
3D Modeling in Orion
Bob Tolbert
CTO, OpenEye
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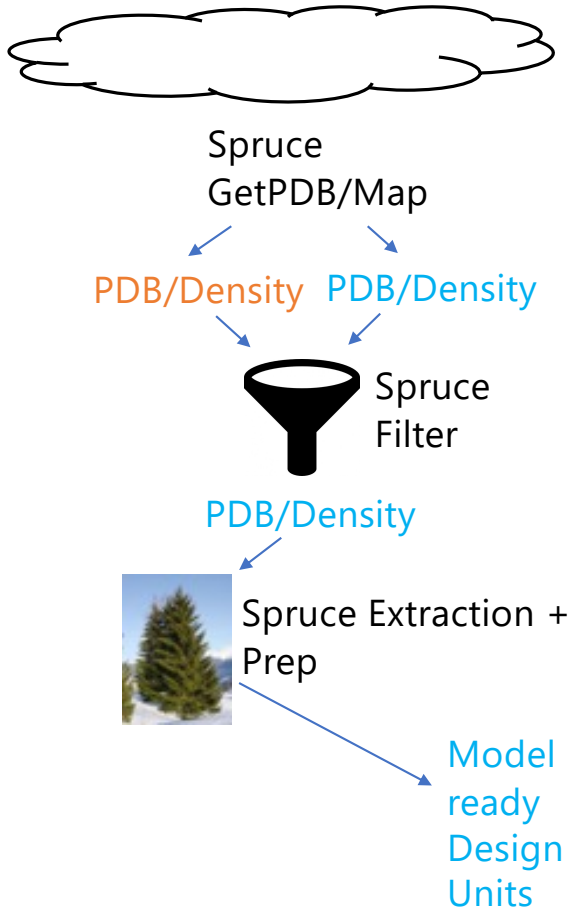
Agenda

- Automated Protein Prep - Spruce
- Prepared structure storage – MMDS
- Interactive 3D modeling
- 3D Workflows
- Binding Site search - SiteHopper

Protein Prep with Spruce

What can Spruce do?

- Read experimental data
- Filter out problematic structures
- Extract biological unit
- Modelling ready system prep
  - Side-chain and loop modeling or capping
  - Tautomer assignment
  - Protonation
- Structural superposition

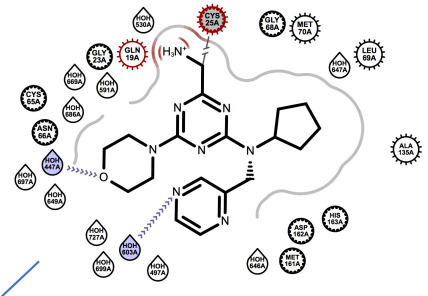


Structure Modeling - Protonation

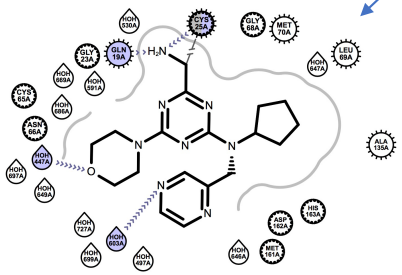
- Spruce protonates the entire system
  - Protein, nucleic acids, ligands, waters, etc.

- Tautomer search tries to improve various interactions
  - Protein-ligand interactions
  - Ligand-ligand interactions
  - Steric clash reduction

Steric clash with protein



Spruce tautomer search



Improved protein-ligand hydrogen bonding

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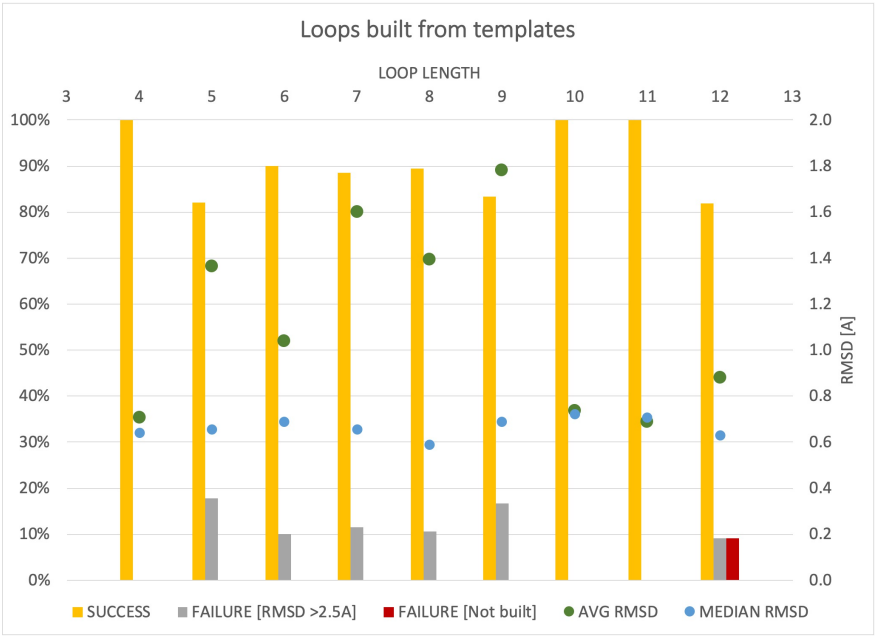
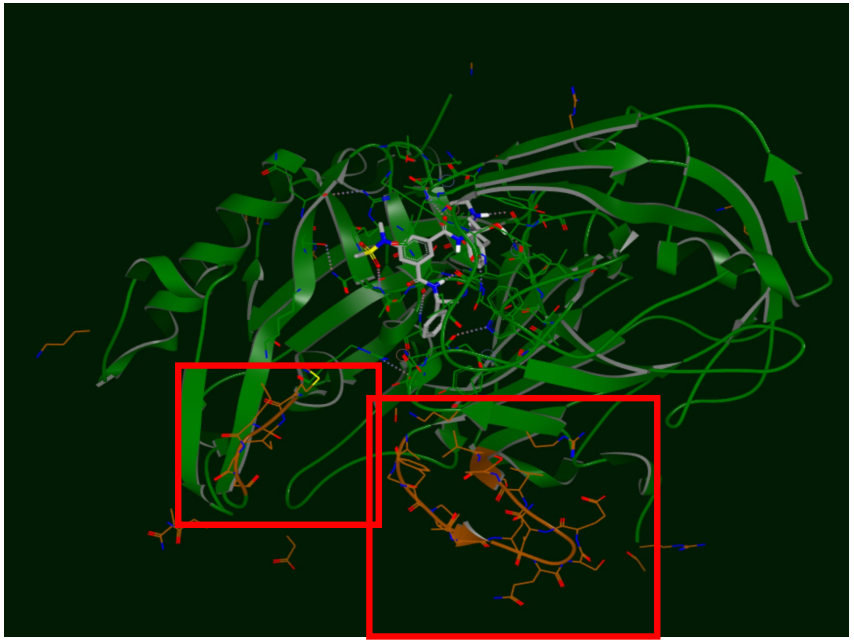
Loop modeling

- Enabled by default in Orion



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



PDB-ID: 3TPP. Modeled pieces in brown

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

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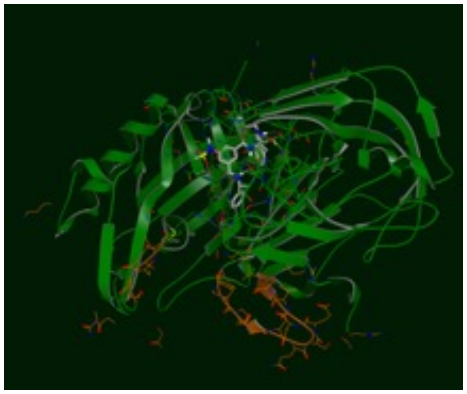
Model Quality Assessment

- Iridium classification for model quality analysis

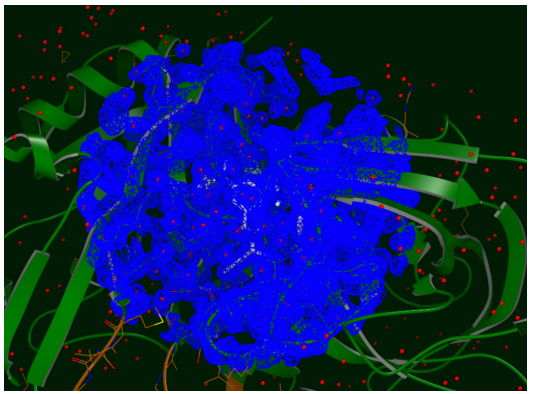
- The quality of the structure data:
  - Give teams ability to understand quality of structures
  - Critical for managing modeling expectations
  - Key to understanding modeling results

