Toolkit & Application 2021.1 Update

Jesper Sørensen

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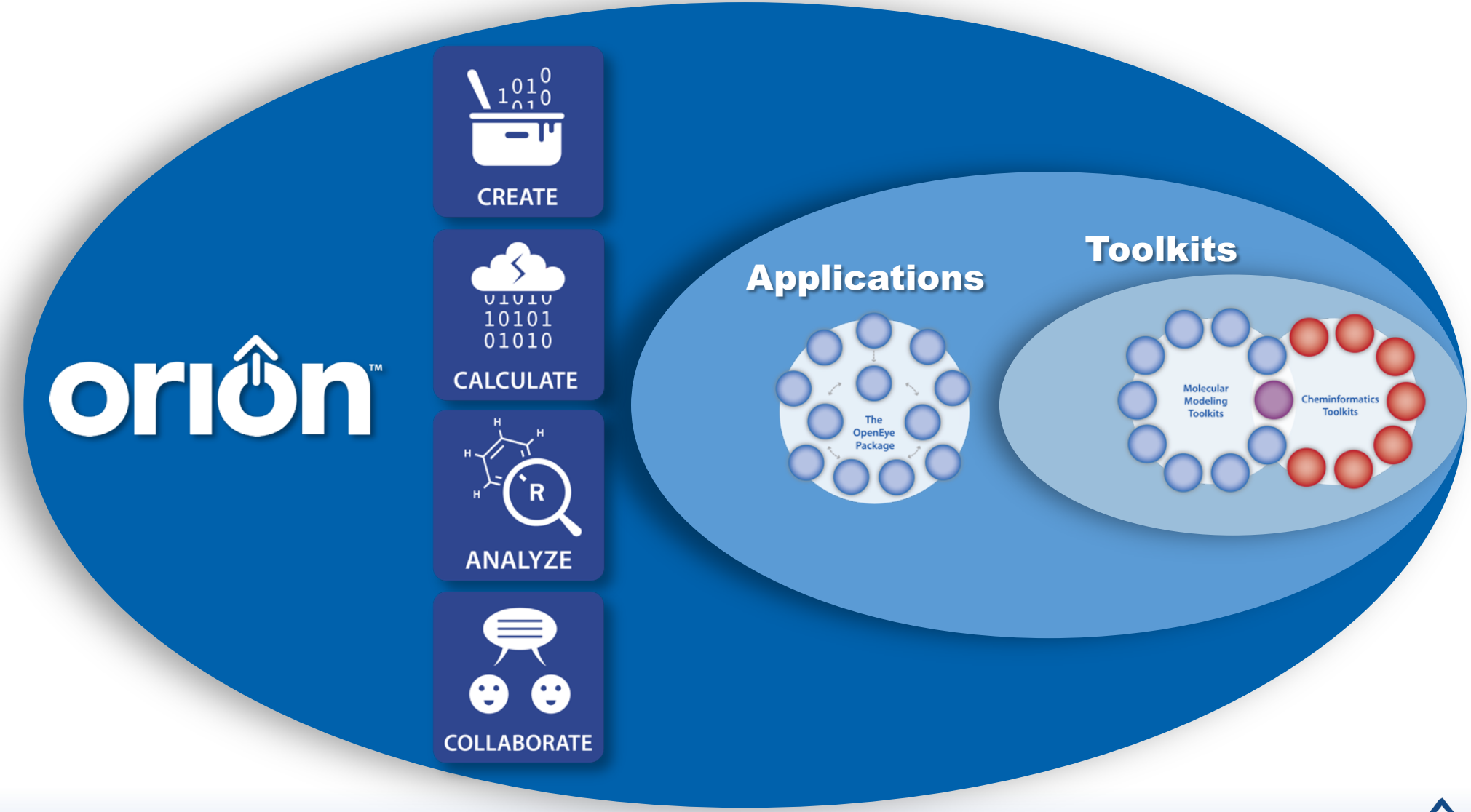
Scientific Tools at OpenEye



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Outline

- Platform & Language Support
- Minor updates
- VIDA 5.0
- Docking receptors
- GPU Efforts

Acknowledgments

OpenEye toolkits and applications development team

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Compiler and Language Support

- Python 3.9 support has been added

- We now officially support C++17
  - GCC 7.4 is our minimum supported GCC compiler
  - Support has been added for GCC 9.x
  - VS2017 and VS2019 are supported

Platform & Language Support

Package	Versions	Linux Platforms	Windows	MacOS*
Python	3.7, 3.8, 3.9	RHEL7/8, Ubuntu18/20	Win10	10.14, 10.15, 11
C++		RHEL7/8, Ubuntu18/20	Win10 (VS2017,VS2019)	10.14, 10.15, 11
Java	1.8, 11	RHEL7/8, Ubuntu18/20	Win10	10.14, 10.15, 11
C#			Win10 (VS2017,VS2019)	
Applications		RHEL7/8, Ubuntu18/20	Win10	10.14, 10.15, 11

* Arm/M1 Mac is not supported at this time

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Toolkit Updates – OEChem TK

- ZSTD has been updated to version 1.4.9
- Better performance for OEZ file format

- OERecord API was released in the Spring 2020
- Switching molecule storage on records to use OEZ

- Toolkit change that will positively affect Orion
- Smaller dataset sizes, faster data transfer, faster read/write

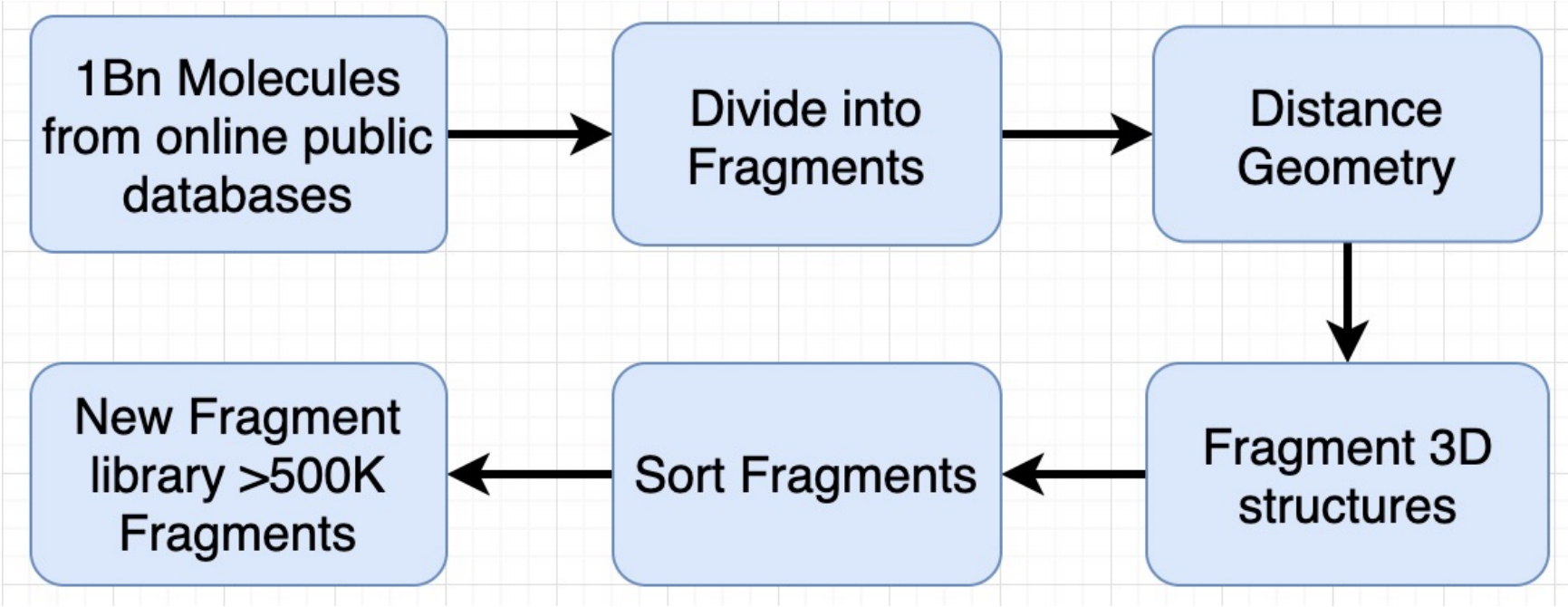
Toolkit Updates – OEChem TK

- Protein residue perception was improved with recognition for standard protein terminal capping groups

- InChI has been updated to v1.06

  Includes support for non-standard InChI strings with pseudo-atoms present

Toolkit Updates – Omega TK



Existing fragments library: ~80K

Toolkit Updates

- Lexichem TK
  - Added support for input of many common drug names
- SZYBKI & Szybki TK
  - AMBER FF14SB support in previous release
  - Parsley 1.2 support in previous release
  - Added Parsley 1.3.0 from the Open Force Field Initiative

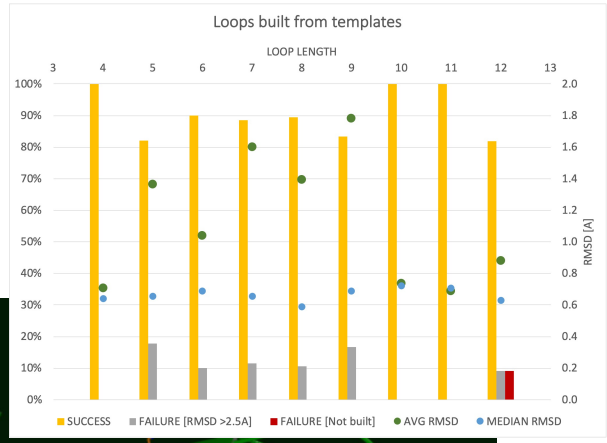
Toolkit Updates – Spruce TK

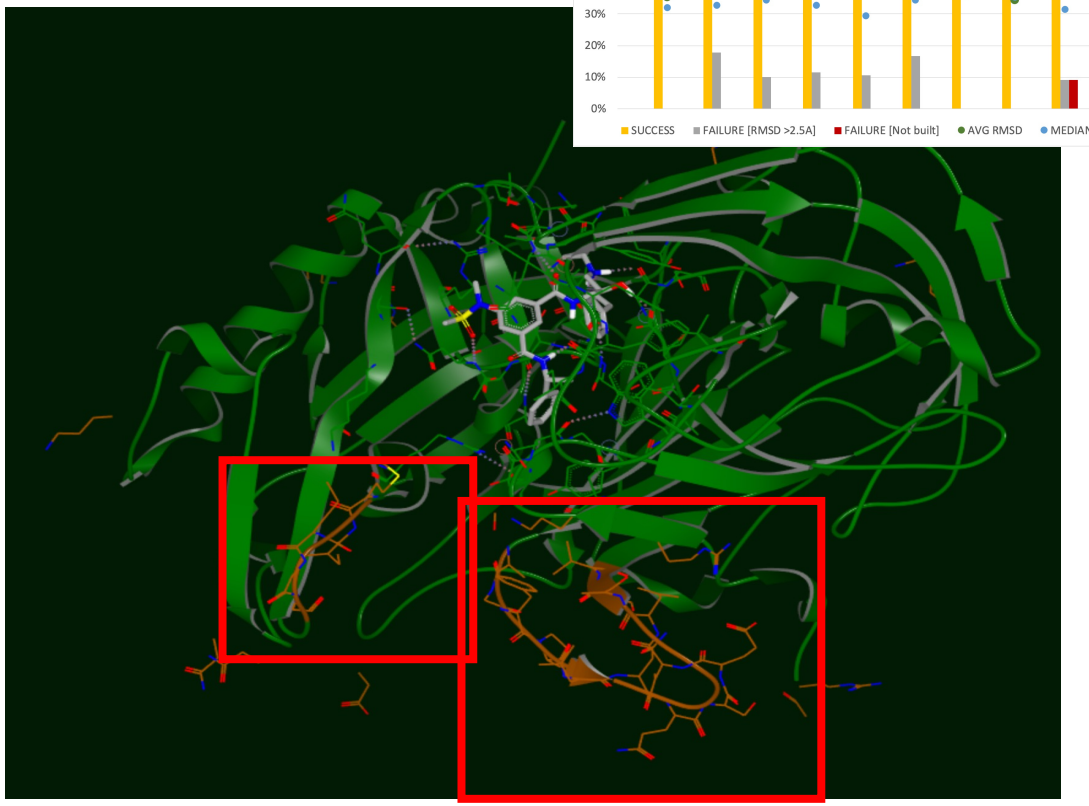
- Spruce TK was released Fall 2019
- Automated structure to model-ready protein preparation
  - Includes Iridium structure assessment
- Loop modeling was added in Fall 2020
  - Loop database available for download
  - Can build a database of corporate structures or e.g. target specific structures

