES
- Improved handling of numerical filters
- Text data stored in Spark project cells can now be copied into the clipboard
- Improved look and feel of the GUI with re-designed toolbars and icons.

Changes in 10.4.0

- New Cresset reagent databases derived from eMolecule building blocks, replacing previous reagents based on ZINC
- Updated ChEMBL and ZINC fragment databases
- New Results table columns:
 - The TorsFreqFrag frequency is computed by analyzing all dihedrals associated with rotatable bonds within the bioisosteric replacement (Schärfer et al. 2013, Guba et al. 2016). For each such dihedral, the frequency of that torsion as recorded in the Cambridge Structural Database (CSD) is assessed; the lowest frequency found across all analyzed dihedrals is reported as the TorsFreqFrag frequency. 'Low' values are a possible cause for concern
 - TorsFreq: For each new bond formed in the result molecule, the frequency of that torsion as recorded in the Cambridge Structural Database (CSD) is reported. Torsions associated with a low frequency are a possible cause for concern
 - The Attachment Point Type columns record the atom type of the fragment atom which is being attached to the starter molecule, facilitating the assessment of chemical feasibility. For example 'Nsp3' in the 'Attachment Point 1 Type' column means that the fragment atom which is joined to the first bond of the starter molecule is a sp3 hybridized nitrogen.
- New external REST service for properties, enabling the connection to an external web service to import external properties and data as additional project columns in the Results tables
- User preferences can now be imported and exported using the corresponding buttons in the Edit → Preferences menu
- New export of MEP surfaces in the CCP4, Cube, Insight and MOE formats
- Improved Radial Plots to support enhanced Multi-Parameter Optimization:
 - A weight can be associated to each property in the Radial Plot to calculate a single numerical score for each molecule which represents the overall fit of the compound to the ideal profile
 - The score can be used to rank the molecules and colour molecules, columns, and radial plot by score
- Improved Spark Search dialog:
 - More intuitive to use
 - Provides information and warning notifications to support the correct set-up of the Spark search
- Improved Spark search options:
 - Improved substructure filtering at calculation time now enables the specification of multiple substructure(s) to be present or absent in the replacement fragments. The substructures can be specified either using SMARTS patterns or by drawing a substructure in the Molecule Editor
 - Improved behavior of 'Automatic constraint of fragment size' option to support fragment growing experiments: if the portion of the starter molecule being replaced consists of one atom only, no constraint will be applied
 - New option to control hardness of protein excluded volume command line Spark (sparkcl)
- Improved filtering on structure enables visualization of molecules that include or exclude a specific substructure specified by a fragment drawn using a Molecule Editor
- Any applied filters are now saved with the project
- Double clicking on any result table cell will select the content of that cell, which you can then copy in the clipboard by right-clicking and selecting 'Copy' from the context menu

- Rotating a torsion in the Molecule Editor will display a graph of the torsion energy
- Project Notes promoted to separate window for recording experimental details
- Improved visualization of protein active site:
 - Protein active site radius control in Protein Display Toolbar
 - Active site radius now saved with the project
 - Separate display of H-bonds and steric clashes
 - Measurements can be individually cleared
- AccelrysDraw and ChemDraw structures can now be pasted directly into the Molecule Editor
- Improved import/export of PDBs (PDB importer now correctly importing DNA/RNA)
- Improved interface to CEBroker enables easy disabling
- Improved tooltips
- Fixed bug where 2D similarities using ECFP4 circular fingerprints were not calculated correctly.

Changes in 10.3.0

- New tile view
 - View results in a tiled layout to see multiple results at a glance
 - Customize tiles to include
 - radial plots
 - the new tags
 - selected other data
- New tags feature enable the tagging of any result with a custom label
- New filtering using SMARTS pattern of fragments at calculation time enables the specification of a particular substructure to be present or absent in fragments
- New post-result filtering on structure enables visualisation of results that include or exclude a specific SMARTS pattern
- Updated databases
- New reagent patterns and databases for aromatic alcohols and nitriles
- New protein importer for loading proteins from PDB files
- Improved wizard with cleaner looks and smoother workflow
- New option to control the minimization of newly formed molecules
- New options for sdf file processing that enables multiple sdf tags to be recorded for any parent fragment and reported in the final results table
- New option to control the minimization of conformations of fragments committed to the database
- New button to limit display of protein atoms to those close to the ligands
- Introduced integration with Cresset's Engine Broker to enable calculations to be performed on a Linux cluster from Windows, Mac and Linux clients
- New preferences to enable control of information that is shown in the results tables and tile views
- New option to use a protein excluded volume for visualization but to ignore it in the calculations
- New 'Notes' column enables the collection of thoughts about specific results
- Improved database download tool - faster operation and clearer GUI
- Improved default location for the creation of databases on windows
- Improved Windows installation location to fit with Microsoft policies
- Improved Protein display options to include ribbons