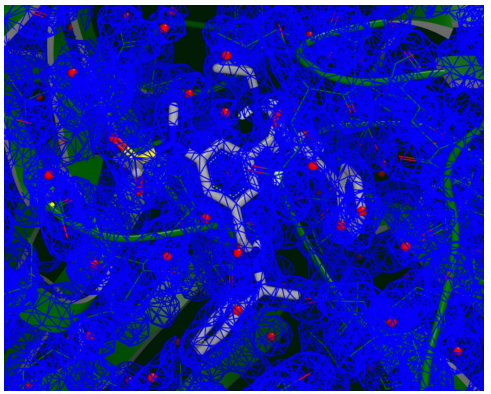
Visualization of DesignUnits

3D view

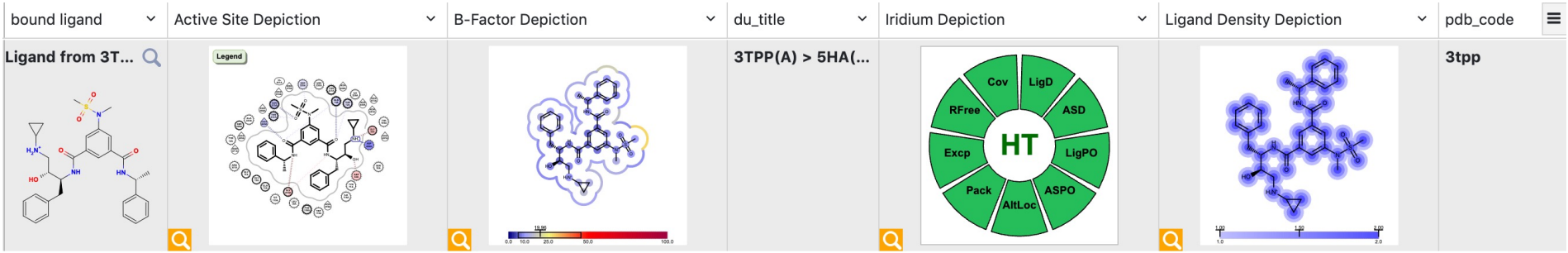


Electron density grid visible around binding site*





Analyze page: Depictions on records – quick way to view input structure-based design datasets



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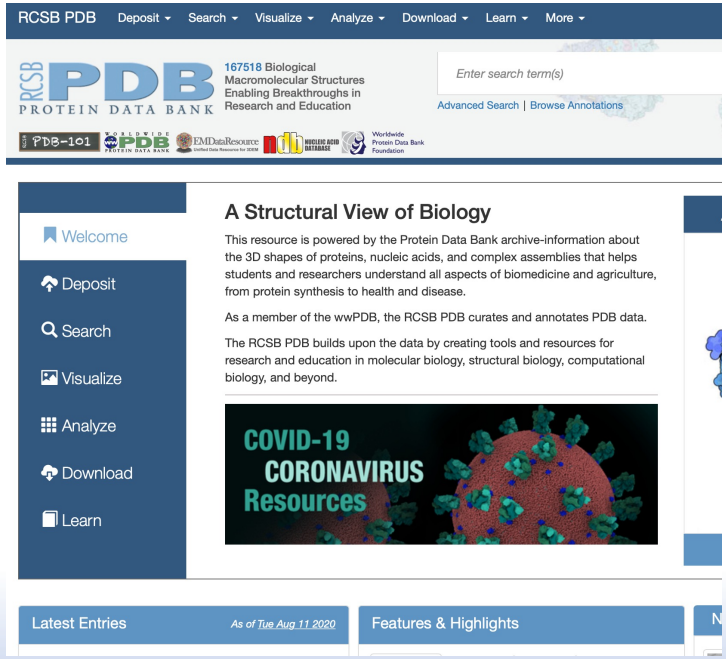
Spruce - Enabling structure-based modeling

- Consumers of OEDesignUnit
  - OEDocking – FRED/HYBRID
  - POSIT
  - SZYBKI
  - SZMAP
  - STMD/NES/General MD
  - SiteHopper

Prepared Structure Storage - MMDS

The Data

- Target structures (complexed with “ligands”)
- Public data source: “The PDB”
  - RCSB – US
  - EBI – Europe
  - PDBj - Japan



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Guide to Pharmacology

IUPHAR/BPS
Guide to PHARMA

Home | About | Targets | Ligands | Diseases | Resources | Advanced search | Immuno Portal

- GPCRs
- Ion channels
- Nuclear receptors
- Kinases
- Catalytic receptors
- Transporters
- Enzymes
- Other protein targets
- Target search

An expert-driven guid…ets and the substances that act on them.

Quick links

Targets

G protein-couple…
Ion channels
Nuclear hormone…
Kinases
Catalytic recepto…
Transporters
Enzymes
Other protein tar…

Ligands

Approved drugs
Synthetic organics
Metabolites
Natural products
Endogenous peptides
Other peptides

…new to Guide to PHARMACOLOGY

…avirus (Covid-19) - view our information page

…tabase version 2020.3 (19 Jun 2020) - full details in our blog post

…st release includes:

…RS-Cov-2 protein family which includes 13 members and is found under …nti-infective targets' in our hierarchy

… emerging oncology target, ACSS2, has been added plus two inhibitor …obe compounds (example 265 and ADG-207).

…dates have also been made to targets across 20+ different protein families …er 200 ligands are now marked as antibiotic and more than 100 of these have with links to Antibiotic DB

- Improvements have been made to ligand summary pages. Key information, such as synonyms, curator comments, links to activity graph and SMILES and InChI Keys have been prioritised.

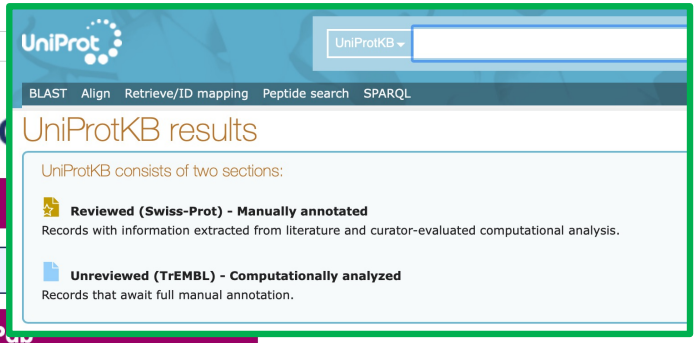
Please read our latest Database Report (April 2020) - download/view PDF

GtoMP…

IUPHAR/MMV Guide to Malaria Pharmacology

Visit the IUPHAR/MMV Guide to MALARIA PHARMACOLOGY portal
Launched in September 2019 to provide optimised access to GtoPdb data for the malaria research community

