

innovative science • intuitive software

What's New in the Cresset Desktop Applications: Flare[™], Forge[™], Spark[™] Giovanna Tedesco, Senior Product Manager

Overview of Cresset desktop applications

Ligand Based

- > SAR analysis
 - > Qualitative



- > Quantitative
- > Bioactive conformation hypothesis
 - > Beyond simple pharmacophores
- > Interactive 3D molecule design
 - > Informed, effective design

> Scaffold hopping



> R-group design

Structure Based

- > Ligand design focus
 - > Protein-ligand docking
 - > Protein-ligand minimization
- > Protein electrostatics
- > Ligand electrostatics
- > Electrostatic complementarity
- > Water position and stability analysis
- > Ligand binding energetics
- > Customizable interface

> What's the future for desktop applications?



lare



Modern ligand-based workbench for SAR analysis and molecule design



Ligand-based workbench for SAR analysis and design



- Uses ligand alignment as a basis for molecule design and SAR analysis
- > Ligands aligned and scored to a reference or 'template' using their electrostatic and shape properties
 - > Electrostatics and shape
 - > Substructure
 - > Shape only

- > Decipher SAR and communicate the results
 - > Activity Atlas and Activity Miner
- > Create predictive 3D-QSAR models
 - > Field QSAR and Machine Learning models for regression and classification
- > Build detailed hypothesis of bioactive conformation
 - > Work in 3D on targets with no structural information
- Design new molecules in 3D
 Property profile not just activity
- > Virtually screen thousands of compounds on your desktop
 - Electrostatic/shape similarity or QSAR model predictions



Forge 10.6: Focus on models

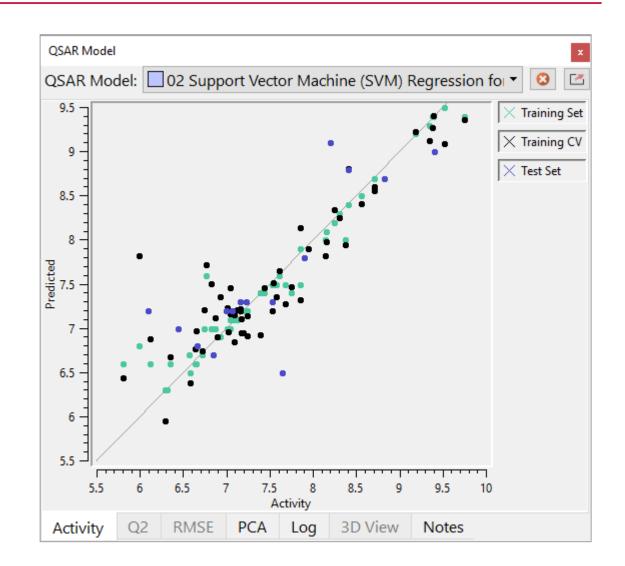
- > Released January 2019
- > Focus on QSAR models
 - > New Machine Learning methods
 - > Regression
 - > Classification
 - > New Activity Cliffs summary method in Activity Atlas
 - > Enhanced model support and viewing

- > Lots of new or improved features
 - > Improved Molecule Editor
 - > Improved handling of large projects (1000+ ligands)
 - > Auto-assign to roles using Murcko scaffolds
 - Enhanced filters (main GUI and Activity Miner)
 - > Improved GUI (2D structures, Column management, z-clipping of protein only, improved 3D graphics....)



ML regression models

- > Predict activity for new compounds
 - > Inform design of new ligands
 - > Screen small libraries of compounds
- > Support Vector Machine
- > Relevance Vector Machine
- > Random Forest
- > k-Nearest Neighbors
- > Use 3D descriptors
 - > Electrostatic and volume





ML classification models

- > Activity data is categorical
 - > 'high', 'medium', 'low'
 - > activity data which can be converted into categories (e.g, % of inhibition data)
- > Predict category for new compounds
 - > Inform design of new ligands
 - > Screen small libraries of compounds
- > Support Vector Machine
- > Relevance Vector Machine
- > k-Nearest Neighbors
- > Use 3D descriptors
 - > Electrostatic and volume

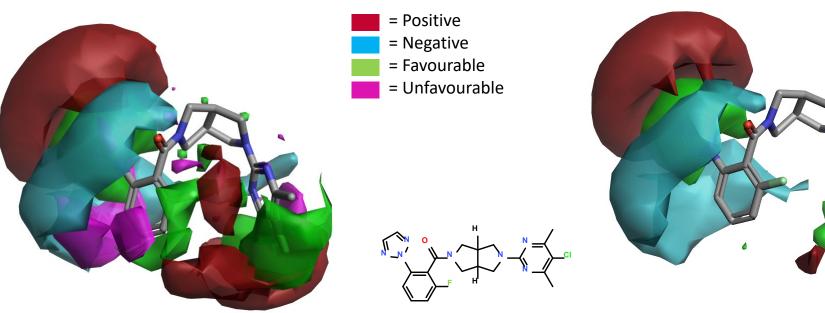
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	1	0	5	0	
Act	2	1	5	0	
	3	1	0	3	
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Activi	tv	Q2	RMS	E PC	CA Log 3D View Notes



New summary of activity cliffs in Activity Atlas[™]

- > More detailed SAR maps
 - > Gives less importance to the strongest activity cliffs
 - > Use for small to medium size data sets

- > Original method still available
 - > Focus on prevalent SAR signals
 - > Use for larger data sets
 - > e.g. patent data





Improved GUI for model calculation

Choose the type of model

Forge Processing		×
	Calculation Method	Delete Existing
Conformation Hunt:	No Calculation 👻	*
Alignment:	No Calculation 👻	\\$
Build Model:	Regression Models 🔹	
	Field QSAR	ä
	Activity Atlas™	75
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15 Test Set molecule	s. <u>Click here to partition the c</u>	lata set.
Show <u>Options</u>		<u>S</u> tart

> Field QSAR, Activity Atlas, regression or classification?