Loop modeling

- Input
  - OEResidue of anchor residues
  - FASTA of expected sequence
  - Extensive control parameters
    - Remove extra residues at the anchors (def: 1)
    - Build disulfide bridges (def: yes)
    - Fuzzy seq search, strict proline (def: yes)

Validation set:
Rossi et al.
(*Prot. Sci.* 2007)





```
DVA between GLU 310 A and THR 314 A
GFPLNQSEVLAS between ALA 157 A and VAL 170 A
```

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Toolkit Updates – Spruce TK

- Improvements to PDB file perception for standard residues
- The superposition API has been refactored from the preliminary API
- OESuperposeMethod namespace
  - Global Sequence, (Binding) Site Sequence, Difference Density Matrix (DDM) ,Secondary Structure Elements (SSE), …
- OESuperposeOptions
- OESuperpose
- OESuperposeResults

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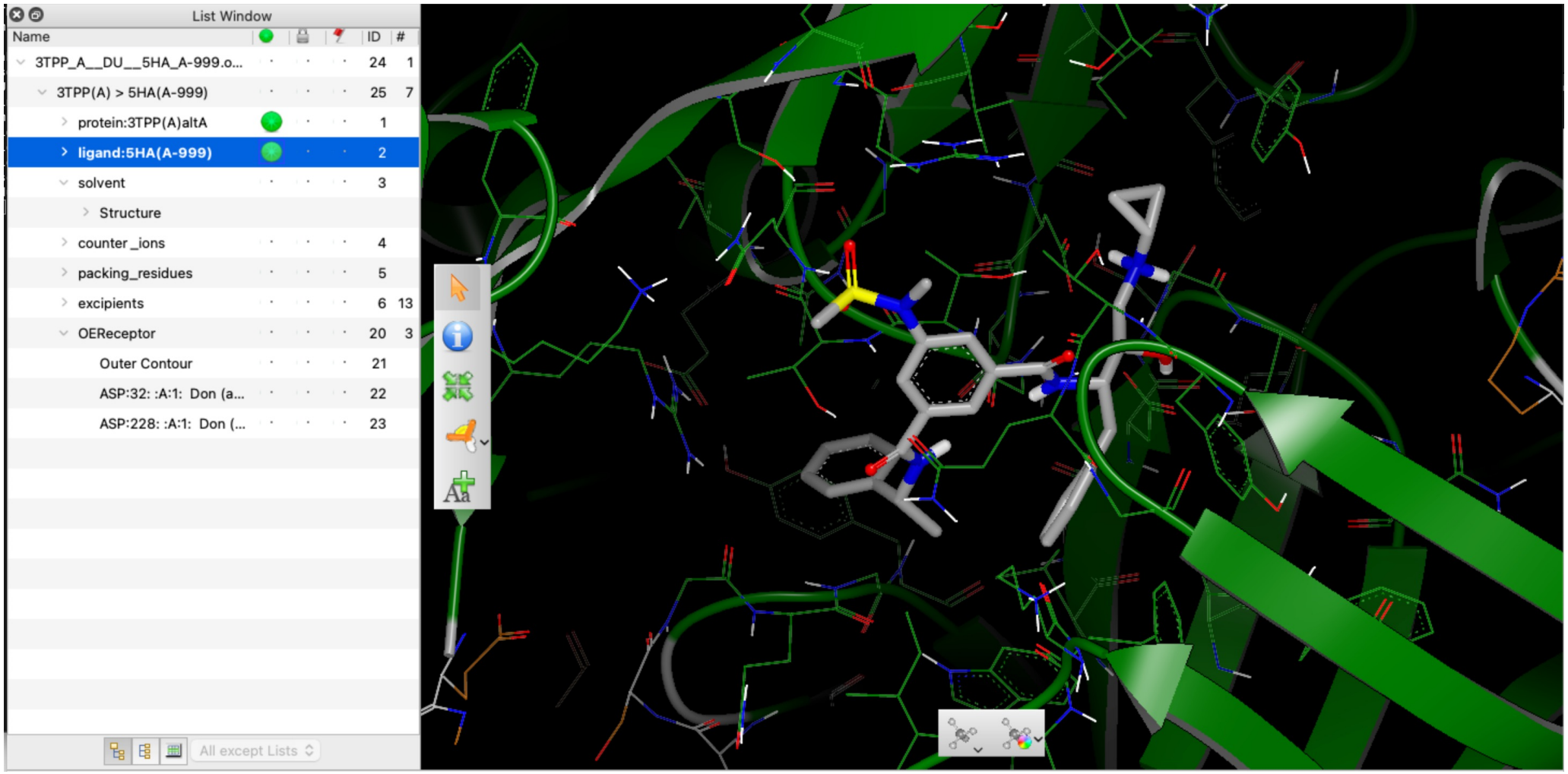
VIDA 5.0

- Python 3
- Qt 5 and PySide2
  - Enables full Qt-library access
- OpenEye Toolkits 2021.1.0
- VIDA will release regularly along side the toolkit and application bundle

VIDA 5.0 – design unit and receptor support



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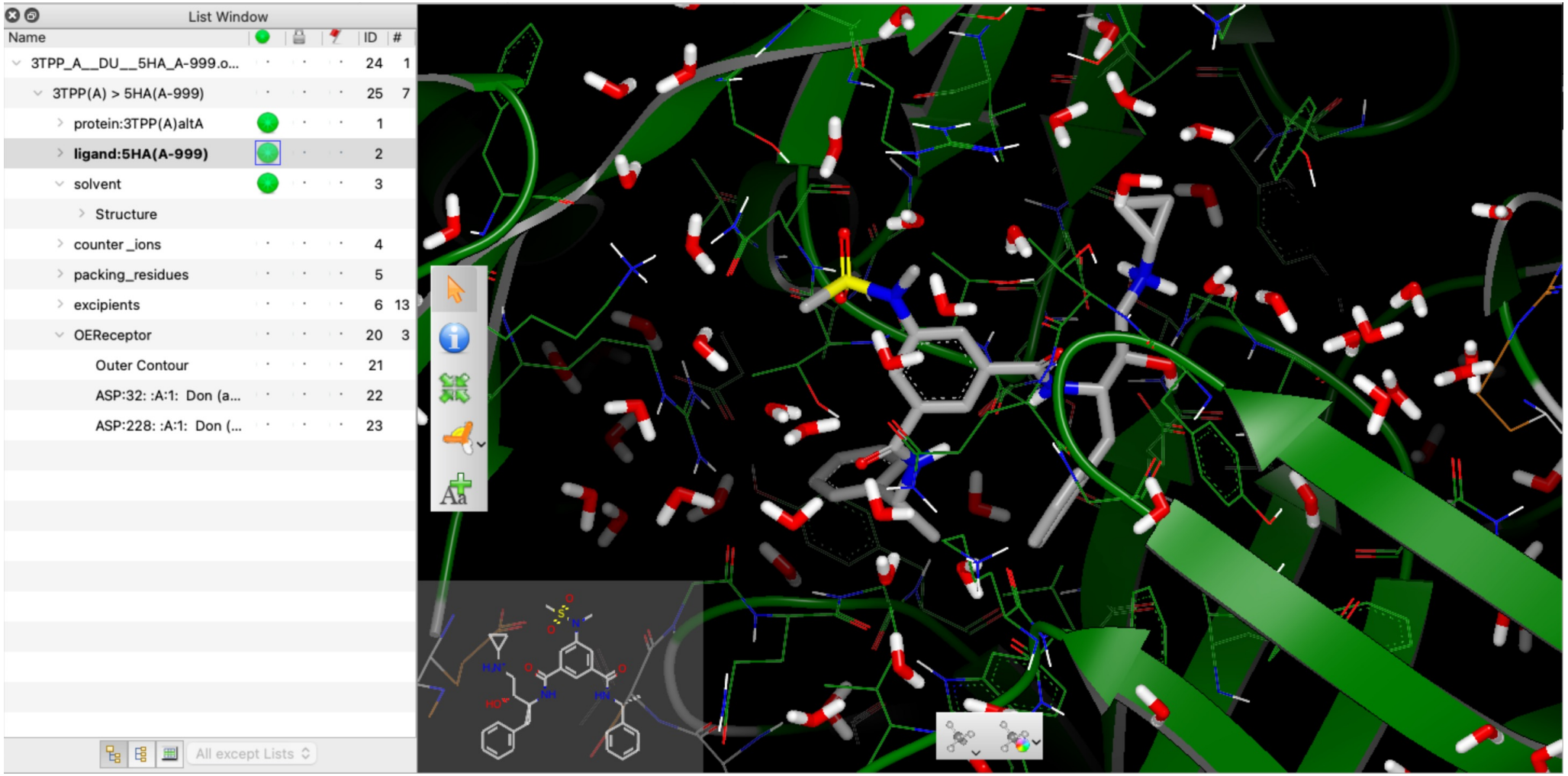

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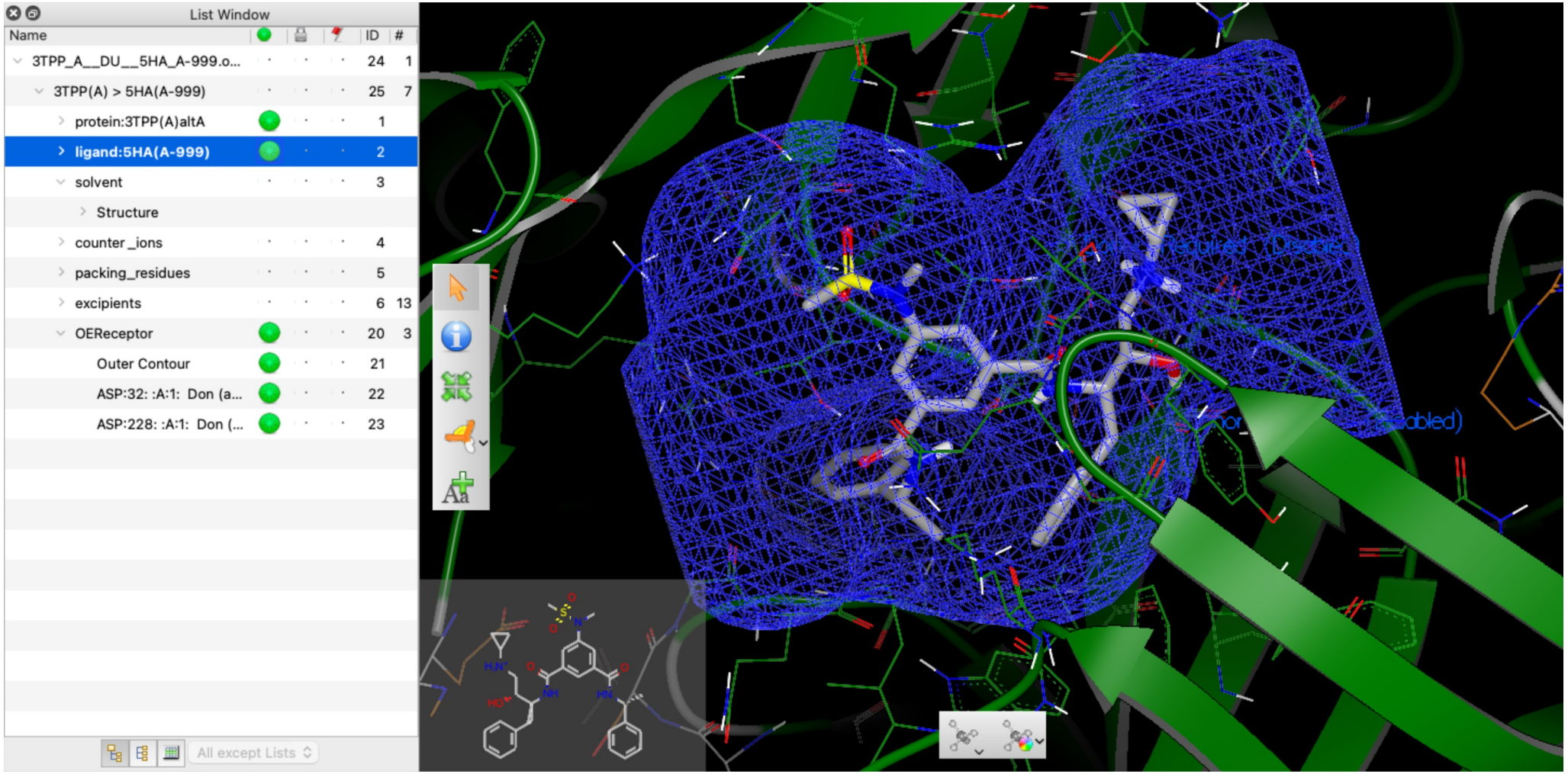