The Concise Guide to



Mapping key between GtoP and RCSB is UniprotKB accession #

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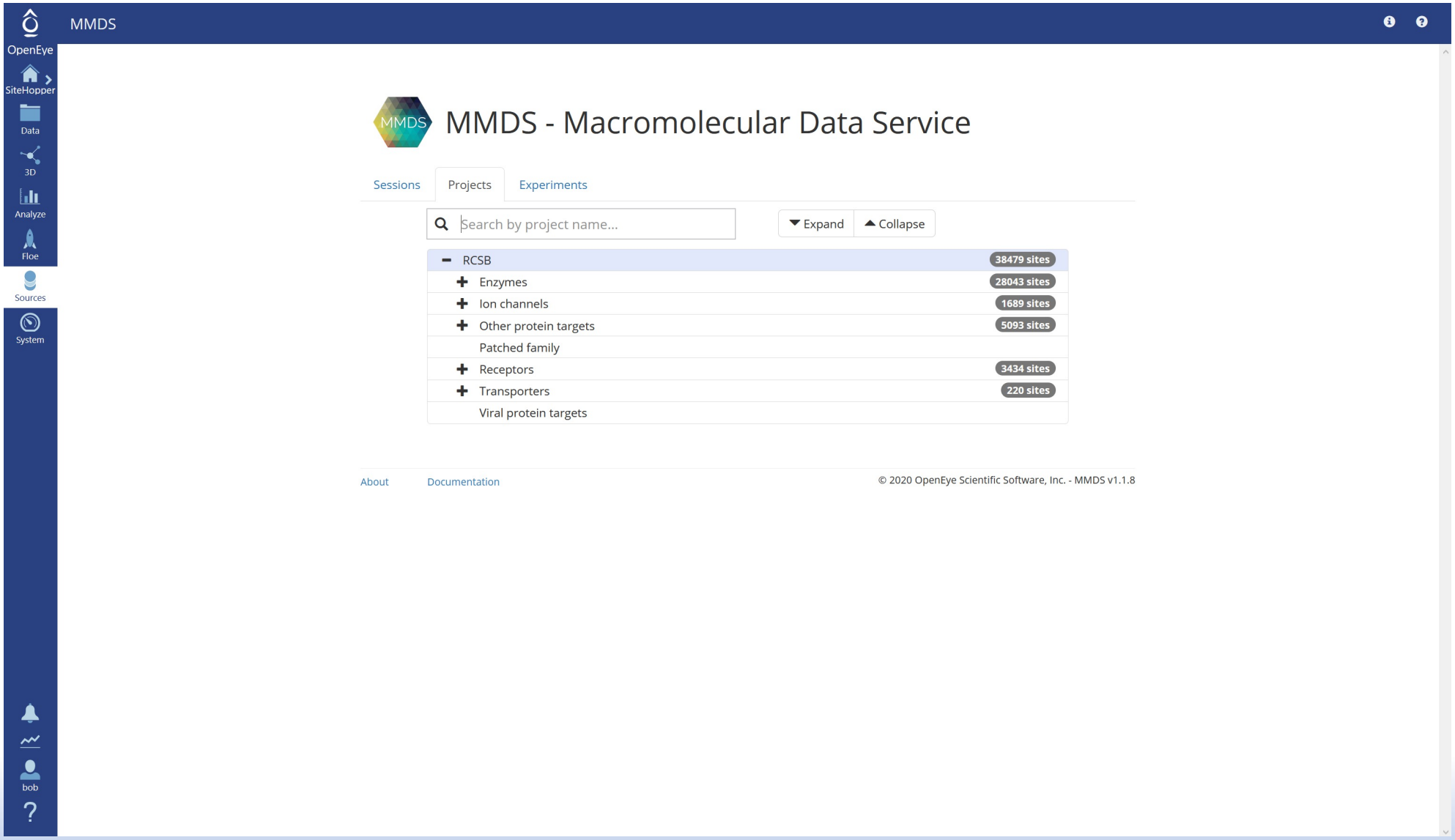
MMDS
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MMDS - Macromolecular Data Service
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RCSB 38479 sites
Enzymes 28043 sites
Ion channels 1689 sites
Other protein targets 5093 sites
Patched family
Receptors 3434 sites
Transporters 220 sites
Viral protein targets
About
Documentation
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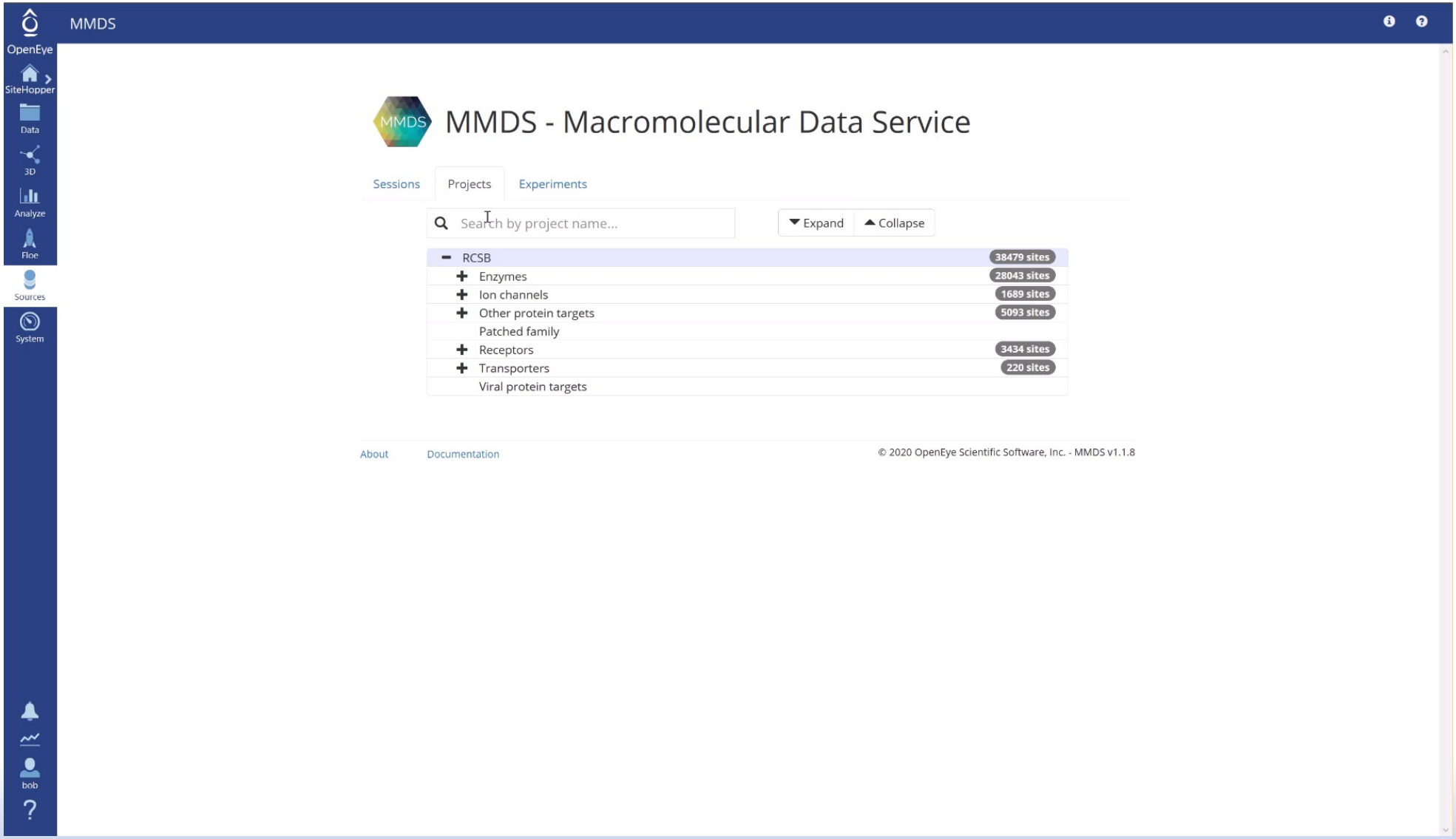
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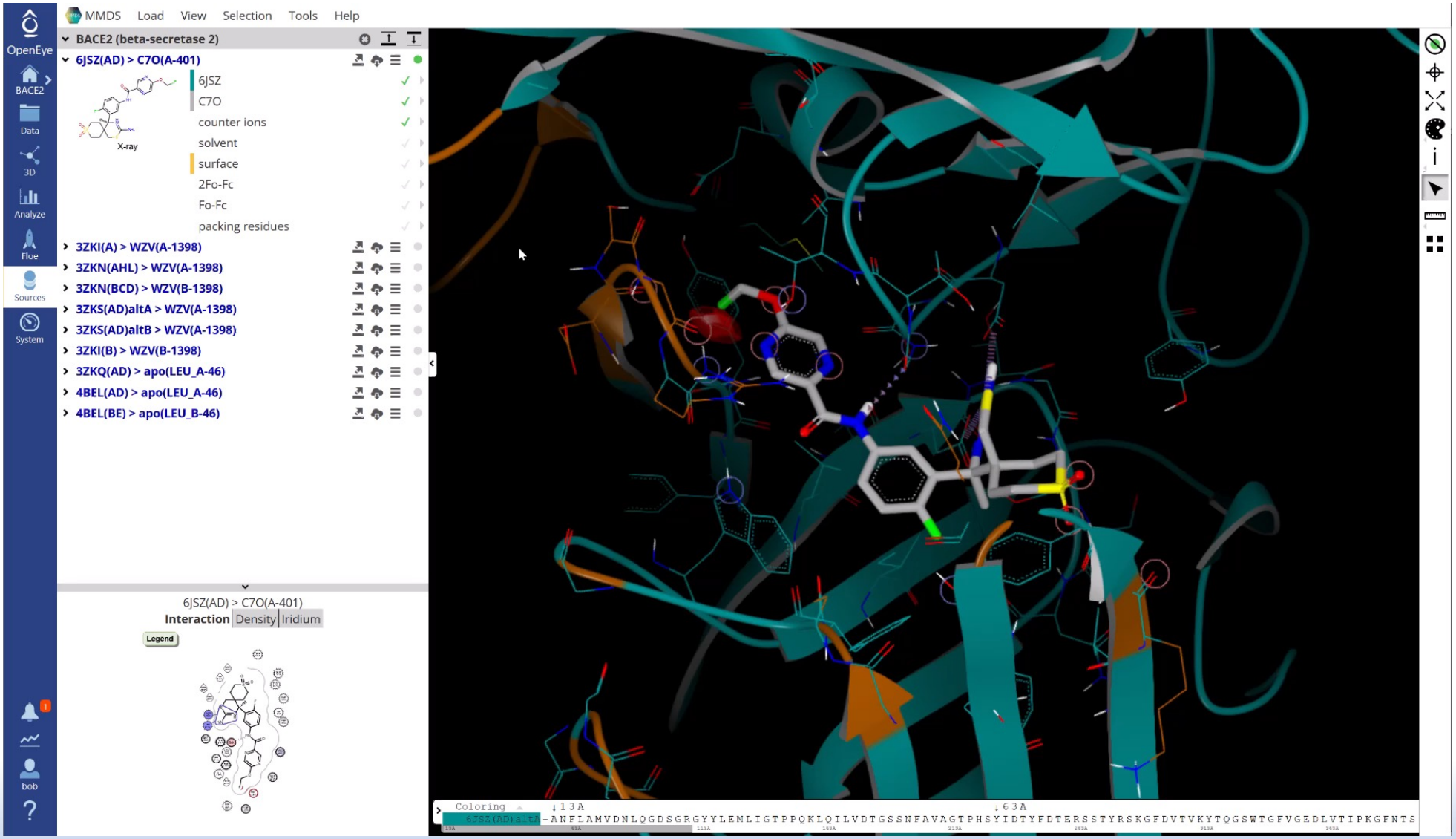
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6JSZ(AD) > C7O(A-401)
X-ray
6JSZ
C7O
counter ions
solvent
surface
2Fo-Fc
Fo-Fc
packing residues
3ZKI(A) > WZV(A-1398)
3ZKN(AHL) > WZV(A-1398)
3ZKN(BCD) > WZV(B-1398)
3ZKS(AD)altA > WZV(A-1398)
3ZKS(AD)altB > WZV(A-1398)
3ZKI(B) > WZV(B-1398)
3ZKQ(AD) > apo(LEU_A-46)
4BEL(AD) > apo(LEU_A-46)
4BEL(BE) > apo(LEU_B-46)
6JSZ(AD) > C7O(A-401)
Interaction
Density
Iridium
Legend
Coloring
6JSZ(AD)altA

