



Flare™ V2.0.1 Release Notes

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About Flare

[Flare](#) is a structure-based design tool for the visualization and analysis of protein-ligand complexes.

Capabilities in Flare V2.0 include:

- Smart import and handling of protein-ligand complexes
- Accurate and reliable protein preparation
- Sequence alignment and superimposition
- Protein interaction potentials
- Electrostatic Complementarity™ scoring
- Accurate docking using Lead Finder™
- Minimization of protein ligand complexes
- 3D-RISM water analysis (using Cresset XED and AMBER force fields)
- WaterSwap analysis – ligand and binding site energetics
- The Flare Python™ API

Flare calculates and displays protein interaction potentials (protein fields) based on Cresset XED force field.^{1,2} This methodology is extremely useful to understand the electrostatic environment of the active site of a protein, comparing protein and ligand electrostatics to improve new molecule design. Protein interaction potentials can also be used to analyze the active site of closely related proteins, to understand how subtle changes in the 3D conformation of the proteins, or in the protein sequence, can influence the electrostatic patterns of the active site. The analysis of the electrostatic patterns of a protein family using protein fields is also useful to inform the design of more selective ligands.

The electrostatic complementarity coloring and scoring functions within Flare are an extension of the protein interaction potential functions. They provide a detailed map and a quantitative score of how well the electrostatics of one or more ligand(s) matches that of the protein active site and can accordingly prove invaluable for the understanding of ligand binding, SAR and the design of new molecules that target the protein.

3D-RISM water analysis,³ based on the XED force field, investigates the location and stability of water molecules in your protein. This information can be used to identify energetically unfavorable ('unhappy') molecules which should be possible to displace from the active site by designing a ligand with the correct shape and electrostatic features. Incorporating energetically favorable ('happy') water molecules in the analysis of the active site using protein interaction potentials will lead to a better understanding of the electrostatic requirements of ligand-protein interaction, and to improved ligand design.

Docking and scoring can be carried out in Flare using BioMolTech's Lead Finder docking algorithm,⁴ now fully integrated in the GUI. The docking engine in Lead Finder combines a genetic algorithm search with local optimization procedures, which make Lead Finder efficient in coarse sampling of ligand poses and following refinement of promising solutions. Three different scoring functions are employed and optimized for the accurate prediction of 3D docked ligand poses, protein-ligand binding energy and rank-ordering of active and inactive compounds in virtual screening experiments.

WaterSwap^{5,6} is a Monte Carlo technique for investigating ligand-protein interactions, which allows the calculation of absolute protein-ligand binding free energies from first-principles, condensed-phase simulations. This method, developed by Chris Wood *et al.* at the University of Bristol, is fully integrated into Flare. Flare also supports advanced processing solutions for remote calculation.

The new Flare Python API enables Flare functionality to be accessed from Python and for you to customize the Flare interface. Python scripts can be run from the Flare graphical user interface (GUI) or by the command line `pyflare`.

1. J. G. Vinter, Extended Electron Distributions Applied to the Molecular Mechanics of some Intermolecular Interactions, *J. Comput.-Aided Mol. Des.* **1994**, *8*, 653-668
2. J. G. Vinter, Extended electron distributions applied to the molecular mechanics of intermolecular interactions II - Organic Complexes, *J. Comput.-Aided Mol. Des.* **1996**, *10*, 417-426
3. R. Skyner *et al.*, A Review of Methods for the Calculation of Solution Free Energies and the Modelling of Systems in Solution, *Phys. Chem. Chem. Phys.* **2015**, *17*, 6174-6191
4. O. V. Stroganov *et al.*, Lead Finder: an approach to improve accuracy of protein-ligand docking, binding energy estimation, and virtual screening, *J. Chem. Inf. Model.* **2008**, *48*, 2371-2385
5. C. J. Woods *et al.*, A water-swap reaction coordinate for the calculation of absolute protein-ligand binding free energies, *J. Chem. Phys.* **2011**, *134*, 02B611,
6. C. J. Woods *et al.*, Rapid Decomposition and Visualisation of Protein-Ligand Binding Free Energies by Residue and by Water, *Farad. Discuss.* **2014**, *169*, 477-499

Supplied Binaries

Flare functionality is delivered through a graphical user interface (GUI) with two interlinked binaries (Flare, FieldEngine). However, the GUI will call specific binaries to perform specific tasks.

Flare	The main graphical interface for Flare
pyflare	Python scripts can be run from Flare GUI or by the <code>pyflare</code> command line tool. This binary gives you access to all Flare methods directly from the command line enabling you to automate and script your workflows.
FieldEngine	<p>The calculation engine for Flare. 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). 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>

Supported Platforms

Minimum specifications

Hardware	Specifications
RAM	2GB
Processor	Intel i5 processor or equivalent
Disk space	1GB

Recommended specifications

Hardware	Specifications
RAM	16GB
Processor	Intel i7 processor or equivalent
Disk space	1GB

Supported Operating Systems

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

Windows

1. Browse to the Windows folder of the Flare 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 Flare installed, then this will be removed before installing the new version.

Linux

1. Browse to the Linux folder of the Flare distribution media.
2. Install the Flare 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 cresset-flare-<vers>-1.<arch>.rpm
```

or

```
rpm -U [--prefix <path>] cresset-flare-<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 Flare icon onto the Applications icon to install the application in the Applications folder.