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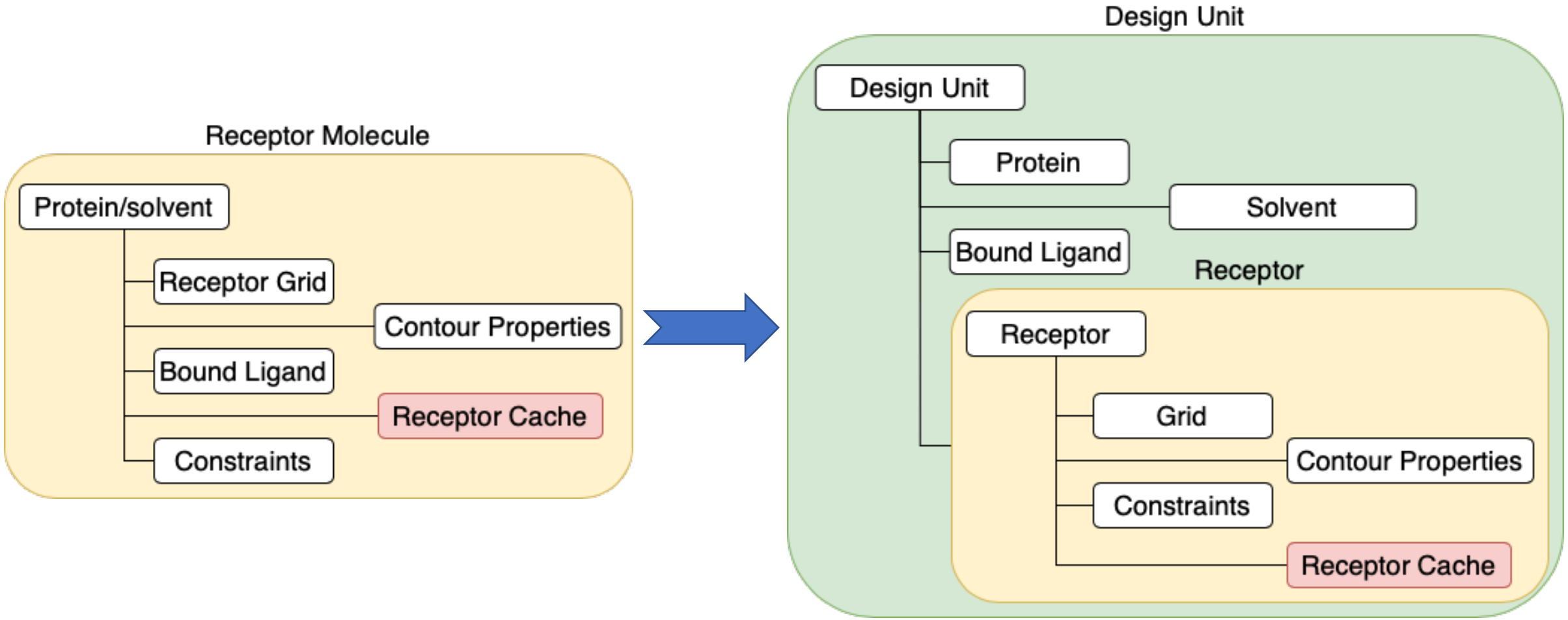
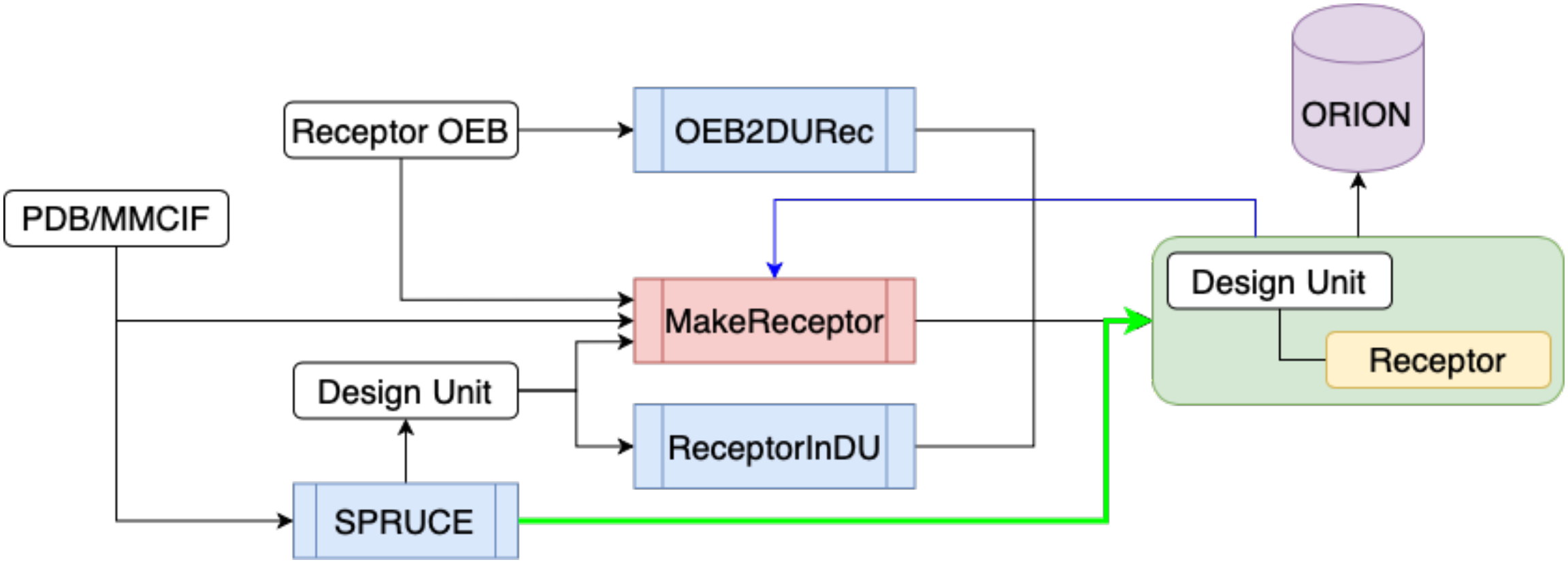
Fall 2020 - Receptor in Design Unit



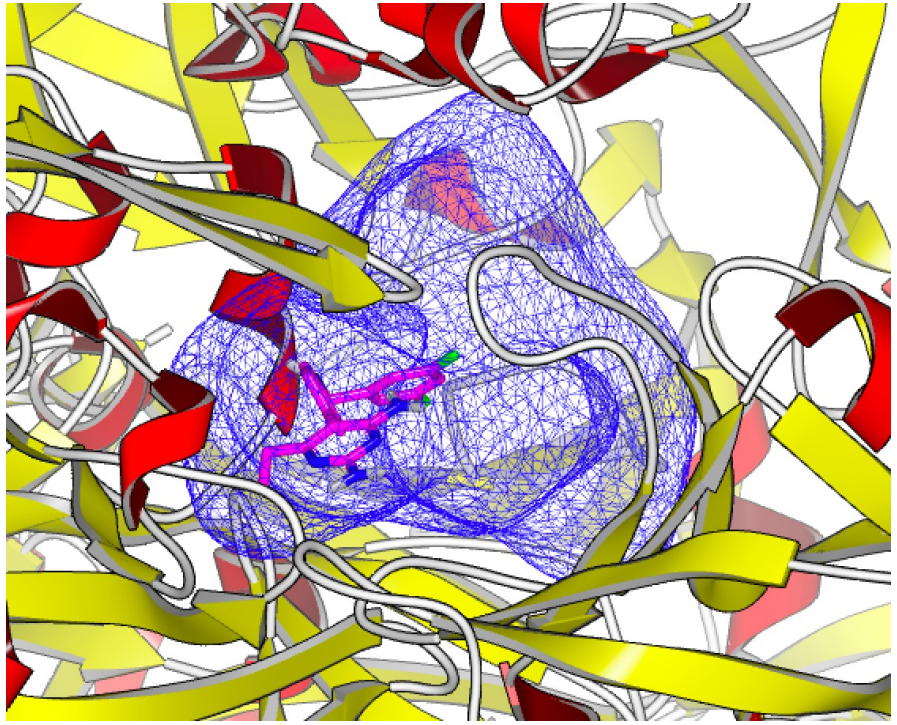
Spring 2021

- SPRUCE now generates docking receptors on design units by default
- MakeReceptor can now read OEDU files (and still OEB files)
- MakeReceptor can now run protein preparation using SPRUCE with a PDB/MMCIF & MTZ input
- Design units with receptors can now be visualized in VIDA