MMDS

→ Prepared DesignUnit storage

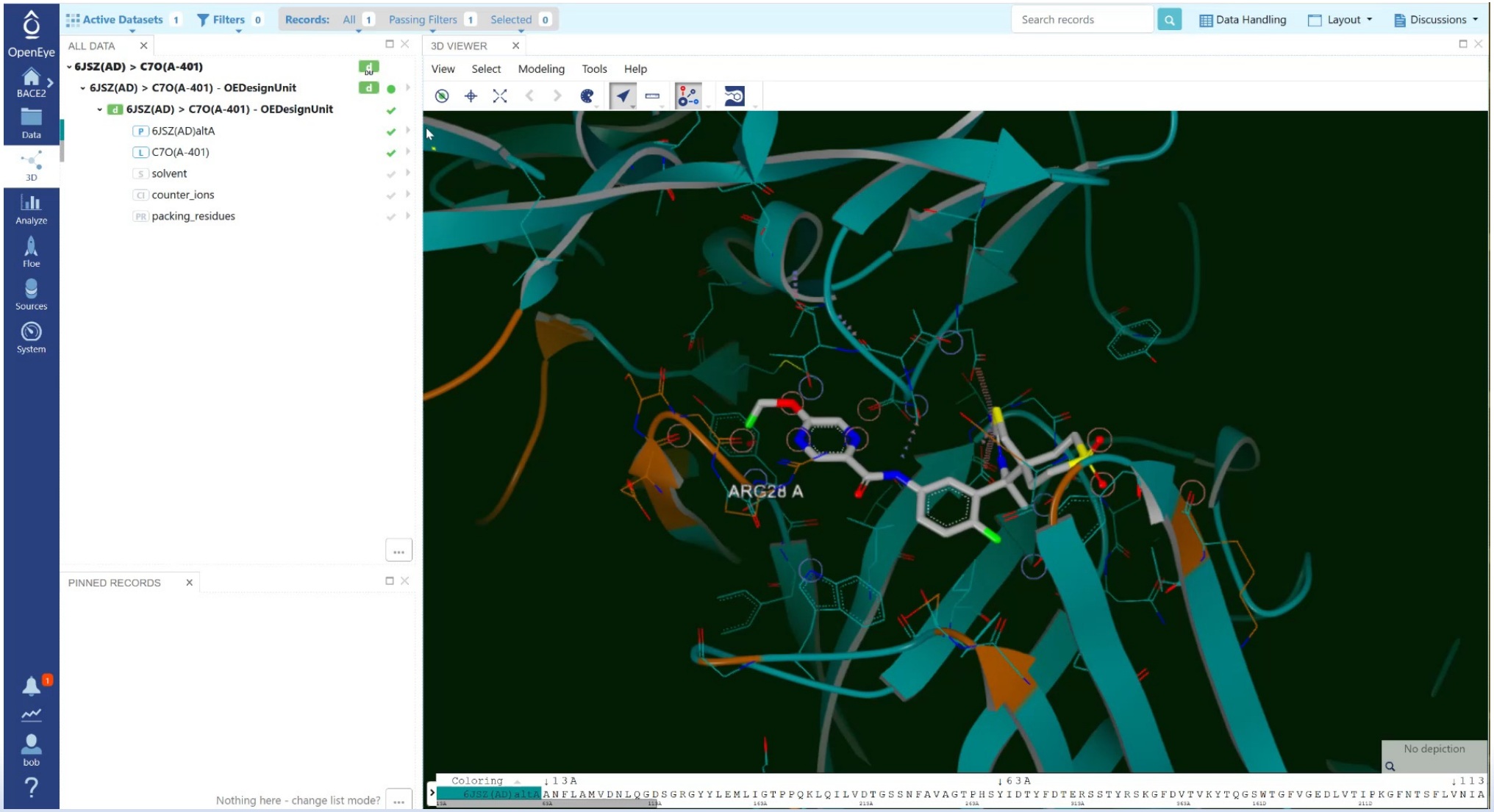
→ Organized by Family and Project

→ Structures ready for calculations in Orion

Interactive 3D Modeling

3D interactive editing

- Duplicate the current OEDesignUnit
- Ligand
  - Edit
  - Minimize in context of protein
  - Save back to OEDesignUnit
- Protein
  - Select a residue
  - Mutate
  - Save back to OEDesignUnit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Records: All 1 Passing Filters 1 Selected 0
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Discussions
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6JSZ(AD) > C7O(A-401)
6JSZ(AD) > C7O(A-401) - OEDesignUnit
6JSZ(AD) > C7O(A-401) - OEDesignUnit
6JSZ(AD)altA
C7O(A-401)
solvent
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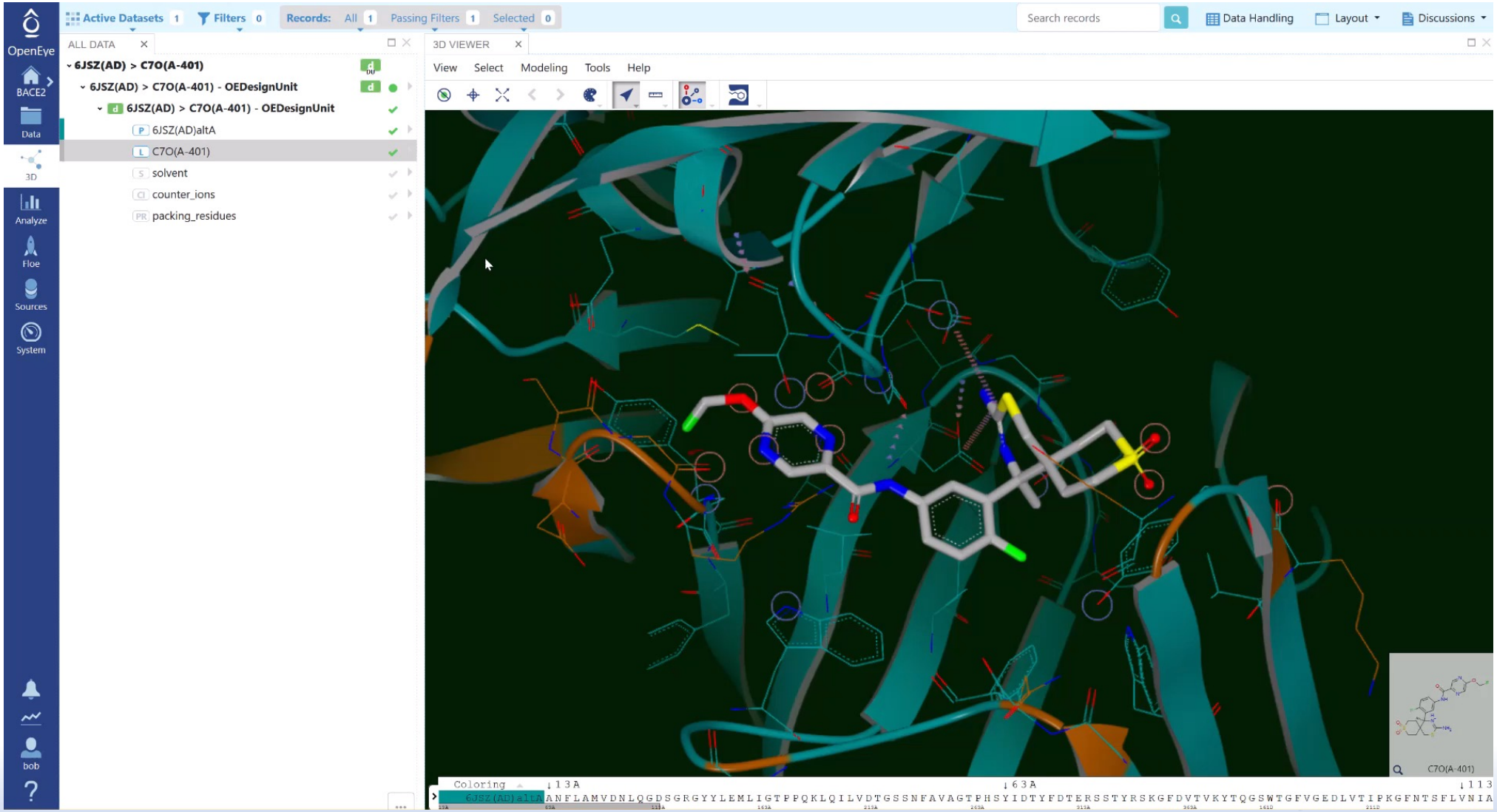
PINNED RECORDS
Nothing here - change list mode?
3D VIEWER
View
Select
Modeling
Tools
Help
ARG28 A
No depiction
Coloring
6JSZ(AD)altA