Choose the desired algorithm

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	Calculation Method		Delete Existing
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Alignment:	No Calculation	*	
Build Model:	Regression Models 🔹]	
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> Automatic or choose one?



Improved GUI for model calculation

Partition the data set from the processing widget

Forge Processing			x
	Calculation Method		Delete Existing
Conformation Hunt:	No Calculation	-	
Alignment:	No Calculation	-	
Build Model:	Classification Models	-	
	Automatic	-	
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Improved GUI for model calculation

Manage activity data

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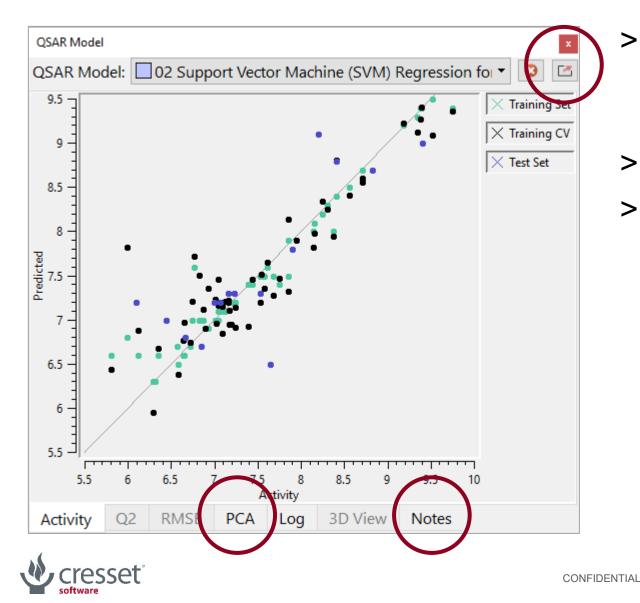


Import/Export custom settings

F	orge Processing	×
	Conformation Hunt Alignment Build Mode	el
	Calculation Method: test	✓ Save As Delete
	Delete existing conformations	Import Export
	Perform Conformation Hunt	Delete All
	Maximum number of conformations	100
	No. of high-T dynamics runs for flexible rings	5
	Gradient cutoff for conformer minimization	0.400 kcal/mol/A
	Filter duplicate conformers at RMS	0.50 A
	Energy window	6.00 kcal/mol
	Acyclic secondary amide handling	Force amides trans
	Remove boats and twist-boats	
	Turn off Coulombic and attractive vdW forces	
	Use external tool for conformation generation	
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	Hide <u>O</u> ptions	1 Conformation hunt will be skipped <u>Start</u>



Improved GUI for displaying model results



- > View multiple models side by side
 - > Compare in 3D
 - > Compare log files
- > Create Notes for models
- > PCA plots to spot subgroups or outliers in your dataset

View multiple models side by side

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Activity Maximum:			Activity Cliff Summary of Unfavorable Shape	Activity Maximum:		Activity Cliff Summary of Unfavorable Shape
Activity Minimum:				Activity Minimum:		
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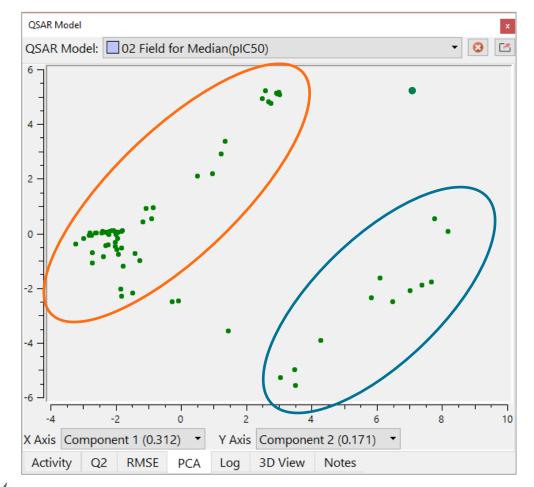


New PCA tab

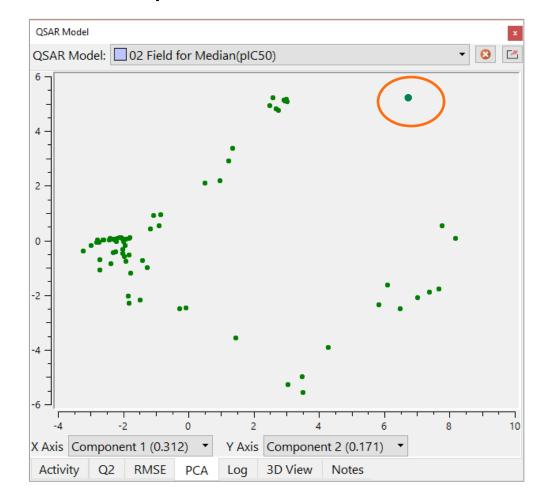
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software