- Improved substructure search for fragments on generic websites
- Unified the last used directories into a single entry - now 'Save as' starts in the last directory used for any task not the last directory used for saving projects
- Improved help text for the command line binaries

Changes in 10.2.0

- New radial plot feature to visually represent multiple result column properties
 - Radial plot for every result molecule in the result table
 - Separate radial plot window to visualize plots for many results
 - Plot optimal values at the center or edge of the radial plot
 - Customize plots to give exactly the properties required for the current target
- New preference panel to configure how standard properties are plotted in the radial plot
- New 'Field difference' display that highlights the change in the field surface potentials of the current molecule with respect to the starter molecule
- New fullscreen mode for the 3D window
- New rock and spin options for the 3D window
- New option to limit the display of the protein to just those surrounding the reference molecules
- New 'Send to' menu to transfer results to Forge or Torch
- Improved visual display of cluster for scaffold cluster method
- New 'attachment type' information that reports the types of atoms that have been connected to the fragment that was used in the result
- New clearer database selection widget in experiment setup
- New fragment parent lookup window providing live choice of lookup location without the need to change a preference setting
- New database generation method that imports conformations enabling the creation of databases from crystal structure information
- New database generation method that converts reagents into searchable databases
 - 17 Methods for conversion of reagents into R groups supplied that cover most reactive species including the processing of amines, carboxylic acids, boronates, isocyanates, and alkyl halides.
 - Easy to customize architecture - add your own transformation or ask us to do it for you
 - Rapidly create databases based on the reagents on your shelf
- New hierarchy for databases using 'Category' and 'Sub-category' to partition databases in the search pane
- New preference to invert the mouse zoom on the 3D window
- Improved database preferences
 - Added ability to add custom search locations for databases to use in searching
 - Added customisable location for database download using the built-in database updater
- New choice of 2D similarity (Merck Atom Pairs or Circular Fingerprints or Circular Pharmacophore Fingerprints) to use in the results window
- New preference to set custom StarDrop model locations
- New databases
 - Significant reduction in file size while maintaining quality
 - Increase in the total number of fragments
 - Updated for ChEMBL release 17

- New reagent databases from processing of reactive species. 17 separate databases supplied
- Improved the database creation algorithm to minimize time spent committing fragments and improve throughput when running with >100 FieldEngines
- Improved the 'Show interactions with protein' algorithm to give better results
- Improved charging of final molecules when fragment or new bond creates a conjugation to a charged moiety
- Fixed bug where physical property data was not exported properly
- Fixed bug where the option to delete an entire cluster of results did not work properly
- Improved documentation for command line Spark
- Removed 'Quick' settings that gave poor quality results and were not much faster than 'Normal'
- Numerous minor improvements or bug fixes

Changes in 10.0.1

- Fixed bug where licensing would erroneously fail after detecting a third party license file
- Updated ChEMBL derived databases (now based on ChEMBL 15)

Version 10.0.0

- Initial release of Spark derived from earlier FieldStere application.

Uninstalling Spark

Windows

Spark can be uninstalled using the standard 'Programs' Control Panel shortcut. Databases can be manually deleted from their install location (usually %APPDATA%\Cresset-BMD\Spark\databases or C:\Program Files\Cresset-BMD\Spark\databases).

Linux

If Spark was installed from a rpm package, it can be uninstalled with one of the following command lines, depending on whether it was installed with the `rpm` or `yum` command:

```
rpm -e cresset-spark-<vers>-1.<arch>
```

or

```
yum erase cresset-spark-<vers>-1.<arch>
```

If Spark was installed by unpacking a tgz file, it will be sufficient to remove the containing folder from the disk.

Databases can be manually deleted from their install location (usually the \$HOME/spark_db directory).

macOS

In the Finder sidebar, click Applications. Drag the Spark from the Applications folder to the Trash (located at the end of the Dock).

Databases can be manually deleted from their install location (usually \$HOME/Library/Application Support/Cresset/Databases).

Known Issues and Bugs

Spark will crash when the File dialog is opened if "Dell Backup and Recovery Application" between versions 1.7.5.64 and 1.9.2.8 (list not inclusive) is used on your computer.

In rare circumstances Spark will crash using invalid SMARTS with the SMARTS filter.

Scaling of GUI elements may be sub-optimal with high resolution monitors connected through legacy VGA cables.

When using multiple monitors with differing text scaling settings the toolbars and other GUI elements can display poorly requiring the layout of the GUI to be reset using Windows menu → Reset Layout.

Occasionally Spark is able to find similarities greater than 1 or less than 0. These occur with small molecules using constraints with a high fraction of shape based scoring.

macOS

On some versions of macOS the selection of atoms in the 3D window does not work correctly making measurement of distances difficult.

In some circumstances, after using the fullscreen function the application reports a crash instead of exiting cleanly. The report is not harmful as it only happens as the application closes and no data is lost.

In the manage columns in results table widget, selecting and dragging many elements between the displayed and un-displayed sections causes the application to crash.

Found a bug or problem that is not listed? Please contact us and help improve our software!

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