Generating Analogs

- Near fragments – fragments are replaced with graph similar fragments from the GSK TCAMS dataset
- MMP replacement – Matched Pairs extracted from ChEMBL
- Sidechain Exploration – select a portion of the ligand to replace with common fragments
- Apply a set of reagents to replace a selected fragment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C7O(A-401)
Coloring
6JSZ(AD)altA

Interactive 3D modeling

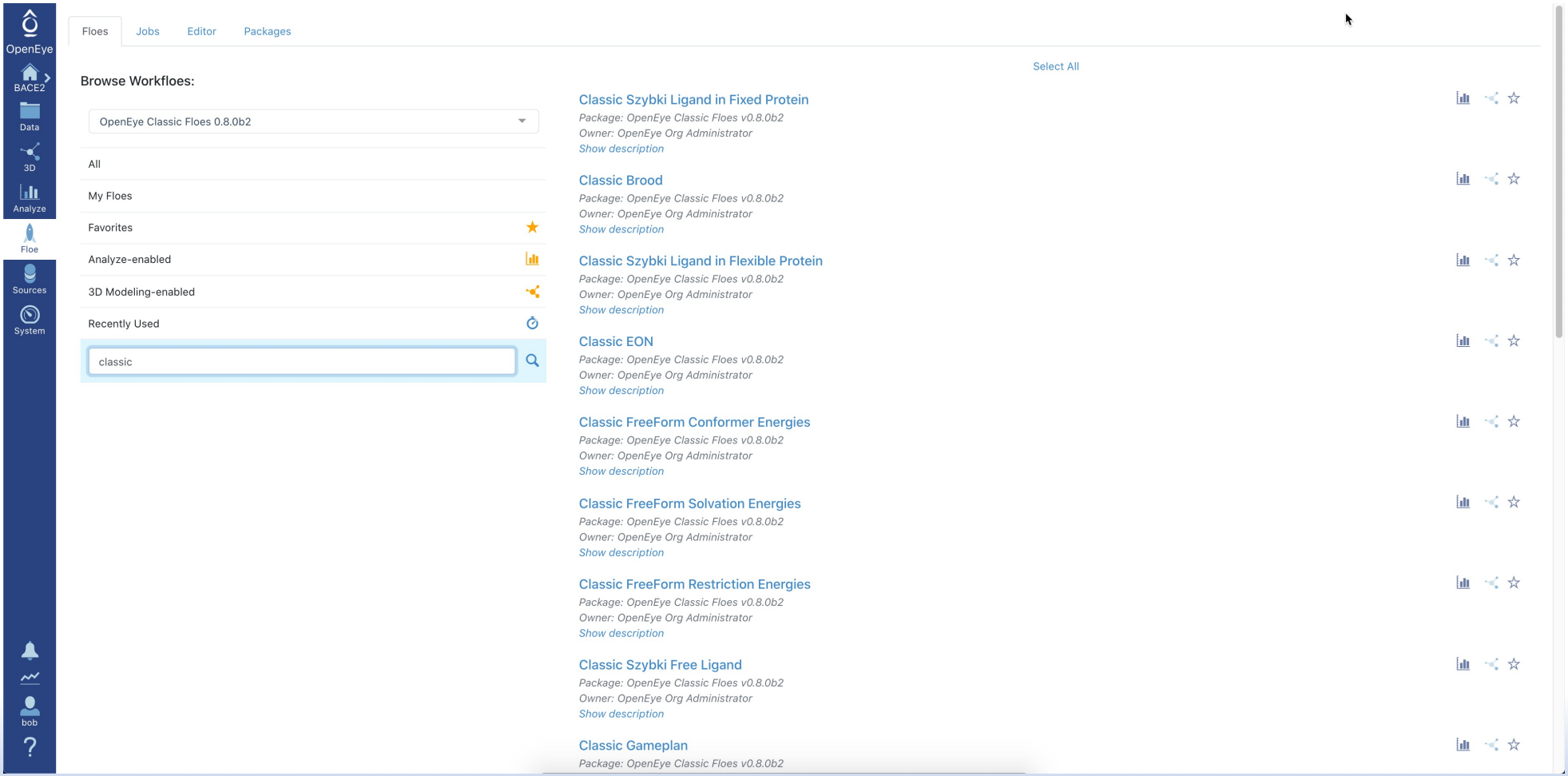
→ Edit ligand in context of the protein

→ Generate analogs

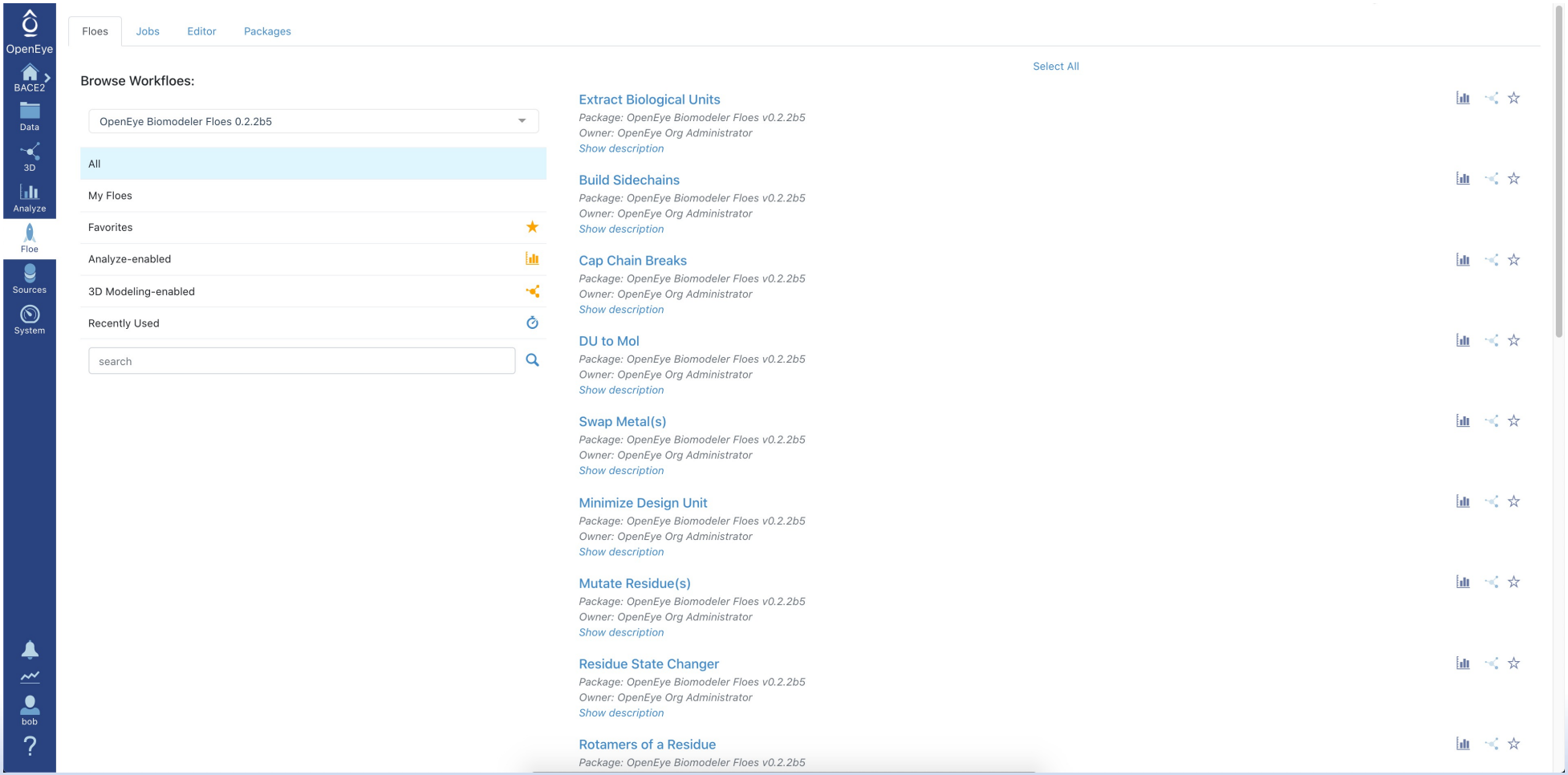
→ Protein editing for last step prep for modeling/MD