Receptor in 2021.Spring



Receptor in Design Unit

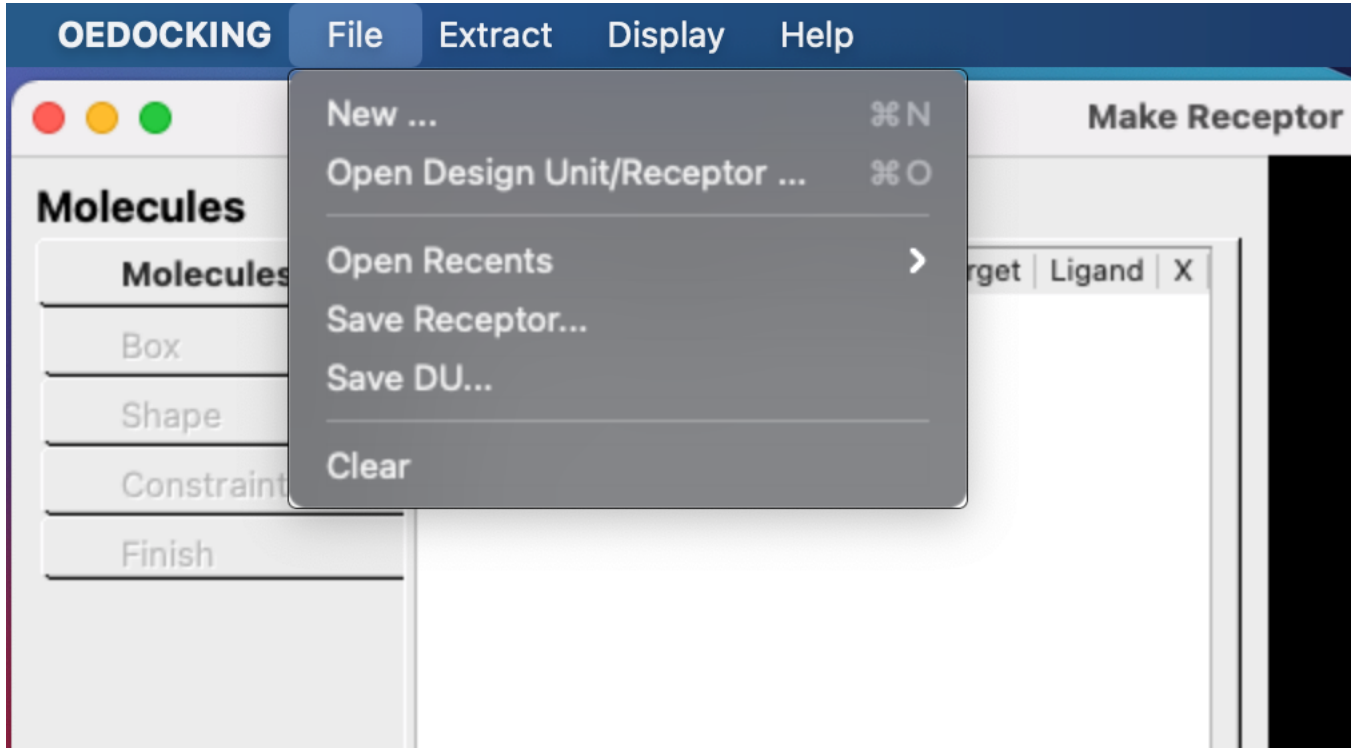


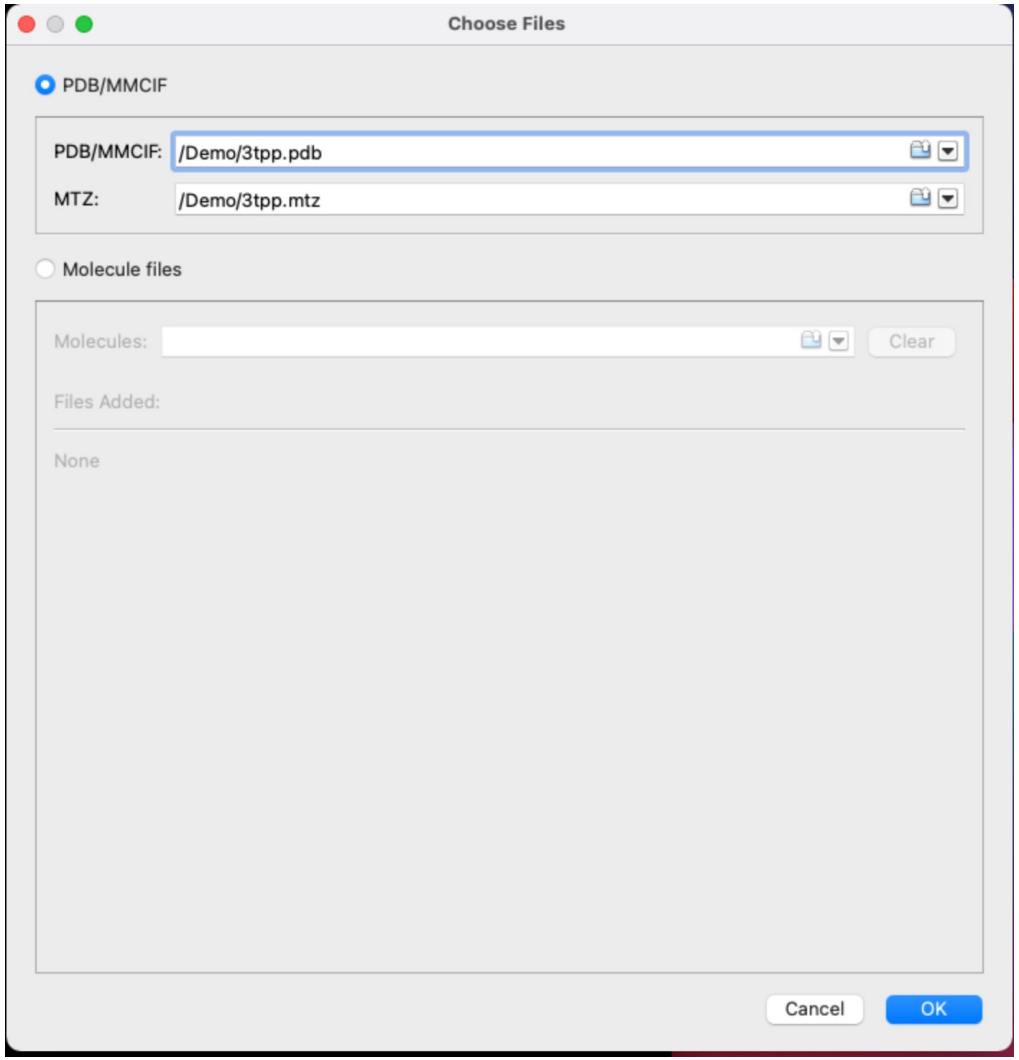
- SPRUCE prepped protein
  - Hydrogens
  - Side-chains and Loops
  - Partial Charges
- Improved pose prediction
  - Flexible-POSIT with AMBER-FF14SB and Parsley
- Better integration to downstream structure based design applications
  - SZYBKI
  - MD

MakeReceptor

- OEDU Native
  - Runs SPRUCE to prepare structure and make design units
  - SPRUCE options available in UI
- Backwards compatibility
  - Works with existing OEB receptor files
  - Ability to choose target (protein) and bound ligand
  - Accept all molecule file formats (PDB, CIF, SDF, MOL, etc.)
  - Ability to combine molecules from multiple files
- Same look and feel, with a widget-based approach

MakeReceptor – New or Open





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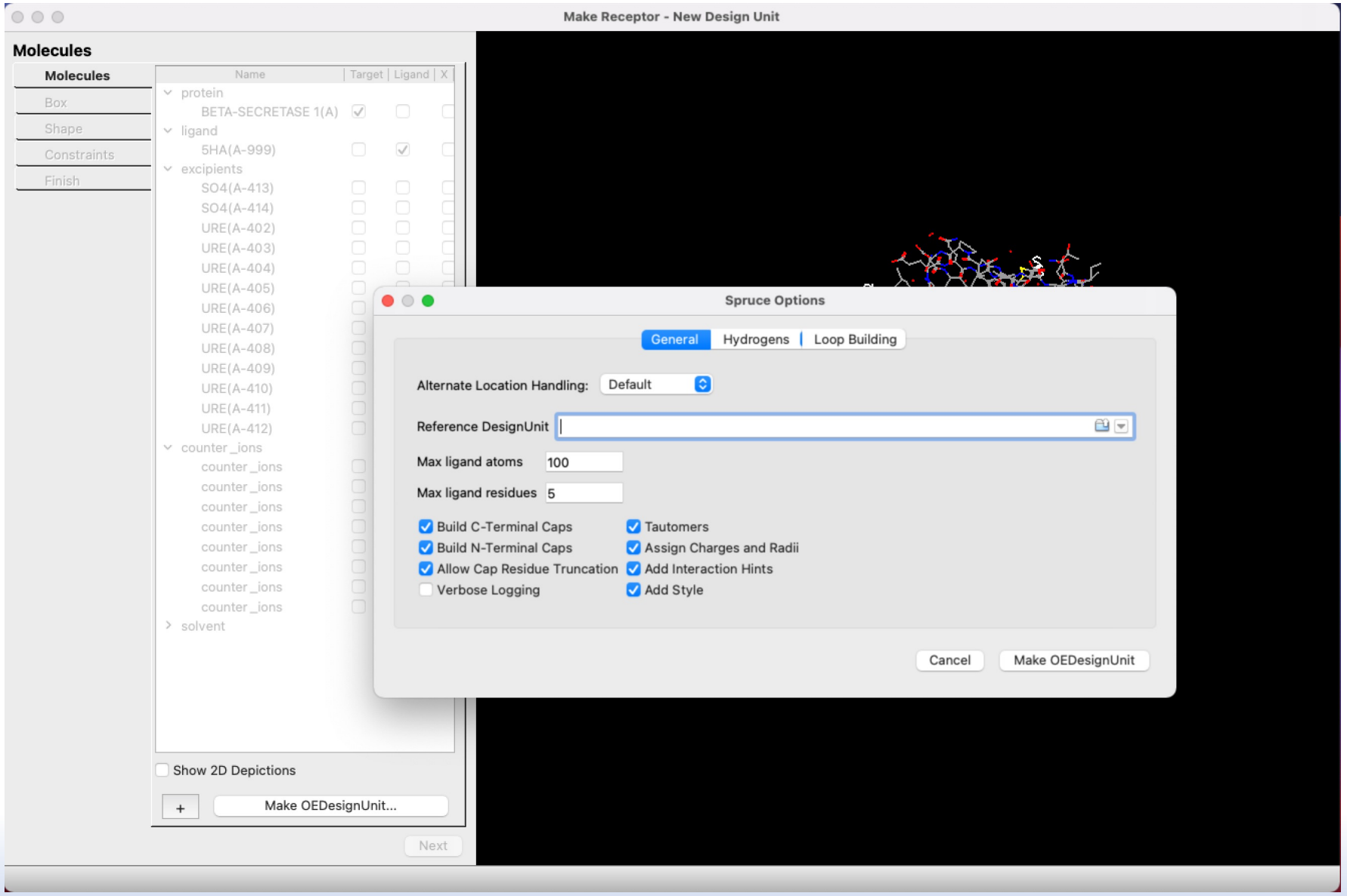
MakeReceptor – SPRUCE GUI



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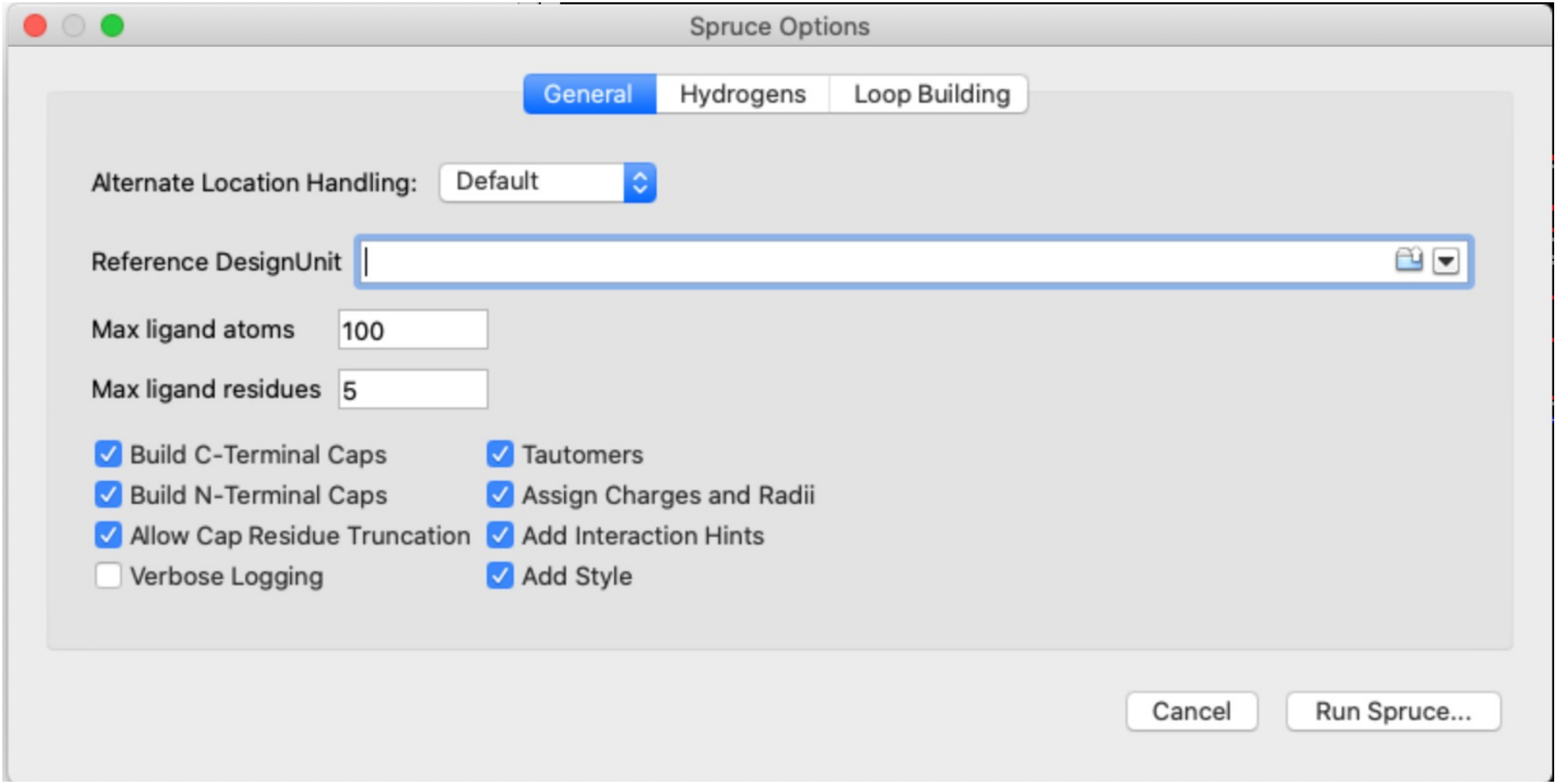