Useful to spot groupings

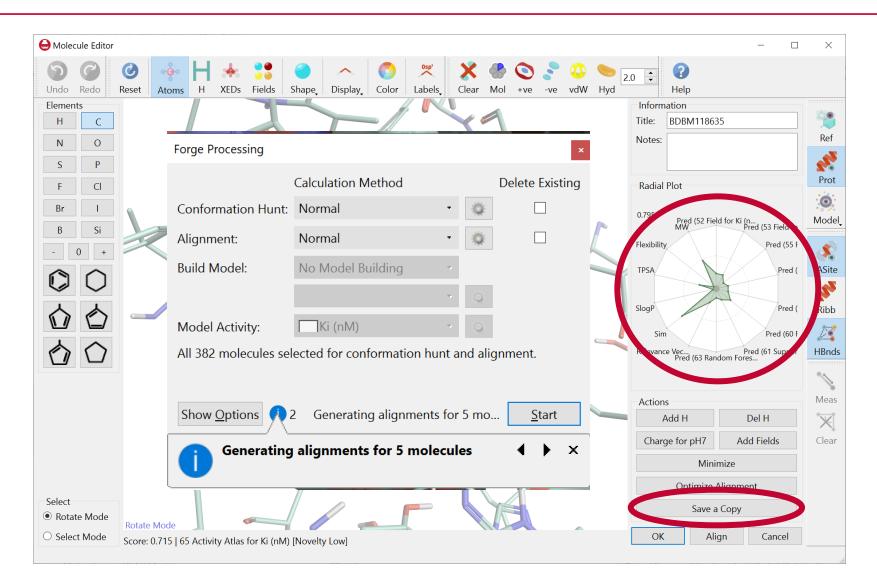


Useful to spot outliers



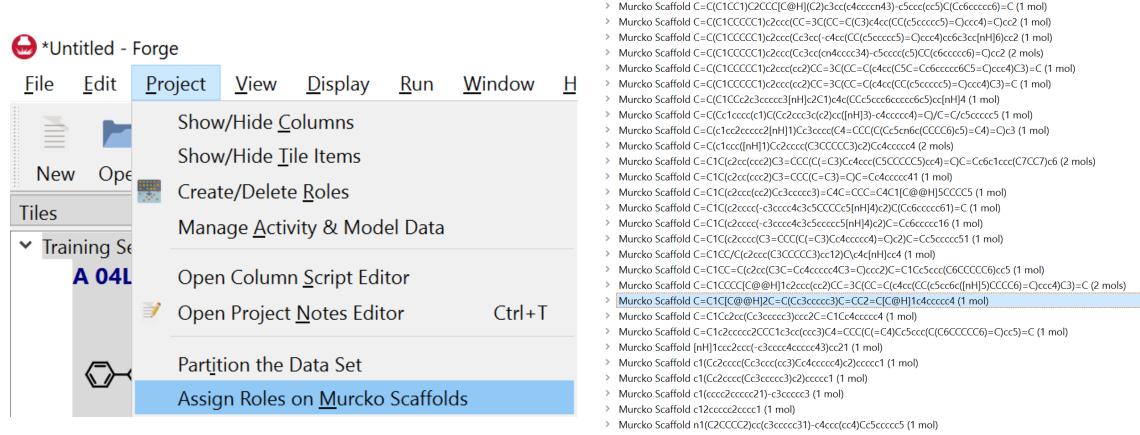
CONFIDENTIAL

Improved editor display and behavior





Automatically assign compounds to project roles

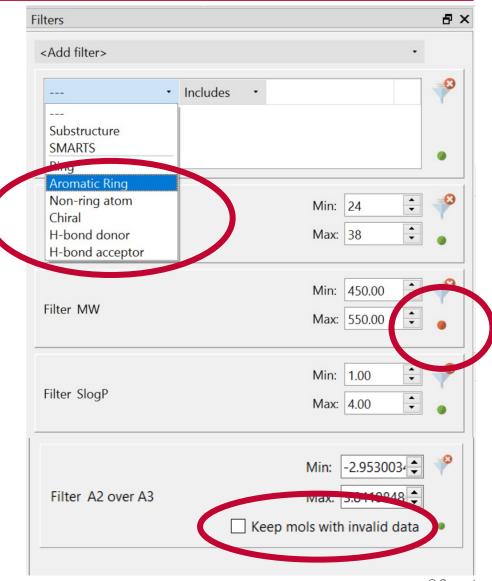


Murcko Scaffold n1([C@H]2CCCC2)cc(-c3ccc(cc3)Cc4ccccc4)c5ccccc51 (2 mols)



Improved molecule filters

- > Prepared SMARTS patterns for
 - > Aromatic ring atom
 - > Ring / Not ring
 - > H-bond donor/acceptor
 - > Chiral
- > Option to enable/disable a specific filter
- > Improved handling of molecules with invalid data in filters and radial plots