3D Workflows

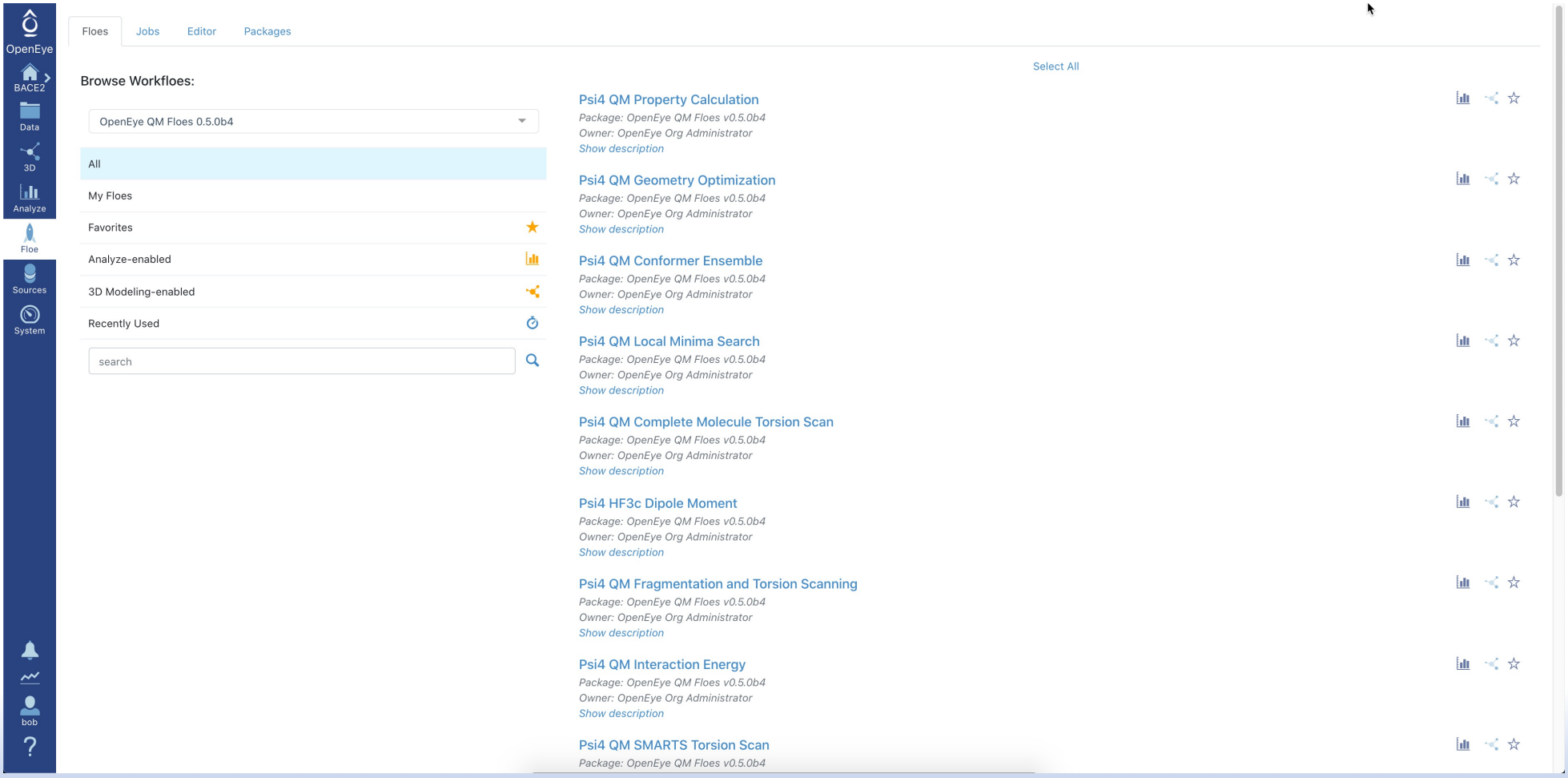
Our traditional apps as workflows



Spruce/Bio-modeling workflows



Large selection of QM workflows



Binding Site Search - SiteHopper

Why compare binding sites?

Protein Motion
Induced Fit
SAR Analysis/Superposition

} Same protein, different structures

Homology Modeling
Selectivity

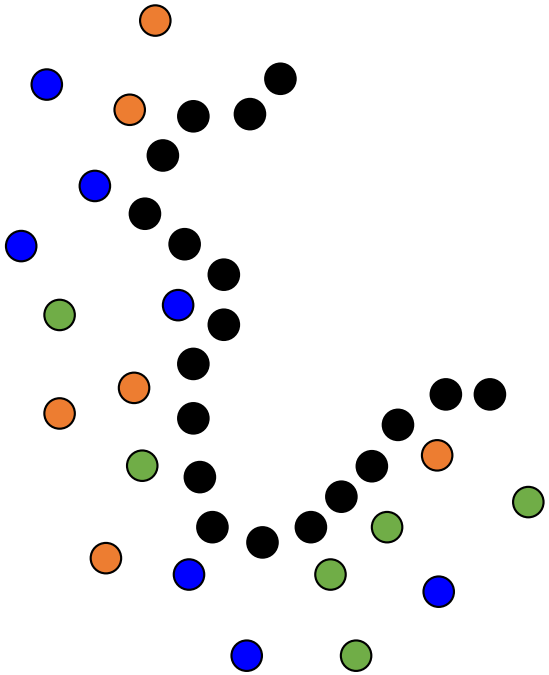
} Closely related proteins

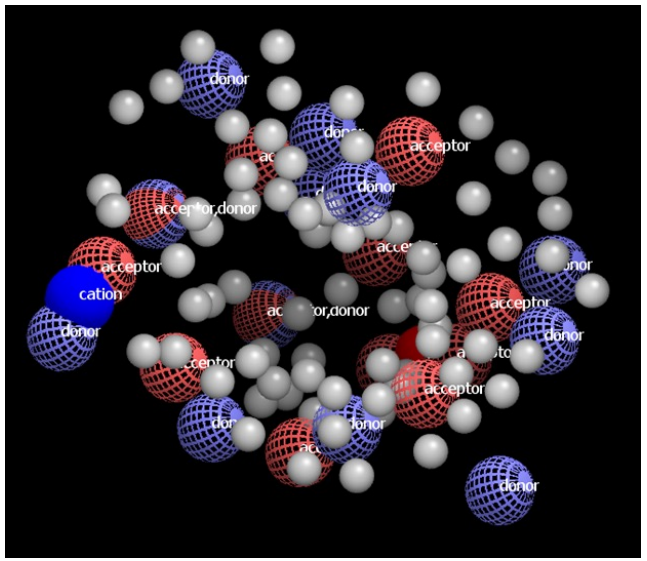
Target Fishing
Drug Repurposing
Side effects