Toolkit Updates – OEDocking TK

- OEMakeReceptorOptions class controls what is included in grid generation and docking

```
mask = (OEDesignUnitComponent::Protein |
        OEDesignUnitComponent::Solvent)
```

New OEMakeReceptorOptions

- New target predicate to select specific e.g. water molecules in solvent component of a design unit

```
pred = “HOH:365: :A|HOH:135: :A”
```

- Enabled auto-constraint perception in toolkit and ability to edit these -> Enables future constraint perception in Orion

Toolkit Updates – OEBio TK

- OEReceptor class in stores the selection predicate
- OESubsetDesignUnit and OEUpdateDesignUnit will now clear the OEReceptor if the mask or predicate are matched in something that updated or removed
- OEDesignUnit class method OEGetComponents now also accepts a predicate in addition to a mask
- OEDesignUnit class has gotten two new molecule based constructors intended for prepared structures.

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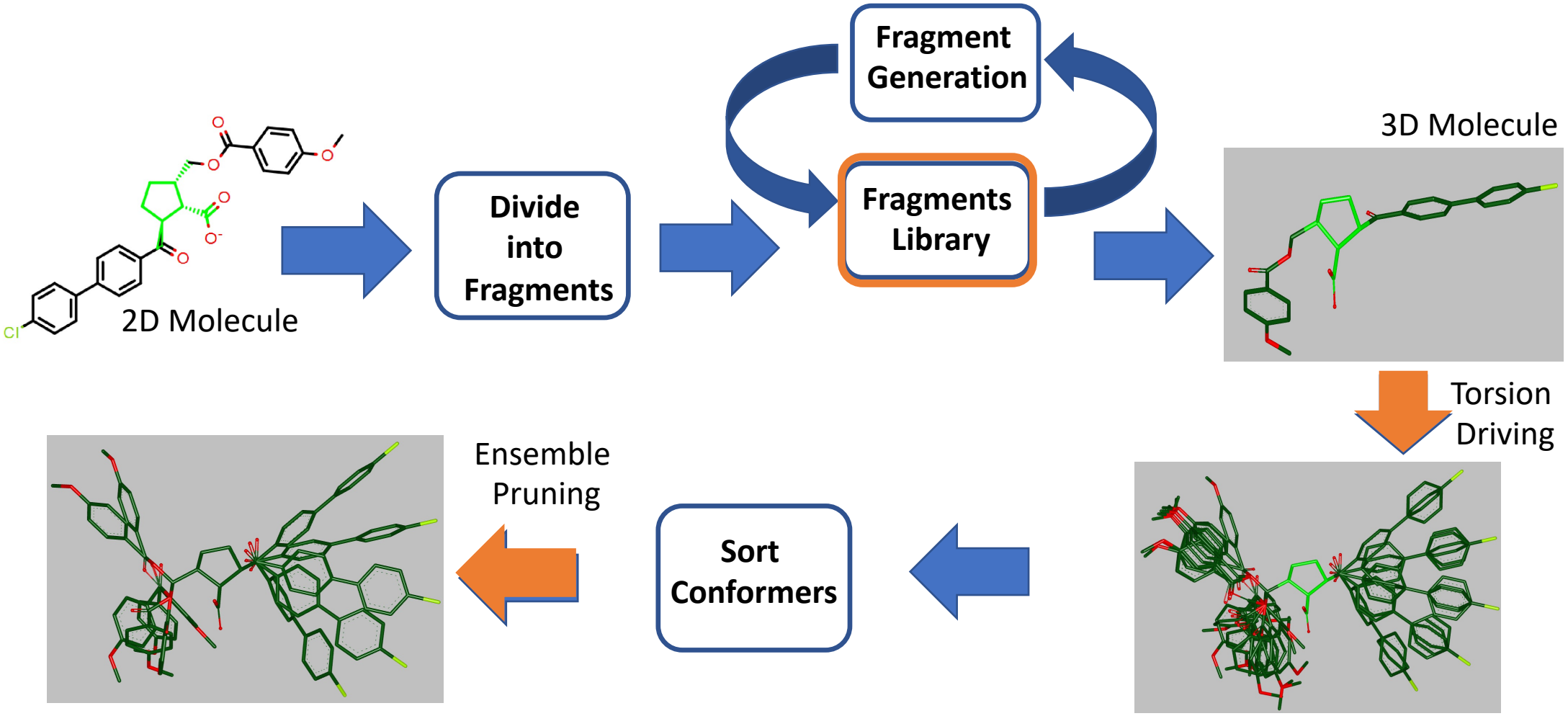
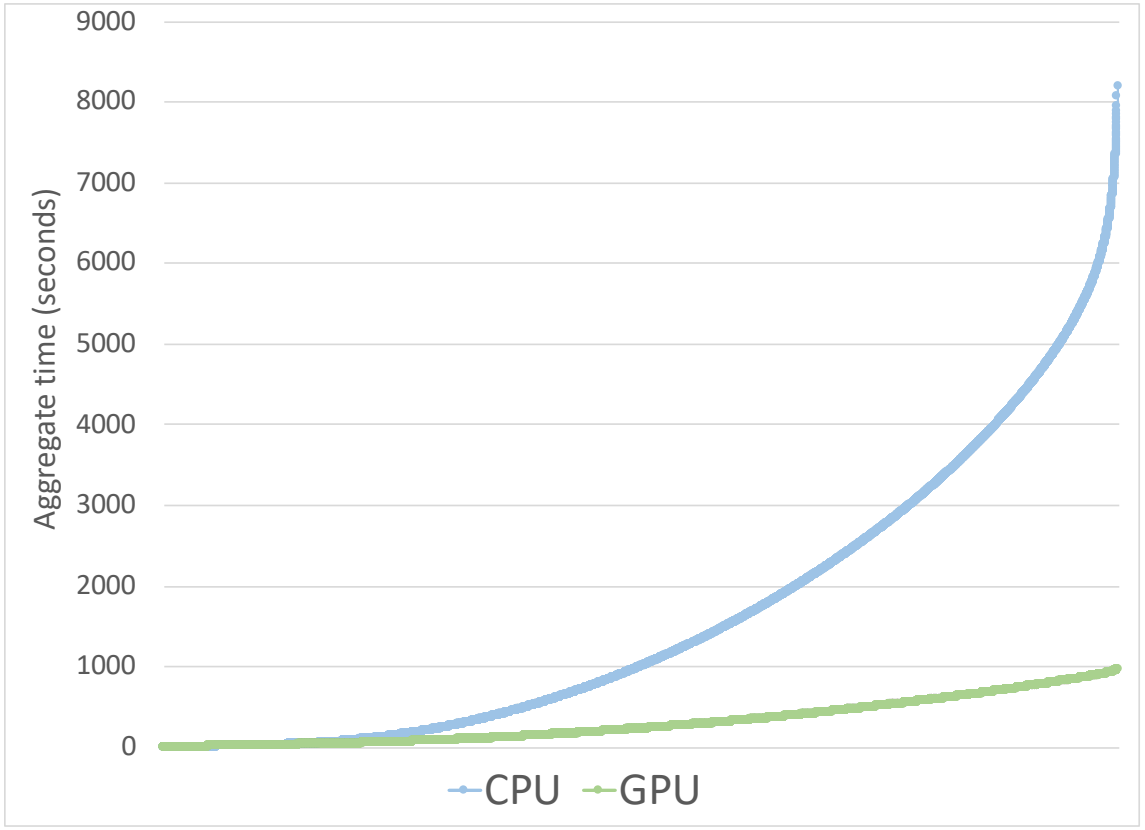
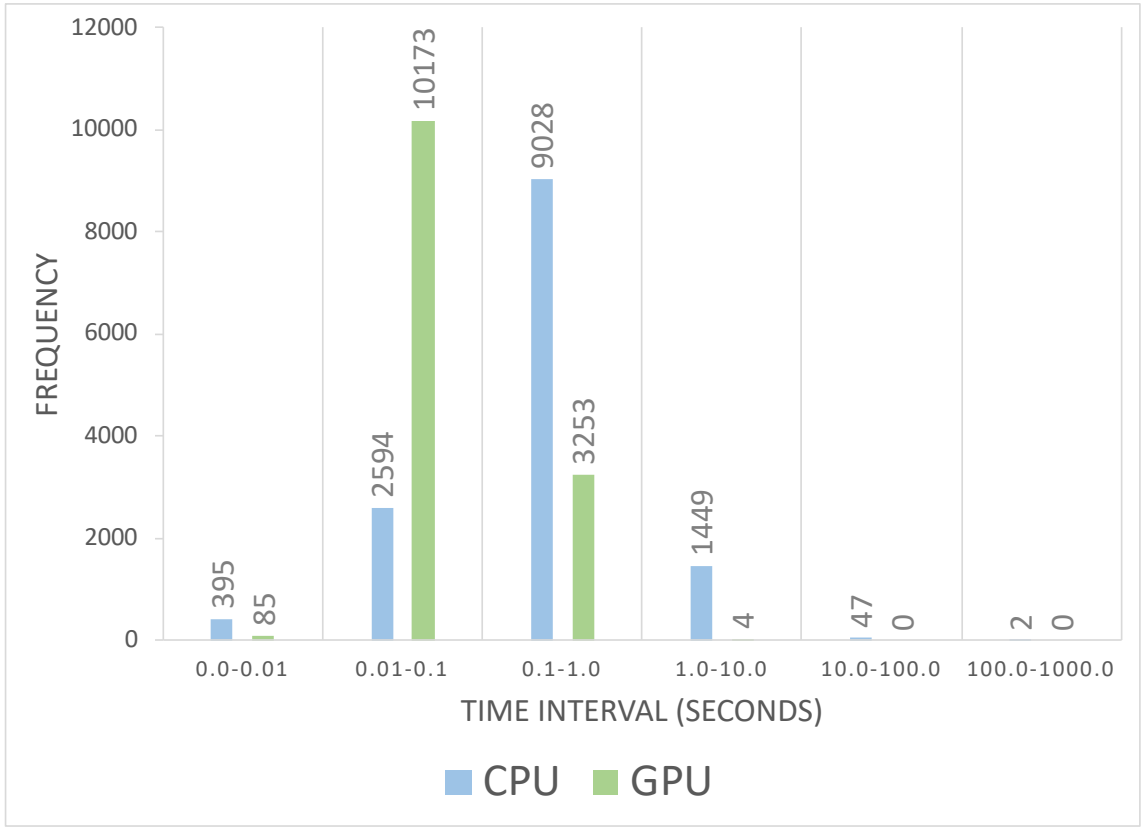
Conformer Generation With OMEGA