Enhanced filtering in Activity Miner™

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parity Matrix	8	
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d1 d1 od od od d3 o	d' d2 d1 d2 d2 d2 d3 d3 d3 d3 d3 d2 d1 d1 d1 d1 d1 d1 d2 d4 d1 d2 pd d1 d2 d3 d1 d2 d3 d1 d ^	Prot
192		
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1307	Disparity Matrix Filters Focus Cpd197, A1 potency: 6.46 (350 nM), A2a potency: 5.92 Similarity: 0.962	2 (1195 nm), A3 potency: 9.4 (0.4 nm)
105	Molecule pairs which do not pass all of the filters below are	
1205	displayed as gray in the disparity matrix.	
1326	Remove All	
310	Δ Activity: A2a potency $\cdot \rangle = \cdot 1.00$	
161	Similarity • >= • 0.950 ÷ 😵	
1273	Δ Activity: A2 over A3 $\rightarrow = -0.00$	
1292	$\Delta \text{ Activity: A2 over A3} \cdot = 0.00 \stackrel{\frown}{\leftarrow} \textcircled{0}$	
1209		
157		
1322		
181 188		
147		
1238	✓ Close	





- > Goodbye Torch, welcome Forge Design
- > New licensing level of Forge that fully reproduces Torch functionality
- > Existing Torch customers get additional functionality
 - > Enhanced Activity Miner
 - > Field differences



Future plans for Forge

> ... more at the end





Fresh insights into structure-based design



Fresh insights into structure-based design



- > Cresset workbench for structurebased design
- > Analyse proteins and inform new molecule design
- > New scientific capabilities extend the range of SBDD methods available

- > Robust enabling capabilities to support new workflows
- > Modern, extensible user interface that is easy to use and easy to extend
- Customisable, scriptable,
 deployable science through Flare
 API and python command line



Flare V2.0: Focus on electrostatics and ligand workflows

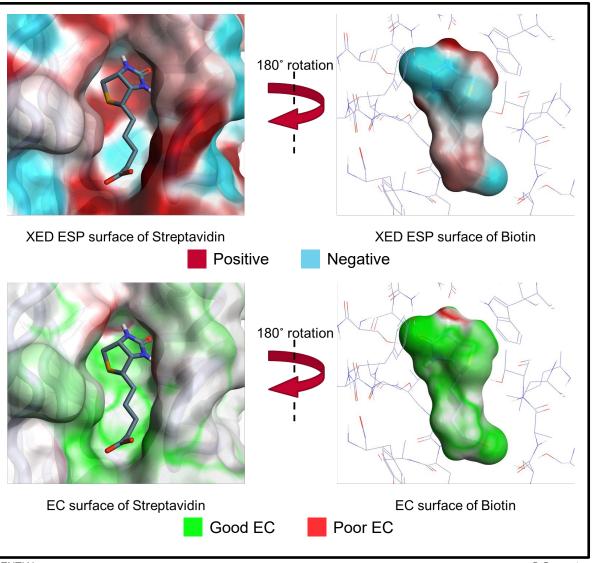
- > Released June 2018
- > Electrostatic Complementarity
 - > Scoring
 - > Maps
- > Ensemble docking
 - > Handling active site flexibility

- > Improvements on ligand workflows
 - > Radial plots/Multi-parametric scoring
 - > Filtering using properties, tags or substructure
 - > Storyboard
- > Flare Python[®] API
 - > Most functions scriptable using Python
 - > Command-line access through pyflare



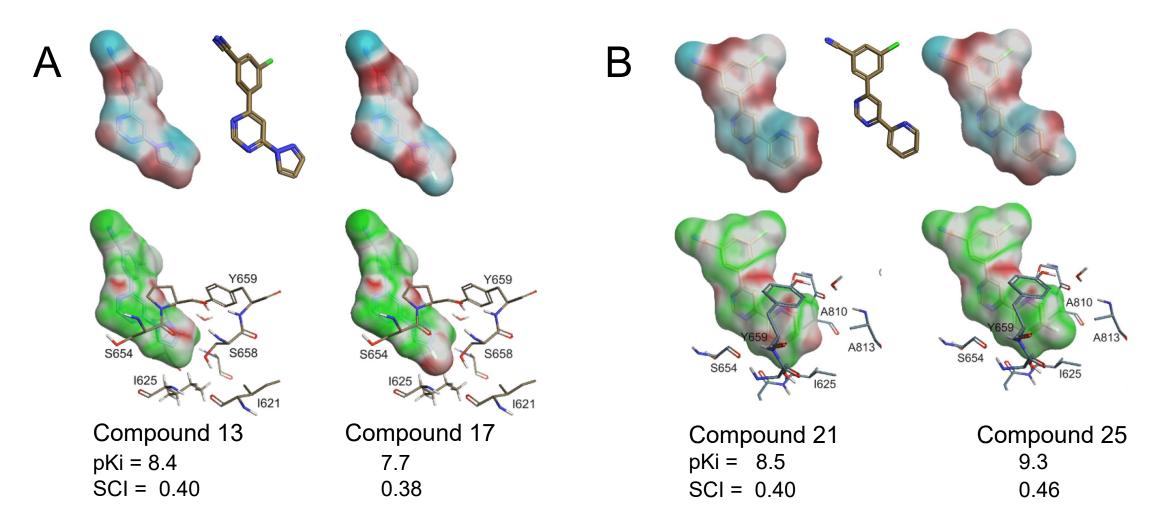
Electrostatic Complementarity[™] as a guide for molecule design

