

3D Modeling in Orion

Bob Tolbert
CTO, OpenEye

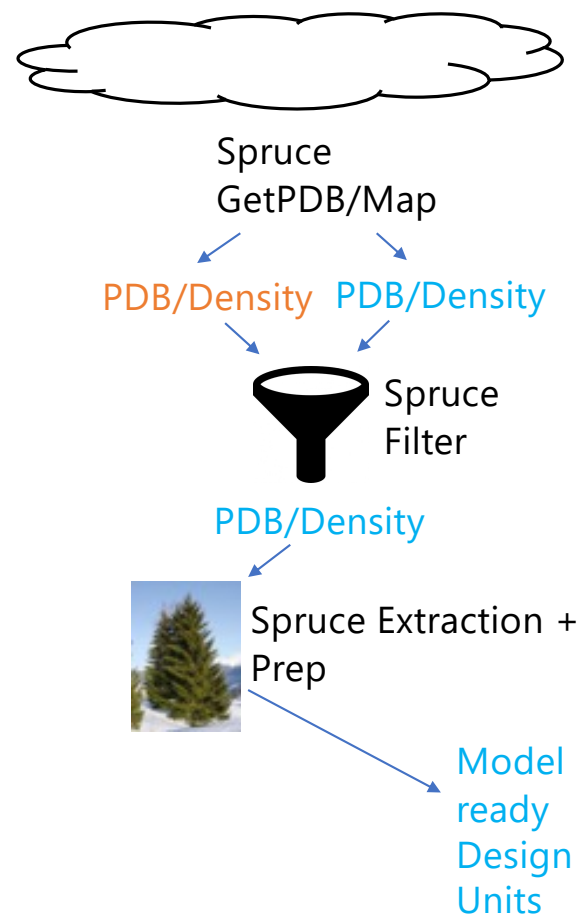
Agenda

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

Protein Prep with Spruce

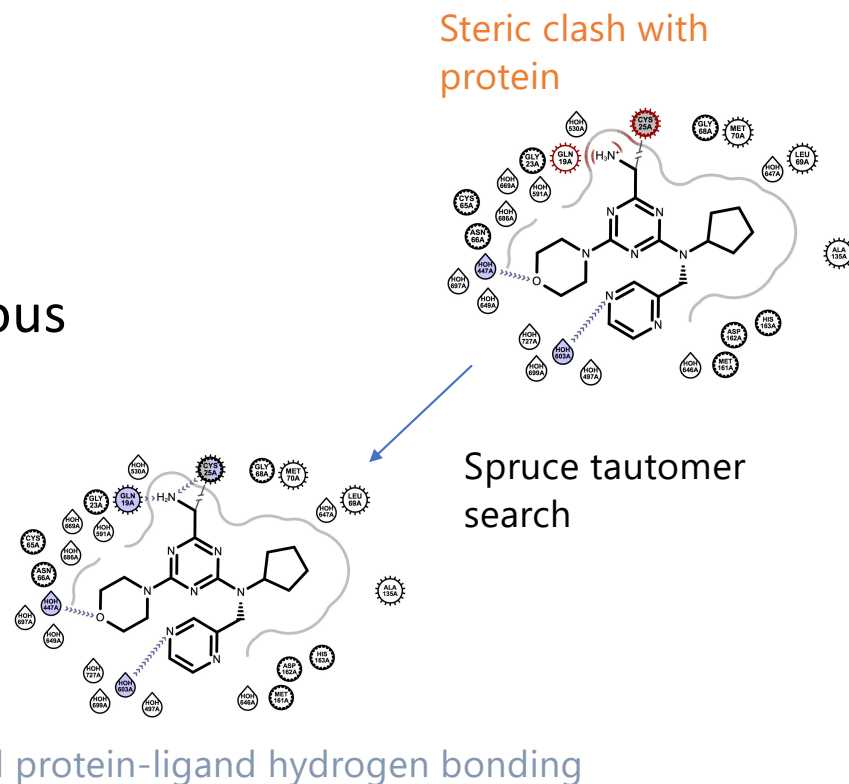
What can Spruce do?