OMEGA Performance with GPU





Dataset: Almela MJ, Lozano S, Lelièvre J, Colmenarejo G, Coterón JM, Rodrigues J, *et al*. *PLoS ONE* **10,** 8 (2015)

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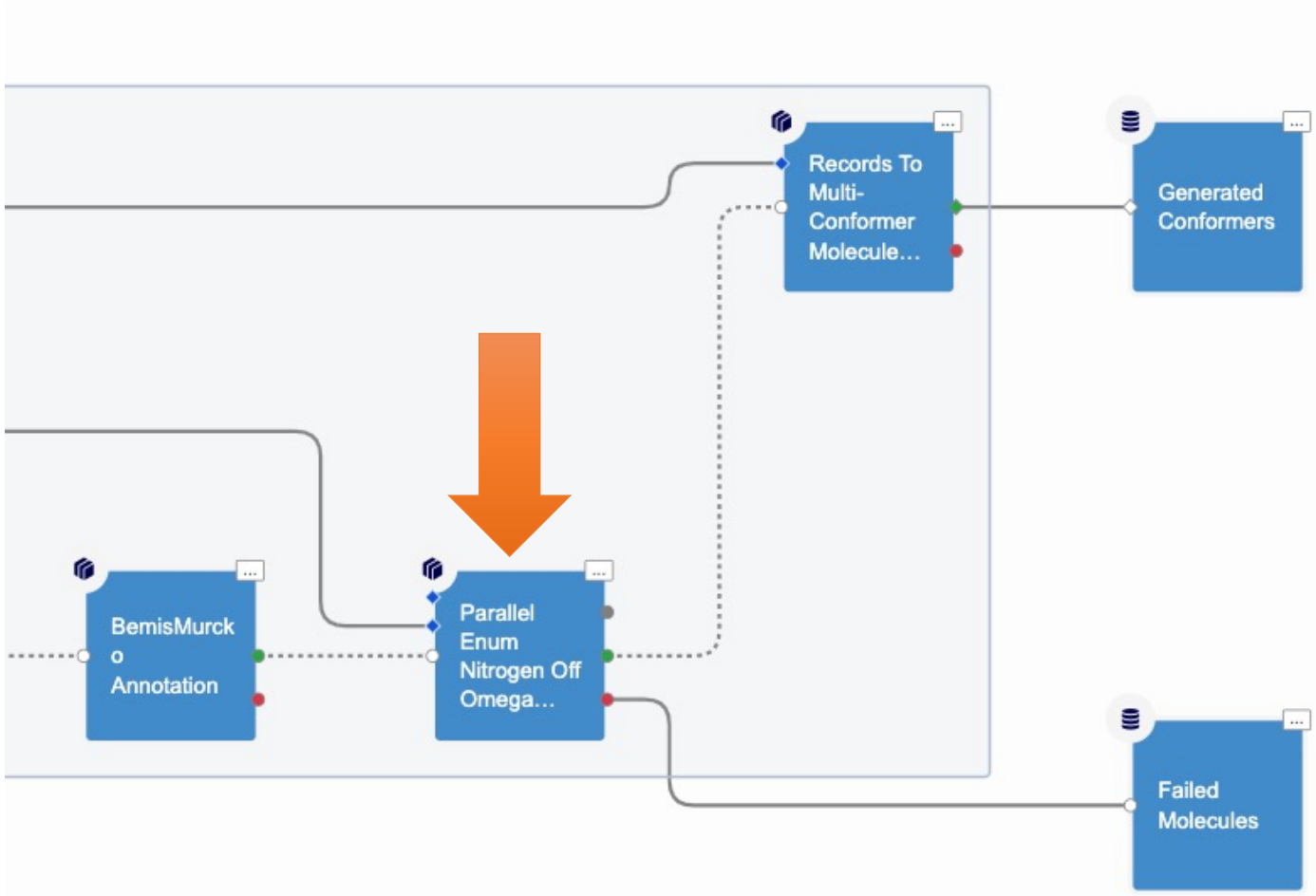
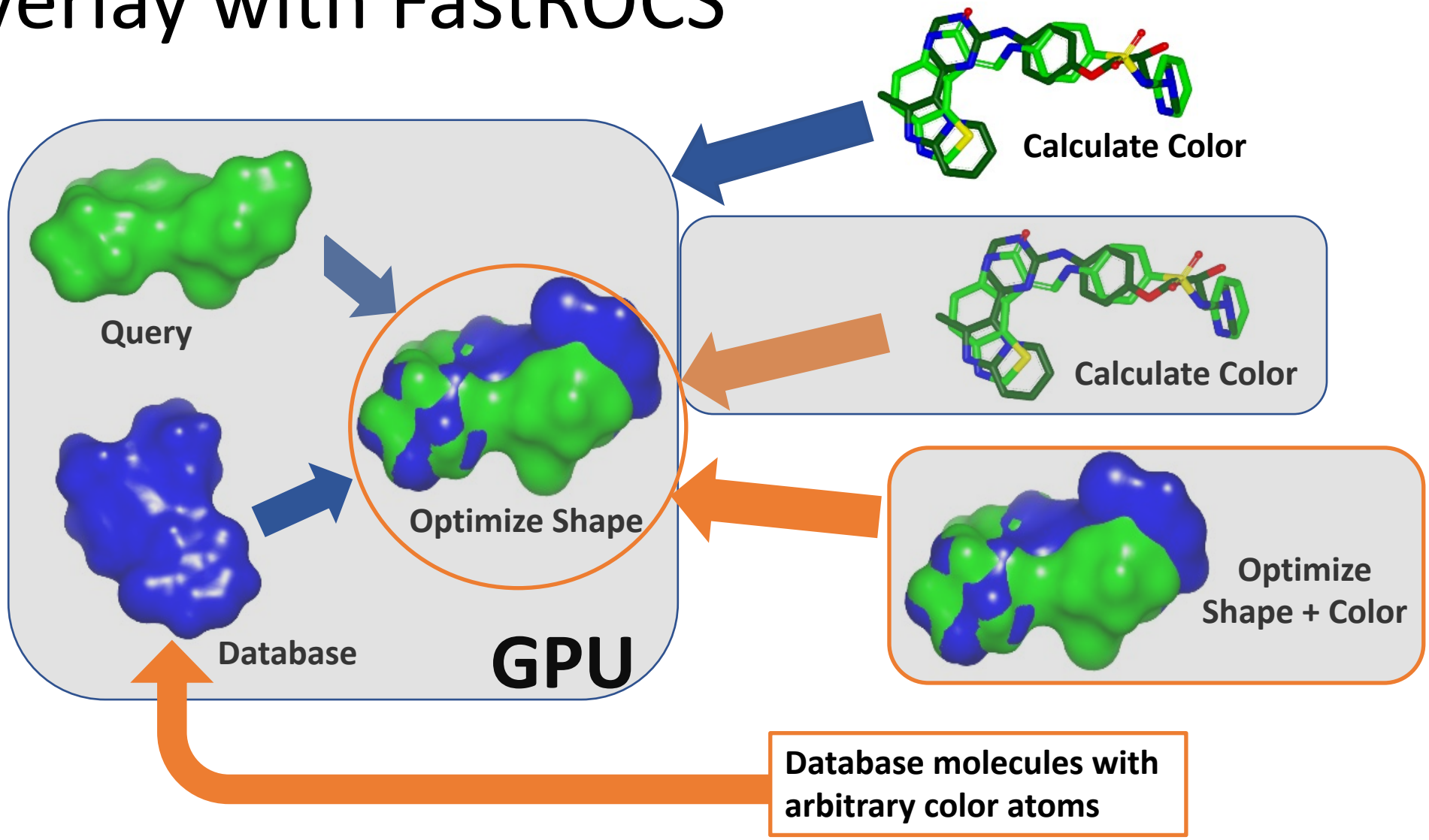
Database Prep in Orion



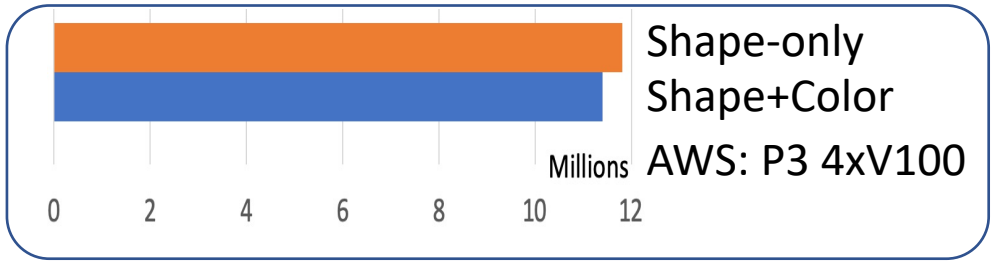
Database Prep Floe

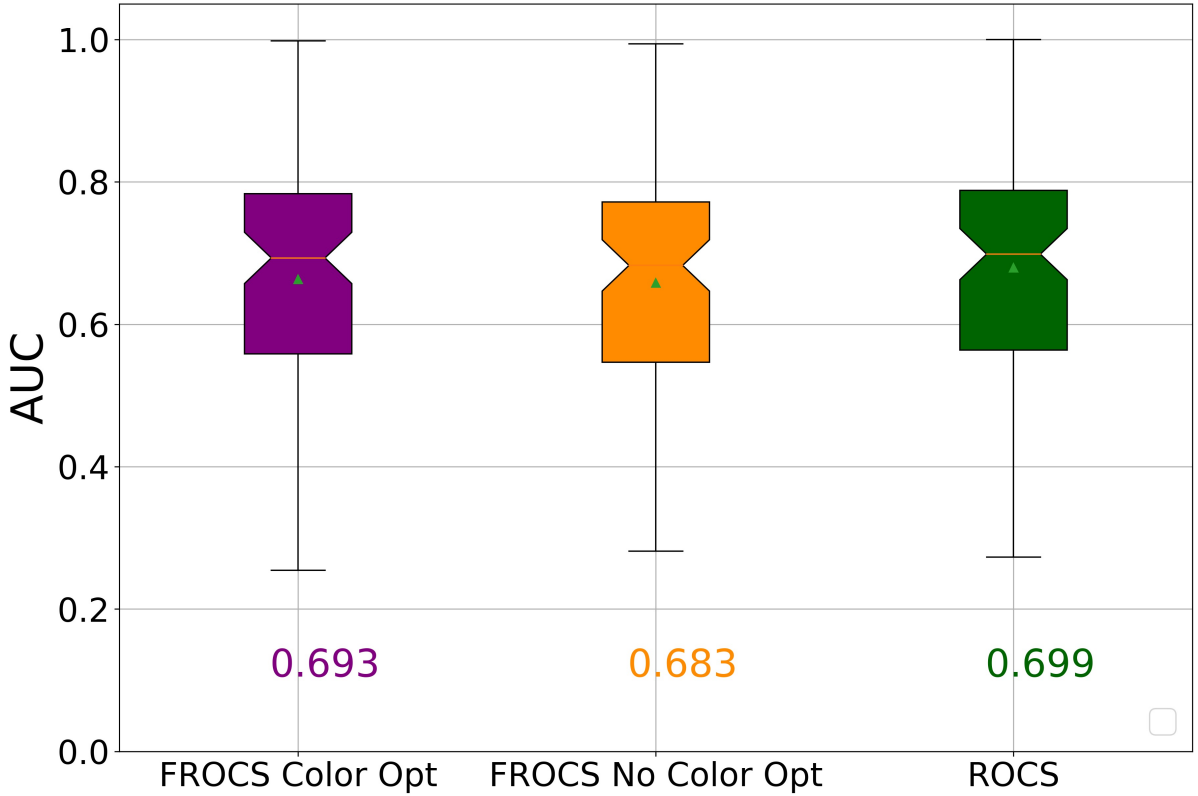
- Multi-threaded OMEGA Cube
  - Cost of GPU Instances
  - Utilize all CPU cores
  - Utilize all GPU cores
- Database prep cost reduction