- > Electrostatic interactions between ligands and proteins are an important factor in recognition and binding energetics
- > Assessing Electrostatic
 Complementarity (EC) provides
 - > Insight of why ligand bind
 - > Inform molecular design
 - > Predict activity
- > Dedicated algorithm to calculate and display where electrostatics are complementary





EC maps and scores inform ligand design –mGluR5



Christopher et al., J. Med. Chem. 2015, 58, 6653-6664



Python API for Flare

- The vast majority of Flare's functions are now scriptable using Python
 - > File I/O
 - > Docking
 - > GUI
 - > WaterSwap
 - > 3D-RISM
 - > Protein prep, alignment, superposition
 - > etc
- > New 'pyflare' executable provides command-line access

> Three collections of Python examples and extensions

> Command line extensions

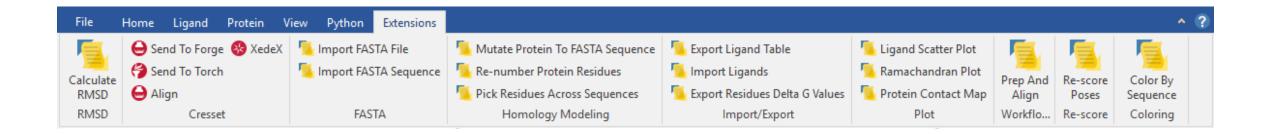
- Cresset developed scripts to use Flare from the command line (pyflare)
- <u>https://gitlab.com/cresset/flare-python-pyflare</u>

> Python Extensions

- > Useful new functionality for all
- https://gitlab.com/cresset/flare-pythonextensions
- > Developer examples
 - > Templates to demonstrate key principles and functionality
 - https://gitlab.com/cresset/flare-pythondeveloper



Python Extensions

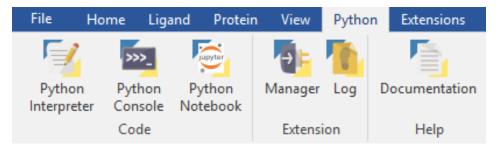


> <u>https://gitlab.com/cresset/flare-python-extensions</u>

- > Cresset supported extensions
- > Significantly expand Flare functionality for free
- > Available for download to all Flare users from a GitLab repository



Python Jupyter notebook



- > The ideal environment for Python enthusiasts
- > Provides a comfortable Python shell environment:
 - > History
 - > TAB completion
 - > Syntax highlighting
 - > Embedding of images, etc.
 - > Editing and running individual code cells
 - > ... and more

 Python Notebook O ColorBy 	-		×
Jupyter ColorBy (autosaved)			
File Edit View Insert Cell Help Not Trus	sted	Kernel	0
► + ≫ P ► ↑ ♥ Nun ■ C > Code ▼ =	CALCHOID		
Flare simply by instantiating the ColorByExtension class and calling its load m	ethod:		^
<pre>In []: colorby = ColorByExtension() colorby.load()</pre>			
Now download any protein of your choice choosing "Download PDB" from the Flare	File men	u:	
🚺 PDB Downloader 🛛 🗙			
PDB download URL: http://files.rcsb.org/view/%1.pdb *			
PDB codes: 1oit			
Multiple PDB codes can be listed			
URL to load: http://files.rcsb.org/view/1oit.pdb			
OK Cancel			
From the AtomColor popup, choose one of two coloring schemes that you have just Flare:	added to)	
🚆 🚳 😰 = "Untitled - Flare – 🗆 🗙			
File Home Ligand Protein View Python Extensions			
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Released November 2018

- > Free, viewer version of Flare
- > Replaces TorchLite

Capabilities

- > View protein ligand interactions
- > View ligand electrostatics
- > Superpose proteins and visually compare
- > Edit ligands
- > Calculate physico-chemical properties for each ligand
- > Radial plots
- > Filters
- > Storyboard



A sneak peek of Flare V3

> Release date: Autumn 2019

> FEP

> Improved docking

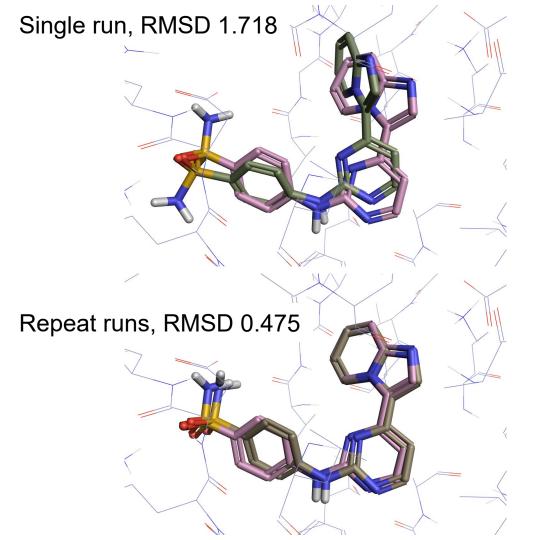
- > Improved 'Accurate' algorithm
- > Template docking
- > Covalent docking
- > Molecular Dynamics
- > 'Forge Design-like' ligand alignment
- > Faster minimization algorithm
- > Improved atom typing in protein prep
- > Improved handling of larger datasets