} Different proteins

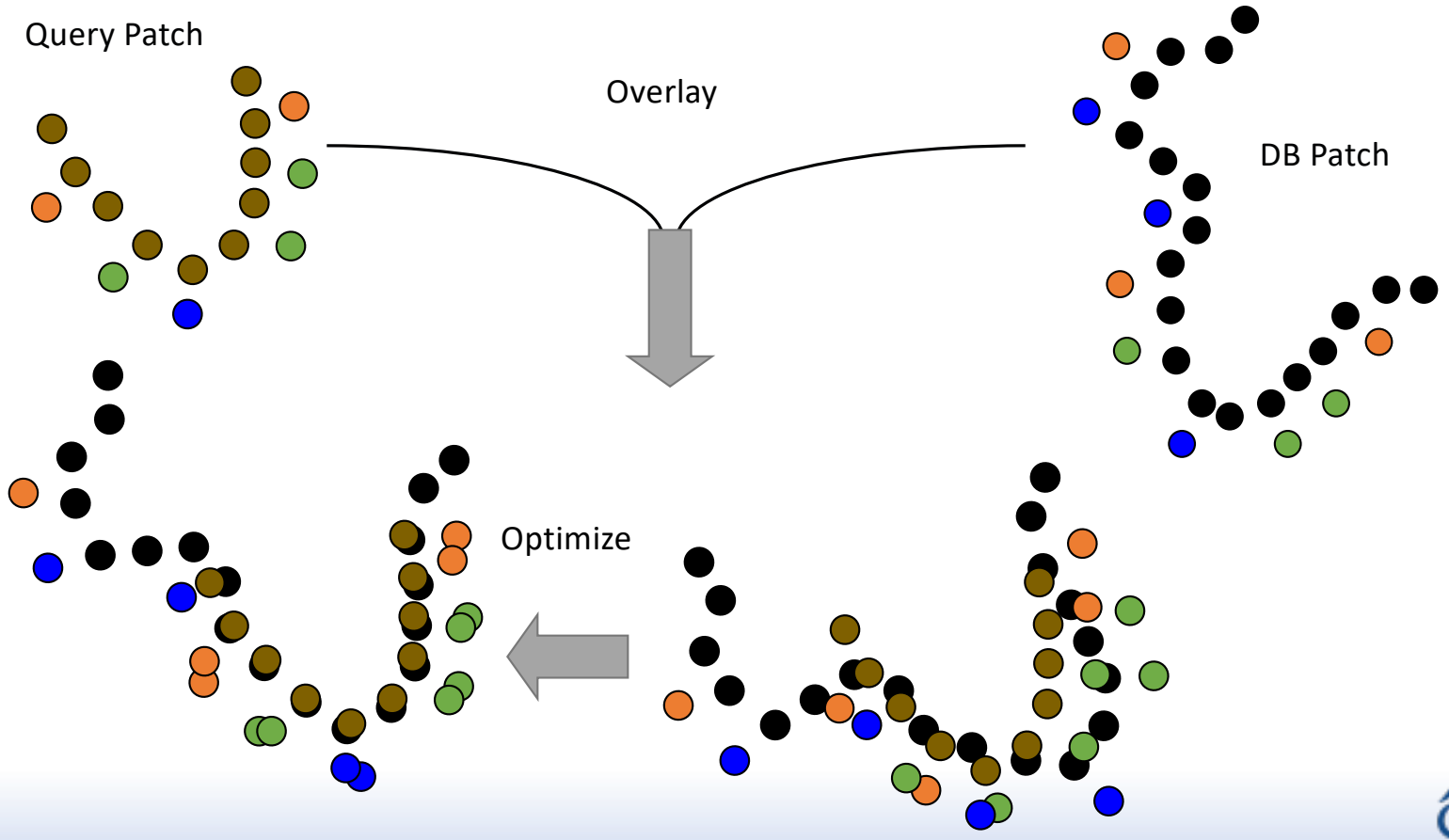
…

Patch: Shape atoms + color atoms

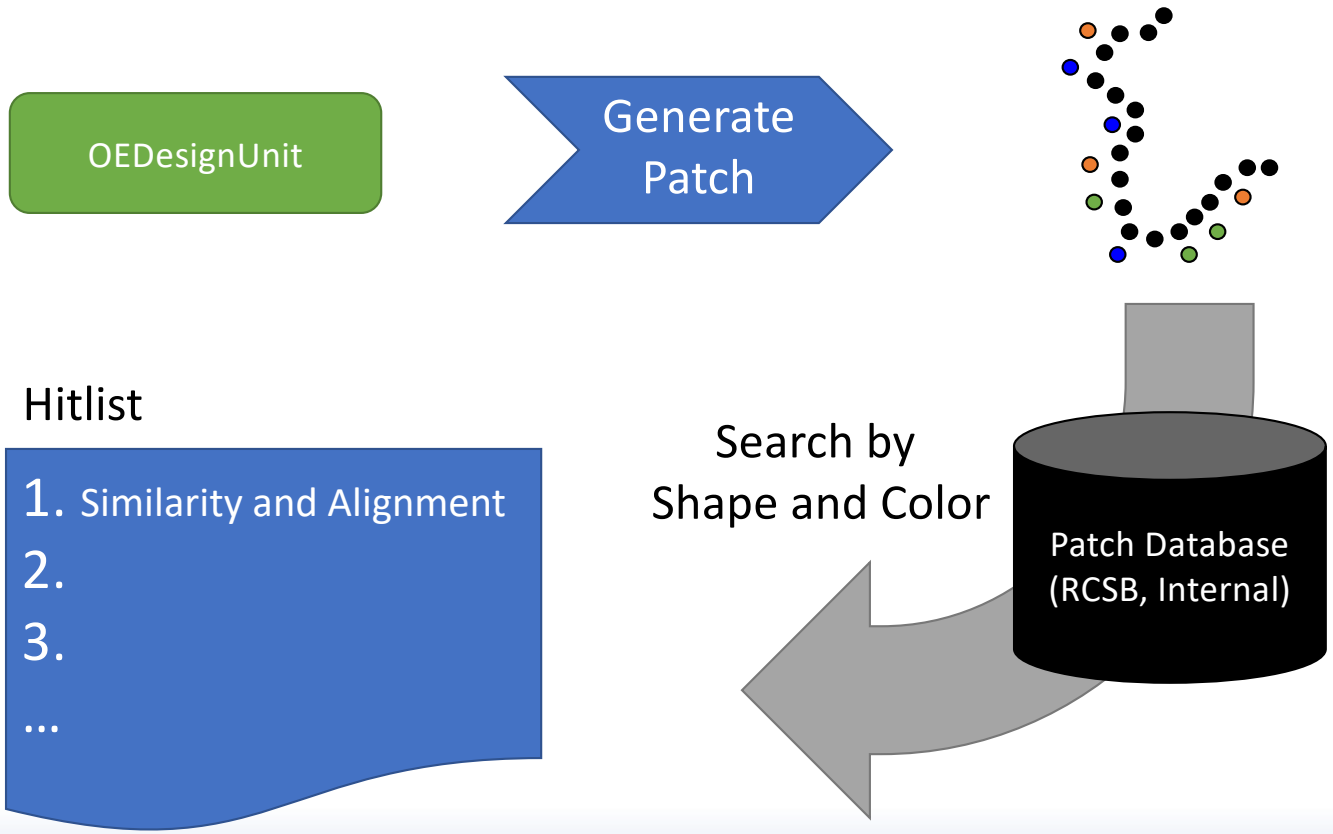




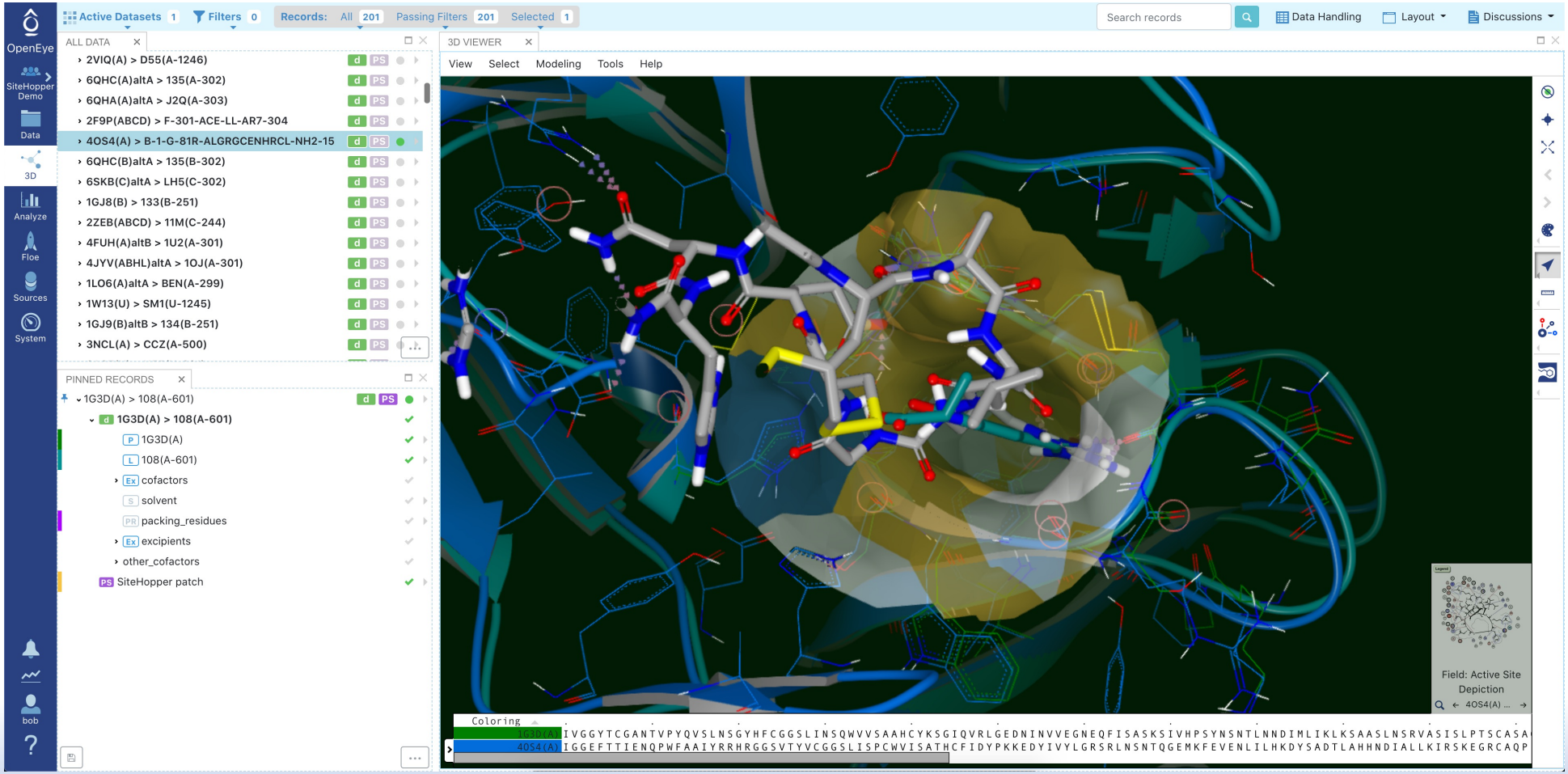
Overlay and alignment: SiteHopper TK



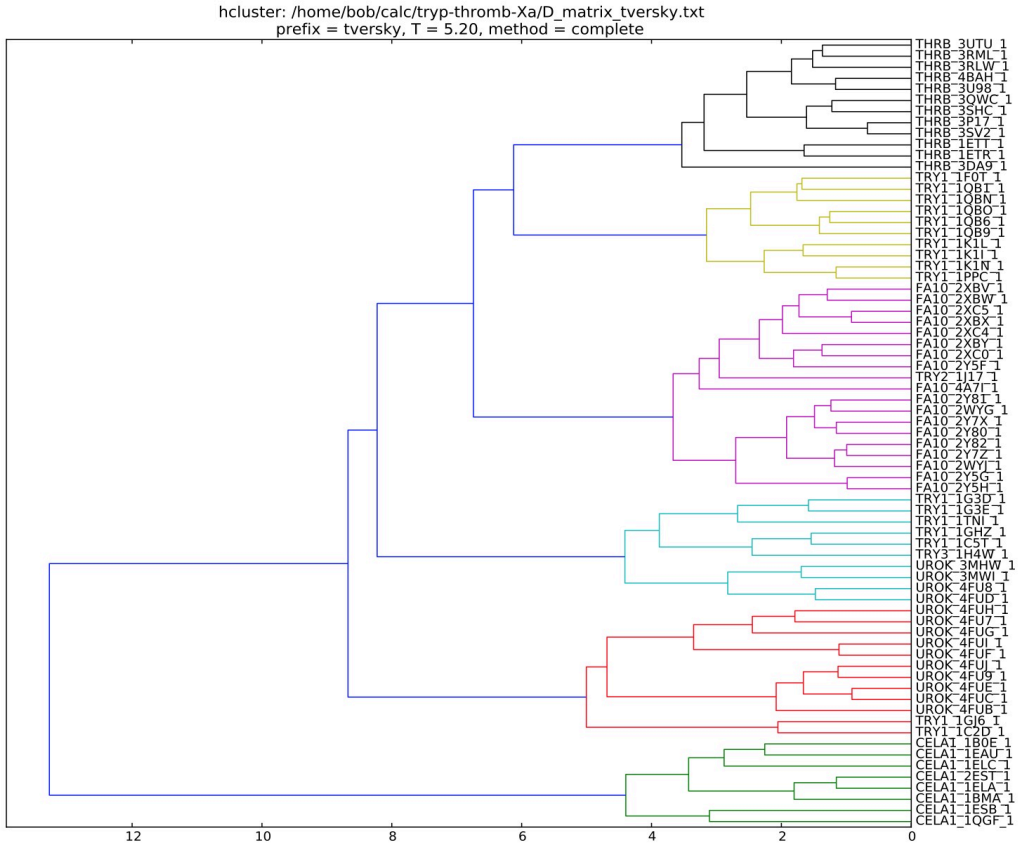
SiteHopper: How it works



SiteHopper results in Orion



SiteHopper clustering



Thrombin

Trypsin

Factor Xa

Tryp/Urok

Urok/Tryp

Chymotryp.

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SiteHopper databases

- MMDS – Guide To Pharmacology data
- Entire RCSB dataset
- OEPocket – new pocket finder in OEBio toolkit
- 3rd Party pocket finder -> OEDesignUnit

SiteHopper

→ Search protein structure databases

→ Cluster sites based on site similarity