Overlay with FastROCS

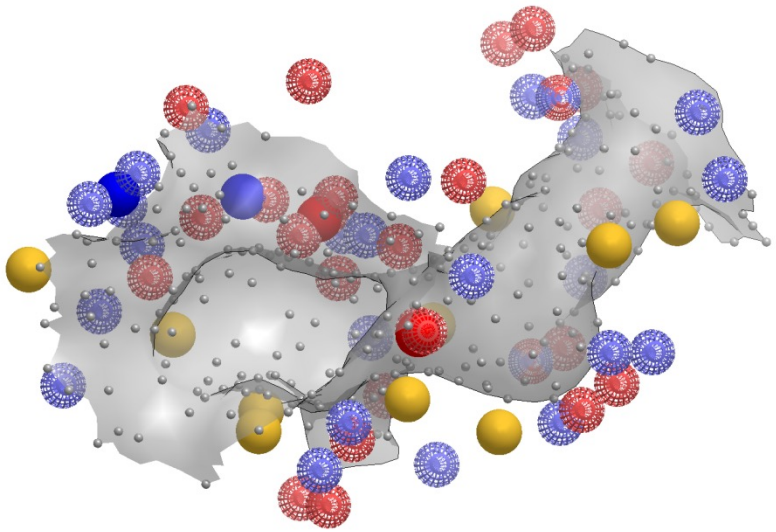


FastROCS Performance and Accuracy





SiteHopper: Comparing Binding Sites



Same Protein Different Ligand

- Protein Motion
- Induced Fit
- SAR Analysis/Alignment

Closely Related Proteins

- Homology Modeling
- Selectivity

Same Ligand, Different Protein

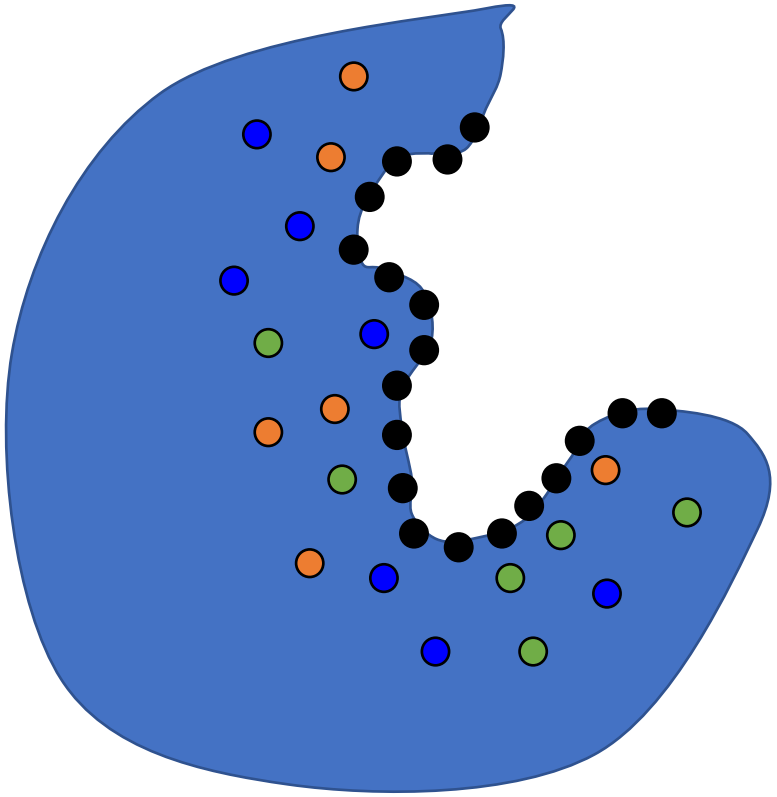
- Drug Repurposing
- Off-target effects
- Target Fishing

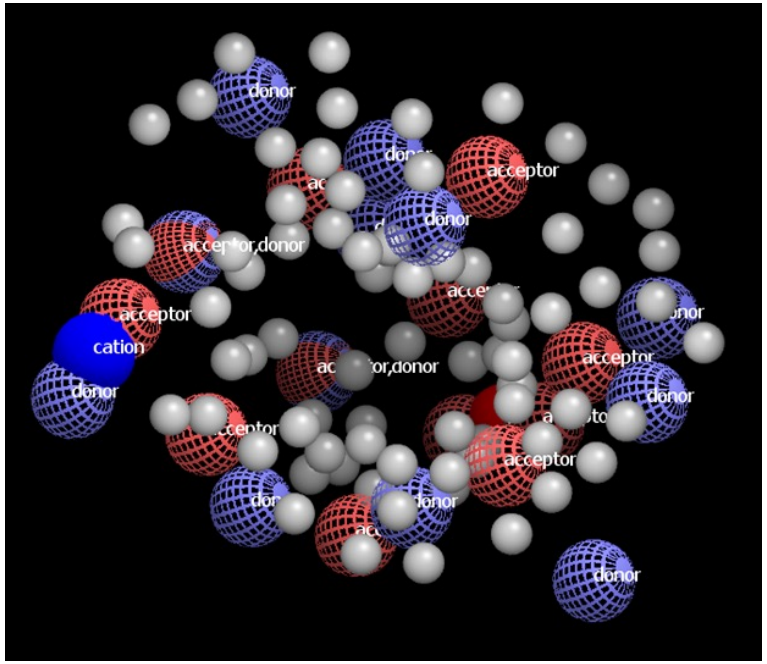
Protein Pocket with Shape and Color

Create Pocket Surface

Create Surface Shape Molecule

Create Protein Color Features





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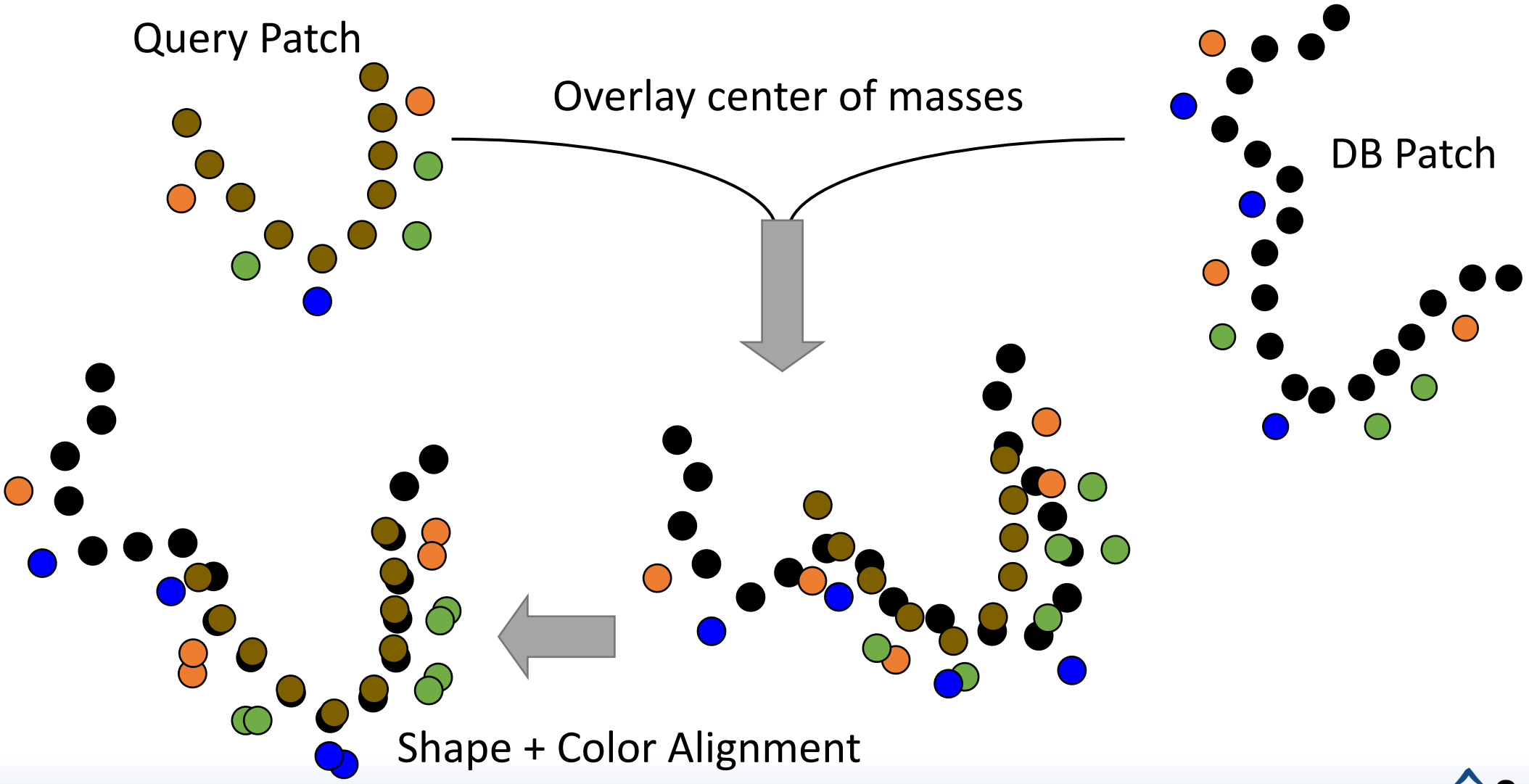
Protein Pocket Overlay

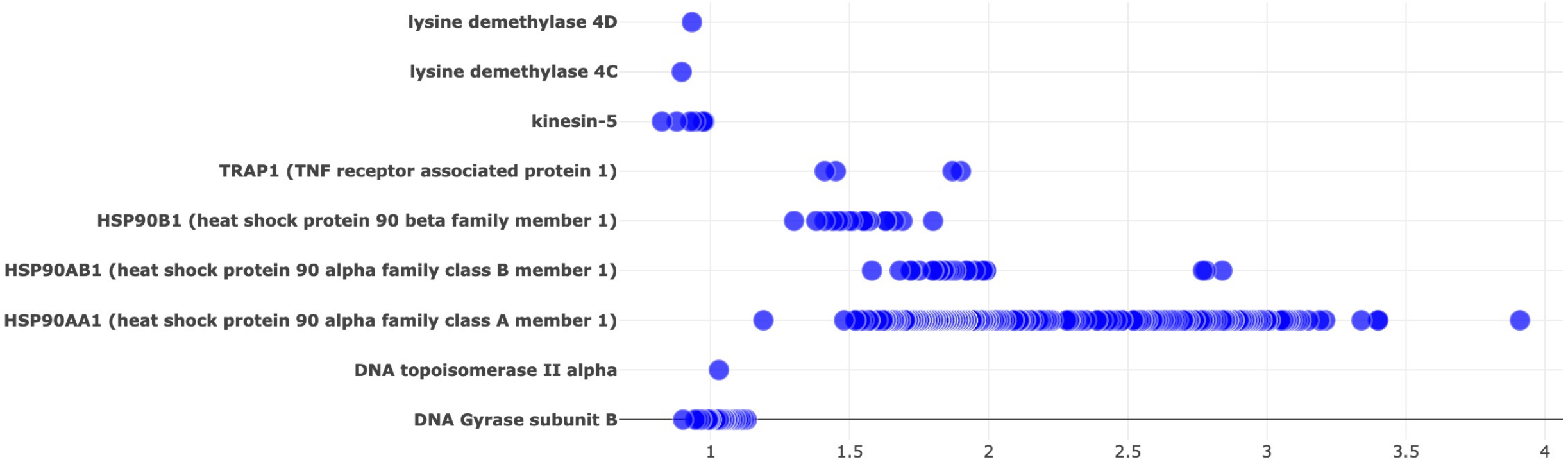


SiteHopper 1.0

- This is the first official release of SiteHopper
  - Linux only and requires an NVIDA GPU card
- Search is done using the GPU enabling searching 250k+ protein binding sites in just a few minutes
- A database can be built from a directory of OEDesignUnit files. We are making a database available for searching based on liganded sites in the PDB (~280k binding sites).