- > Lots of GUI new features and improvements
 - > Edit ligand and proteins the main window
 - > Ribbons for DNA
 - > Ribbon colors and transparency
 - > Improved Contacts panel
 - > Secondary structure in the Alignment table
 - > Filtering the Alignment table
 - > Sequence similarity window
 - > Tile view
 - > Export filters
 - > New Help tab
 - > Atom custom labels
 - > Synchronize 3D view
 - > Send/Retrieve from Blaze
 - >



Improved 'accurate' docking algorithm

- > The docking engine in Flare is based on a Genetic Algorithm
 - > Non-deterministic
 - > Repeat runs may give different results
- > New improved algorithm expands the GA exploration
 - > Run repeat dockings
 - > Keep the best poses from each run
 - > Merge and re-score the separate pools of poses from each run
 - > Keeps the best poses overall
- > 'Accurate' mode slightly slower but gives improved results

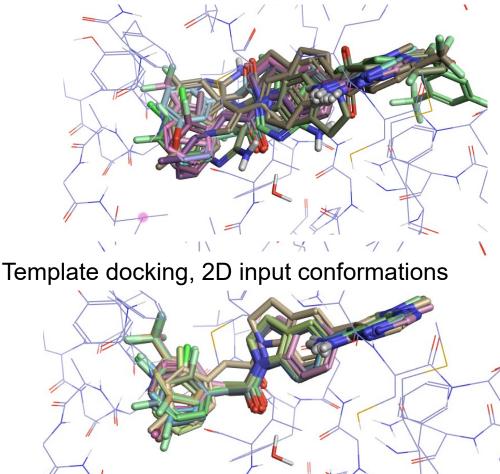




Template docking

- > Choice of 3D starting conformation may have strong influence on docking results
- > Template docking aligns by substructure the molecules to be docked to a template molecule
- > Uses the aligned conformation to 'seed' the docking run
- > Useful to dock congeneric ligands to a known template pose

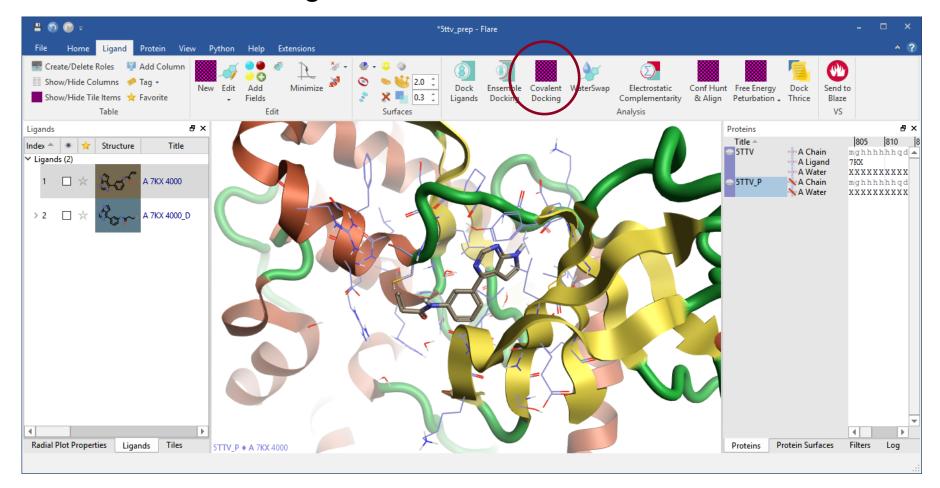
Normal docking, 1 run, 2D input conformations





Covalent docking

> New button in the Ligands tab





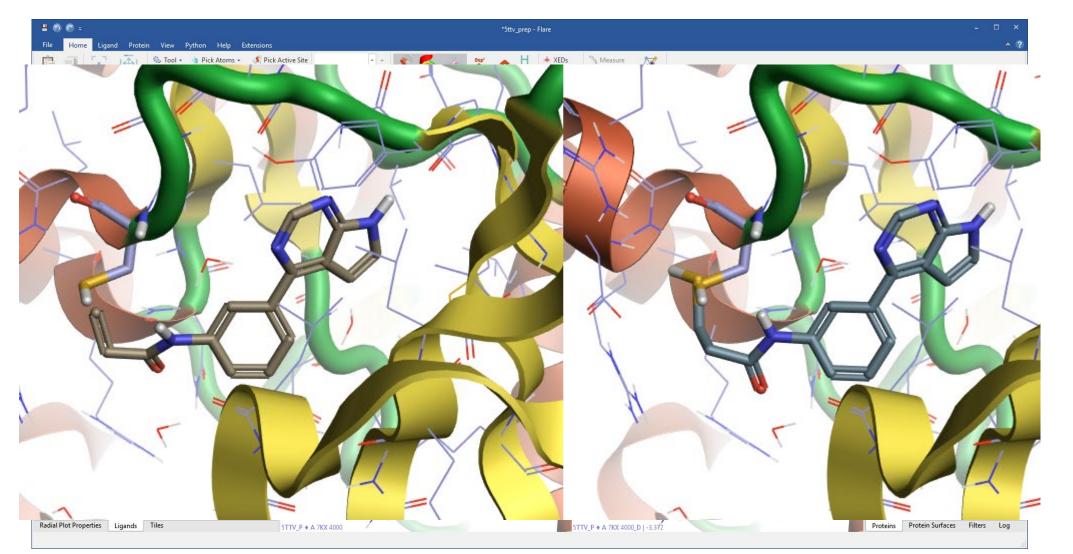
Covalent docking

- > New button in the Ligands tab
- > Choose ligands to dock
 - > Must have covalent warhead
- > Choose protein to dock into
 - > Choose chains to include
 - > Define active site as per standard docking
- > Choose covalent docking residue
 - > Use pull down menus