→ CPU and GPU implementation in new SiteHopper TK

Upcoming Orion Features

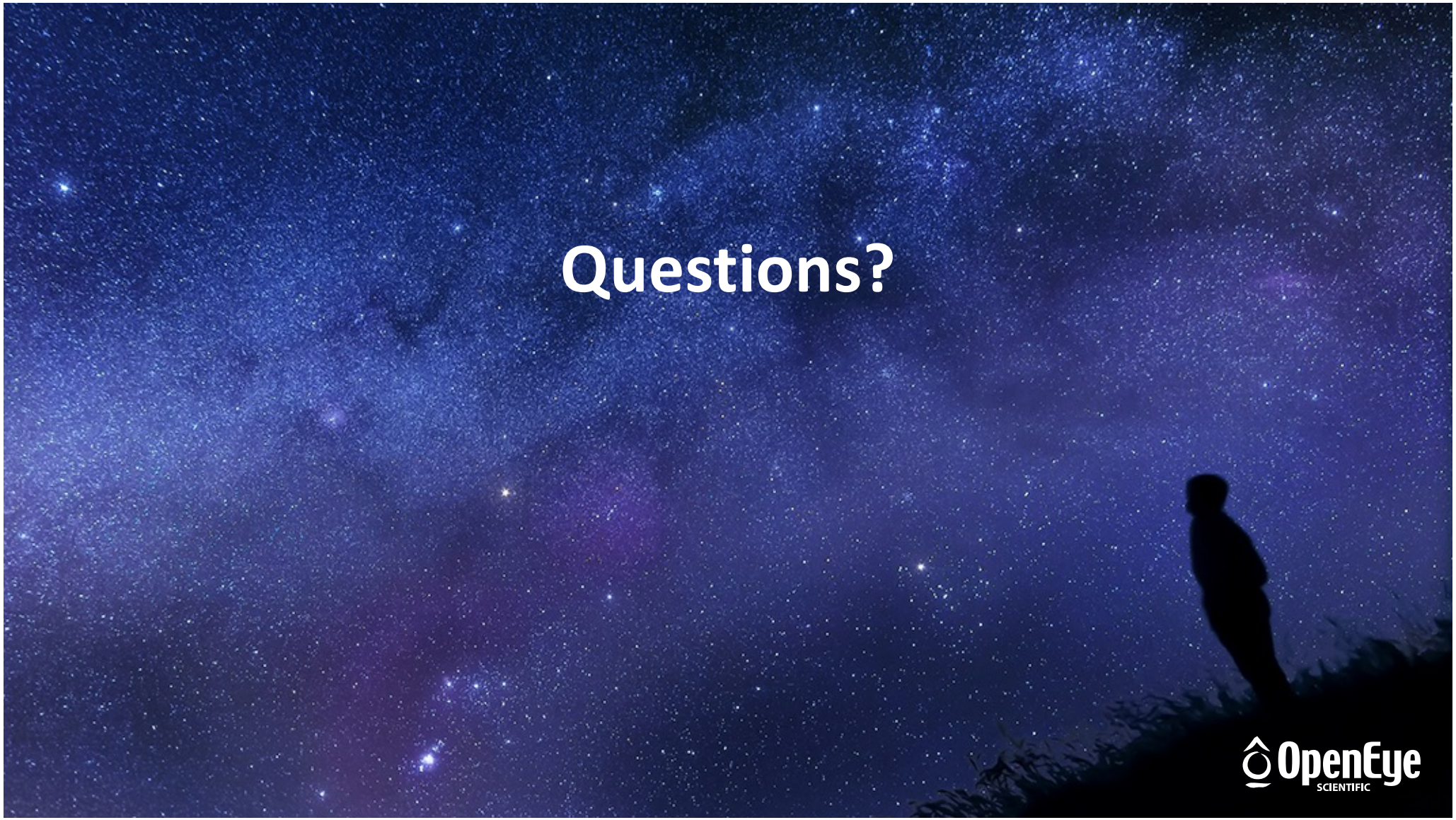
- Shape Query editing (vROCS)
- Receptor editing – Constraints (MakeReceptor)
- Interactive loop building
- Custom SiteHopper queries

Wrap-up

- Automated Protein Prep - Spruce
- Prepared structure storage – MMDS
- Interactive 3D modeling
- 3D Workflows
- Binding Site search - SiteHopper

Acknowledgements

- Jesper Soerensen – Spruce, Protein modeling, SiteHopper
- David LeBard - Spruce
- Kevin Schmidt – Protein modeling and 3D UI
- Joe Moon – Small molecule modeling and UI
- Dan Mermelstein – SiteHopper, GPU SiteHopper


Questions?
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