Orion Search example

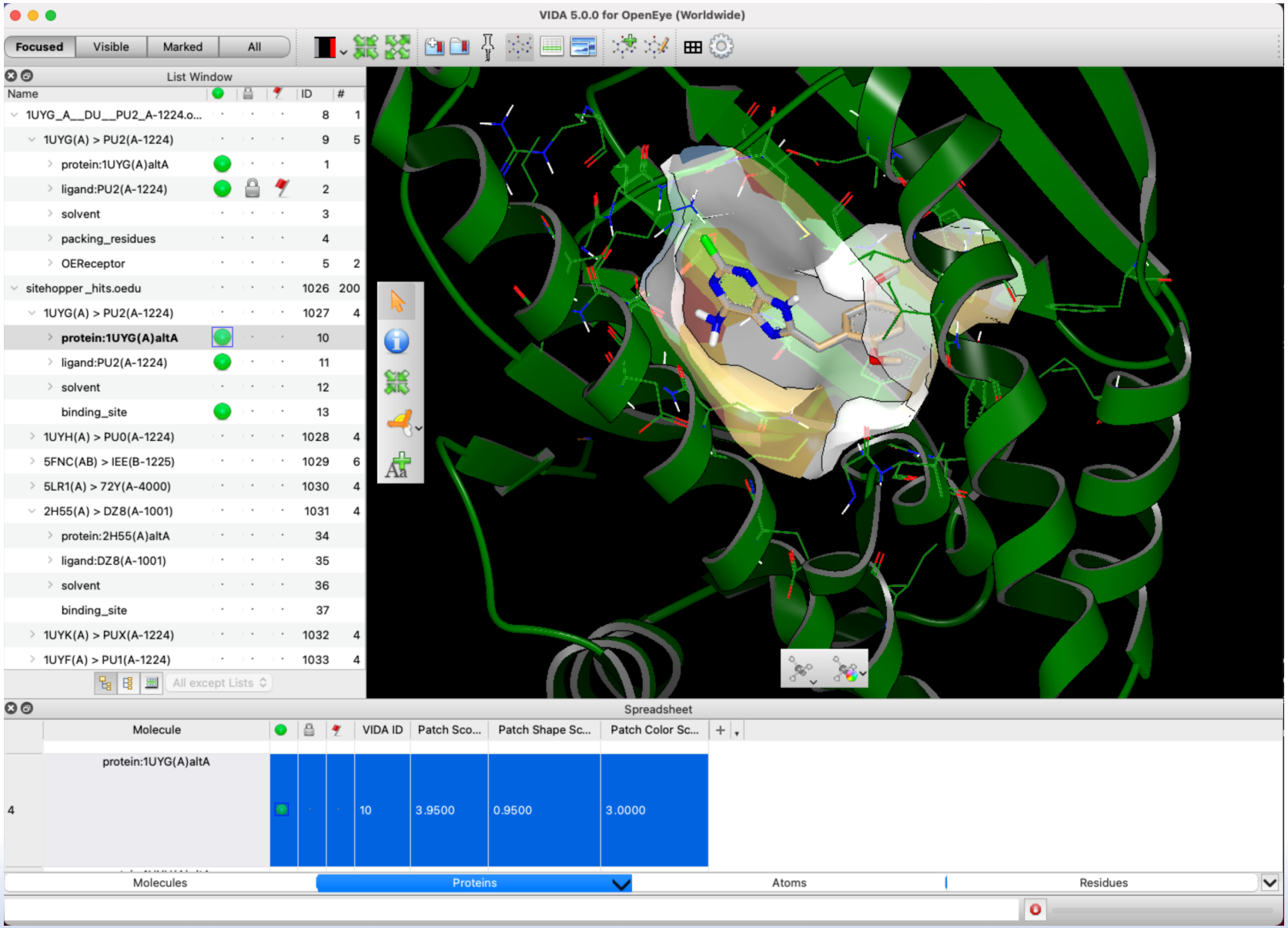
- Query HSP90, 1UYG(A) > PU2(A-1224)
- Database: Guide to Pharmacology in Orion ~40,000 DUs



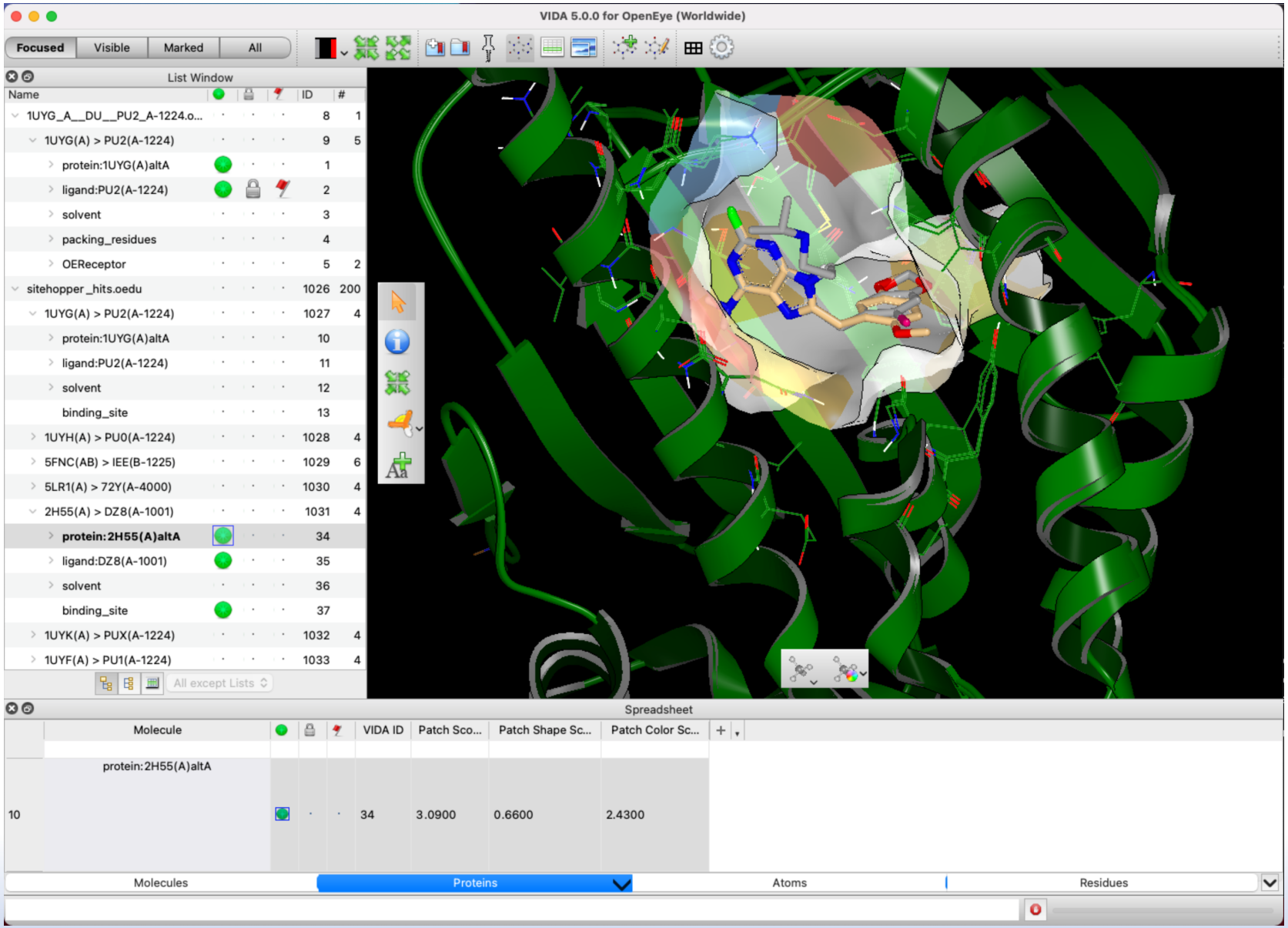
App Search example

- Query HSP90, 1UYG(A) > PU2(A-1224)
- 280,000 liganded DUs from the PDB
- Top 200 hits

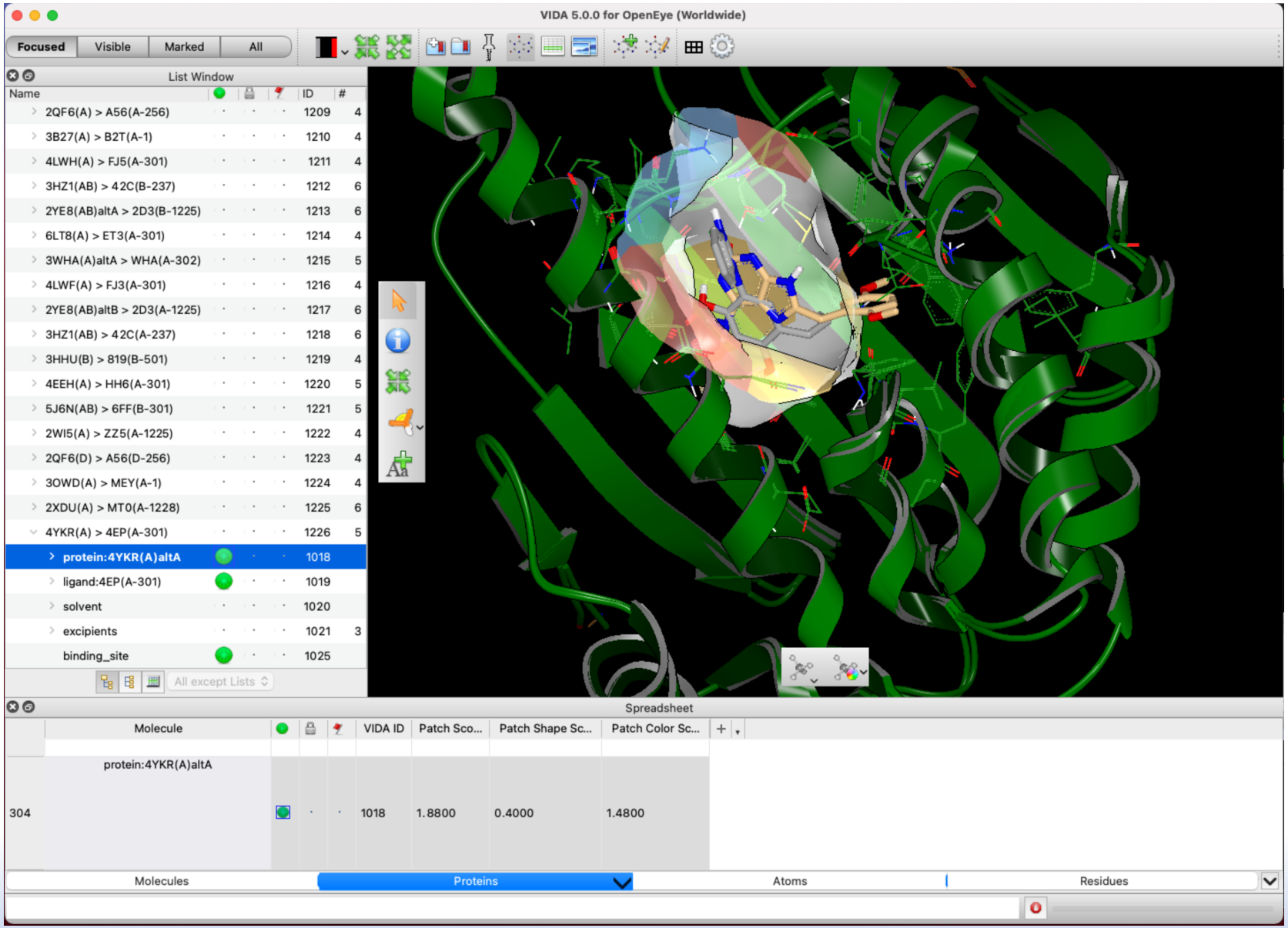
App Search example – best hit (self)



App Search example – top hits



App Search example – hit #200



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orion

OpenEye Toolkits 2021.1.0 will be available in the 2nd Orion release of 2021

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Thank You
The End
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