Flare Covalent Dock	ing Calculation x
Calculation Method	l: Normal 👻
Ligands to Dock:	 Undocked Ligands Selected Ligand
Grid Definition:	 Atom Pick <pre> <pre></pre></pre>
Protein:	5TTV_P
Chains:	A Chain
Residue:	CYS - A CYS 909 -
Copy Ligands:	\checkmark
Show Options 🚺	1 Docking grid contains 390 h Start



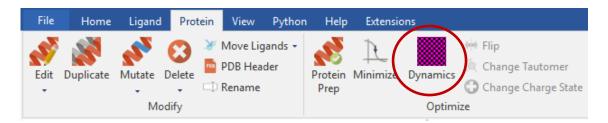
Covalent docking





Molecular Dynamics

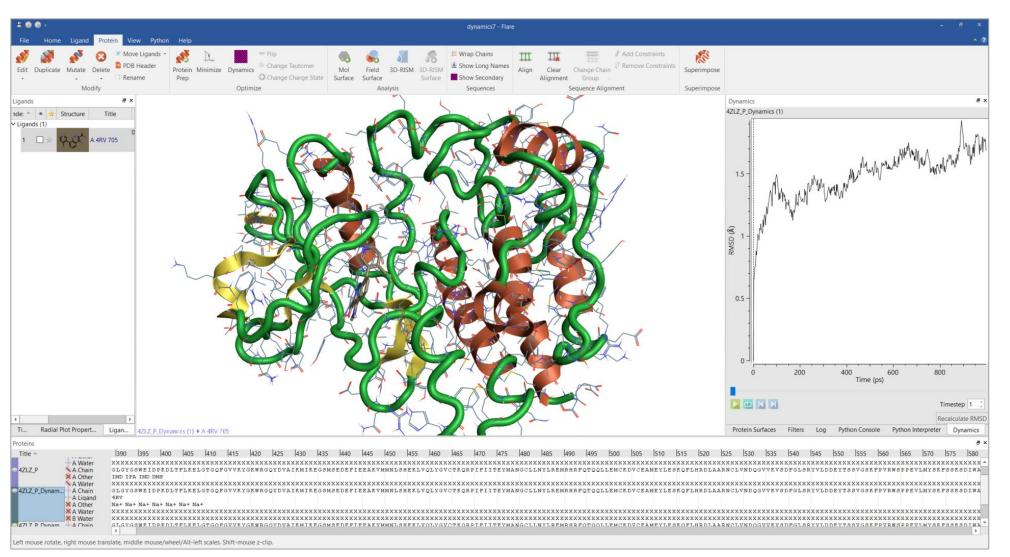
- > Based on OpenMM/AMBER
- > Flare V3 implementation:
 - > Run dynamics
 - > View results
 - > Plot of RMSD
 - > Player to browse through frames
 - > Save frames to project
 - > View log
- > More to come!



Flare Dynamics Calcu	lation		
Calculation Method:	Normal		Ŧ
Protein:	4ZLZ		Ŧ
Ligand:	A 4RV 705		*
Chains:	 ✓ A Chain ✓ A Other ✓ A Water 		
Simulation Length:	100 ps		+
Solvent Model:	Explicit		Ŧ
Show Options		Start	