Start Flare

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→Flare
```

Windows 10

Choose **Start**, and type Flare (the search panel opens automatically as you type). In the search results, click Flare 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/Flare/bin/Flare
```

where *path_to_installation* is the directory where the Flare distribution was unpacked. If Flare was installed from an rpm package keeping the default location, then the installation will be in */opt*.

macOS

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

Licensing

To run Flare, you will require a valid license file which will be supplied by Cresset, usually as an attachment to an email. If you cannot locate your license file, then please contact support@cresset-group.com.

To install a license, start the application and click on the 'Install license' button. Alternatively, the license file can be placed in one of the directories detailed at <http://cresset-group.com/license-file-locations>.

Changes in version 2.0.1

- 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 version 2.0

- New Flare Python API enabling Flare functionality to be accessed from Python and customization of the Flare interface. Python scripts can be run from the Flare graphical user interface (GUI) or by the command line `pyflare`
- New Python tab in the Flare GUI providing access to the Flare Python API functions within the Flare GUI
- New Electrostatic Complementarity Scores, calculated for each ligand based on the associated protein and saved as columns in the Ligands table. These provide three alternative quantitative scores of how well the electrostatics of one or more ligand(s) matches that of the associated protein active site

- New electrostatic complementarity surfaces for ligand and proteins, providing a detailed visual map of ligand/protein electrostatic complementarity
- New electrostatic potential surfaces for ligands and proteins, colored according to the electrostatic potential calculated with the XED force field
- New coloring of protein surfaces by secondary structure and Wimley-White residue hydrophobicity
- New Ensemble Docking functionality, for considering active site flexibility when alternative active site conformations of the same protein are available
- New Filter window, to show in the Ligands table only the ligands that conform to a desired set of rules. Includes filtering on numerical values, text data, Boolean values, tags, ligand structure using either a SMARTS string or a substructure sketched into the Flare Molecule Editor
- New Storyboard window, to capture scenes recording all details from the 3D window that can easily be recalled when needed, including the capability to annotate and rename scenes
- New Radial Plot in the Ligands table to support Multi-Parameter Scoring
- New 3D-RISM Surfaces button, to recalculate and display 3D-RISM surfaces when a completed 3D-RISM analysis is available for the selected proteins
- New 'Promote Pose to Ligand' menu button to promote a chosen docked pose to ligand status
- New 'Delete Docking Grid on Selected Proteins' function to delete unused docking energy grids, reducing the amount of disk space in the saved Flare project
- New spherical clipping of protein surfaces
- New border text displaying relevant information at the edge of the 3D window, especially useful when working in grid mode
- New 'Export all proteins' functionality
- New export file format for proteins as PDB files with Amber conventions
- New export of ligand field surfaces
- New 'Move to protein' menu button to merge a ligand to a chosen protein structure
- New button in Flare Appearance Preferences to swap color of Cresset fields (blue/red)
- Updated Lead Finder and Build Model algorithms
- Updated sire (which contains WaterSwap) to version 2018.1.0
- Updated AmberTools to version 18
- Updated RDKit to version 2018.03.1
- Improved protein superimposition now allowing the superimposition of all proteins vs. selected proteins
- Improved coloring of crystallographic water molecules according to calculated 3D-RISM ΔG
- Improved WaterSwap workflow
- Improved weighting scheme for consensus calculated free energy of binding from WaterSwap runs
- Improved functionality of Protein Surfaces window, now enabling the update of saved protein field and molecular surfaces in terms of transparency, quality and chains included
- Improved definitions for ligand-protein interactions, as fully documented in the Flare manual
- Improved import of peptides as ligands
- The FieldEngine binary now enables the setting of the maximum number of cores the process should use
- Improved performance of multi-threaded docking runs
- Improved layout of the functions in the Protein tab

- Improved display of protein entries in the Protein table: the protein name is now the PDB code/file name for the protein; name column is resizable; background color for the 'visibility' icon matches the color of protein carbon atoms
- Improved right-click menus
- Improved 'mark as favorite' behavior for ligands
- Improved functionality for moving all/chosen ligand(s) from protein(s) into the Ligands table
- Improved logging for most functions
- Improved ligand minimization, protein preparation dialogs
- Improved clipping of front and back Z-planes in the 3D window, now allowing to choose whether the ligands should be affected by the clip planes
- Improved Flare shortcuts
- Lots of additional improvements and bug fixes.

Version 1.0

- Initial release of Flare.

Uninstalling Flare

Windows

Flare can be uninstalled using the standard 'Programs' Control Panel shortcut.

Linux

If Flare 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-flare-<vers>-1.<arch>
```

or

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

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

macOS

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

Known Issues and Bugs

- Flare 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 some occasions, the 3D window may not work smoothly in the Windows, Linux and macOS environment when using very large desktops. The workaround for this issue is to set the environment variable `QT_AUTO_SCREEN_SCALE_FACTOR=0`
- In some occasions, the active stereo (Quad Buffer) on Windows 10 may not work, due to limitations of the NVIDIA graphic driver

- Electrostatic Complementarity scores and surfaces may not calculate correctly if the molecule only contains sp³ carbon, nitrogen and sulfur atoms. The workaround is to quickly minimize the affected ligands before starting the Electrostatic Complementarity calculations.

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

Support

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