Molecular Dynamics results





Editing in the main window





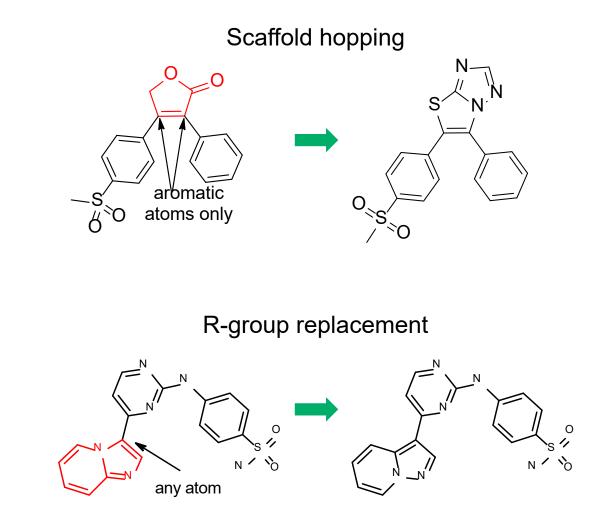


Highly innovative new ideas for your project





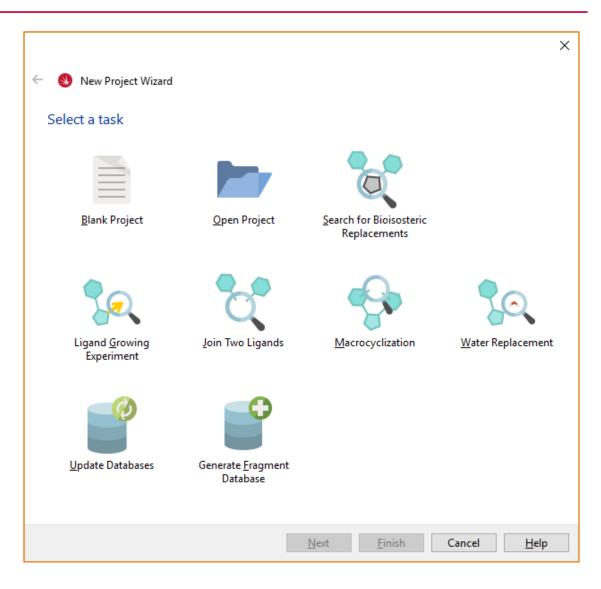
- > Scaffold hopping
 - > Using fragments of real molecules or commercially available reagents
- > R-group exploration
 - > Using commercially available reagents
 - > Monthly updates for updated availability information
- > Advanced bioisostere replacement experiments
 - > Replace in one molecule, score against a second
 - > Fragment growing and linking
 - > Crystallographic water replacement
 - > Macrocyclization





Spark V10.5

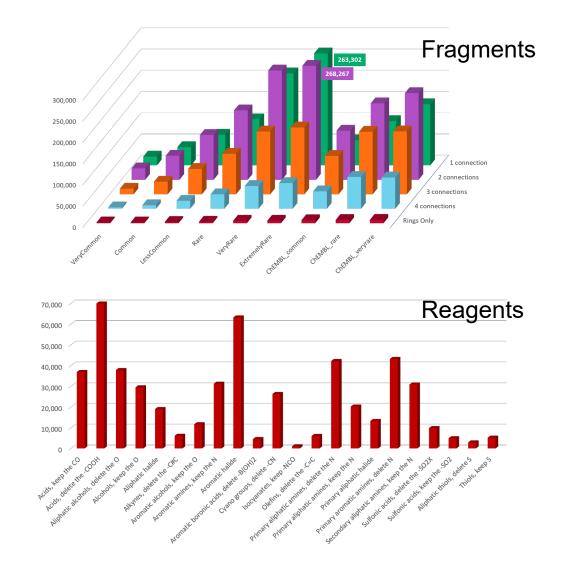
- > Released January 2018
- > New wizards for more complex experiments





Spark V10.5

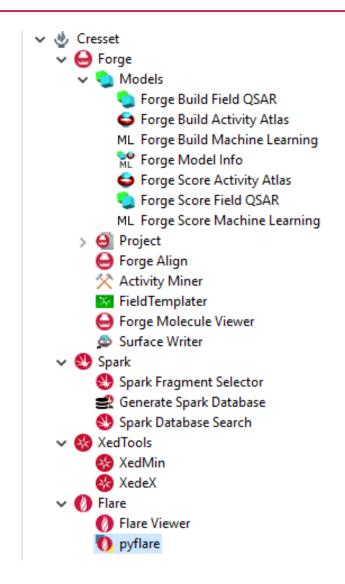
- > Released January 2018
- > New wizards for more complex experiments
- > New databases now distributing 3M unique fragments
- > Other improvements
 - > Enhanced Spark database update functionality
 - > Pharmacophores
 - > Additional similarity metrics Tanimoto & Tversky
 - > 'Flexibility' filter during the search
 - > Annotated Storyboard
 - > Query Editor
 - > New 3D graphic engine





Cresset KNIME nodes and Pipeline Pilot components

- > Released April/May 2019
- > New and enhanced KNIME nodes and PP components to access most recent Forge, Flare and Spark functionality





Forge and Spark: what's next?

Building together the products of the future



I never remember which product I should use	Can I set Spark to make a H-bond interaction with this residue?	I want to compare Activity Atlas maps against multiple proteins, to understand selectivity	
I want to do all my mo work from the same G	UI How do I post-process Spark results in Flare?	I want to use ligand alignment in Flare	
Can I import EC scores in Forge?	I want a docking-scoring-function-like capability to Spark to allow it to score replacements directly against the protein	I want to generate conformers in Forge using the MMFF94 RDKit implementation	
How do	I display cation-pi interactions in Forge?		
Exporting radial plot properties in Forge is great. Can I have it also in Spark?		both ligand- and structure-based baches in my projects	



We listen!

- > We hear you calling for:
 - > New science
 - > Simplicity of product offering
 - > Integration across products
 - > Easier access to our methods
 - > Easier access to third party and in-house methods
 - > Flexibility of licensing
 - > User friendliness



Our vision

> Integrate Forge and Spark into Flare





> The advantages:

- > Simplification of product offering
- > A single, integrated GUI
- > Ligand- and structure-based methods working in synergy
- > Full access to all functionality through the Python API
- > Modern, user friendly architecture
- > Flexible, modular license structure
- > The challenges:
 - > Safeguard the user experience
 - > Keep it easy to use
 - > Keep learning curve at a minimum



innovative science • intuitive software

Let's talk. We listen.

Many thanks to:

Tim

The development and science team (Mark, Nigel, Ken, Paolo, Rosie, Matthias, Martin, Mary M, Joy, Andy S, Andy V)