- 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



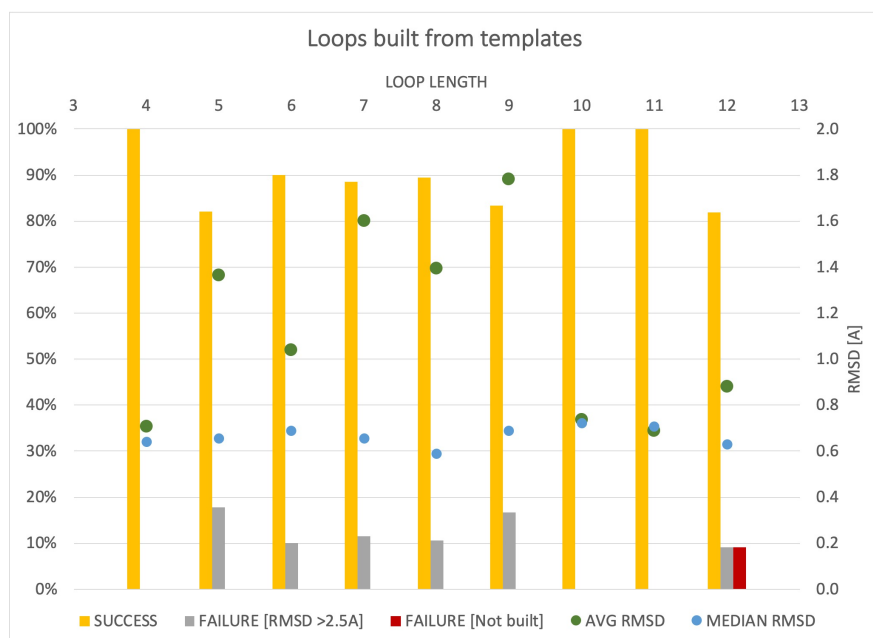
Structure Modeling - Protonation

- 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

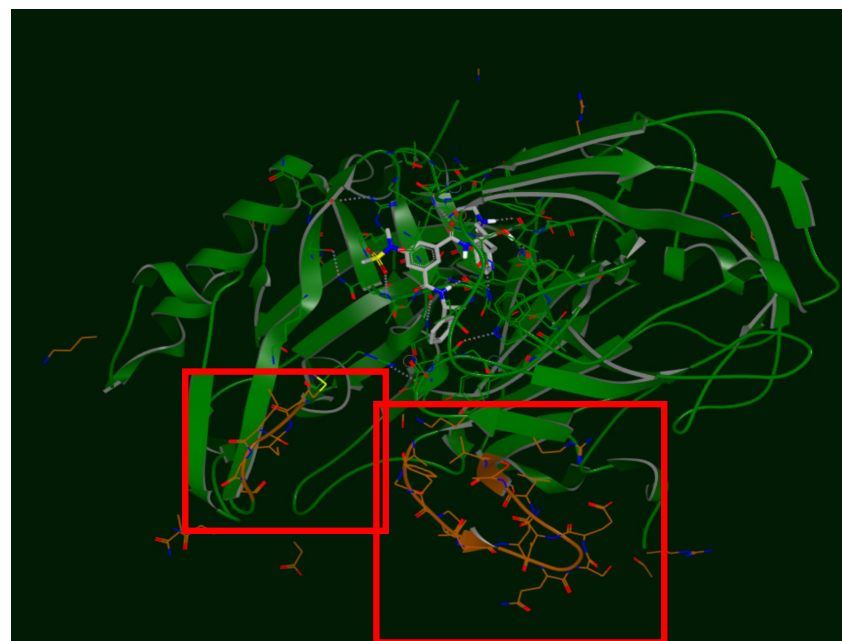


Loop modeling

- Enabled by default in Orion



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



PDB-ID: 3TPP. Modeled pieces in brown

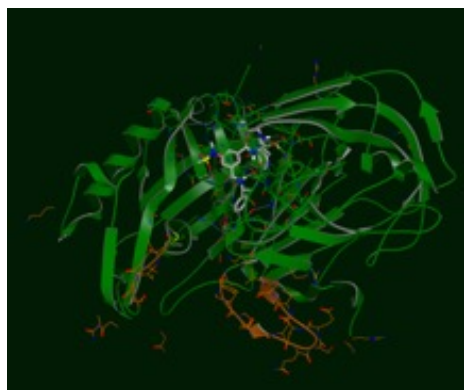
DVA between GLU 310 A and THR 314 A
GFPLNQSEVLAS between ALA 157 A and VAL 170 A

Model Quality Assessment

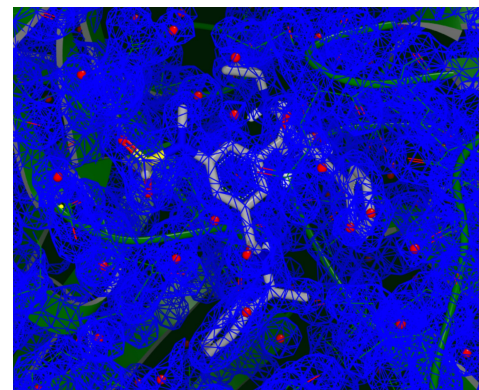
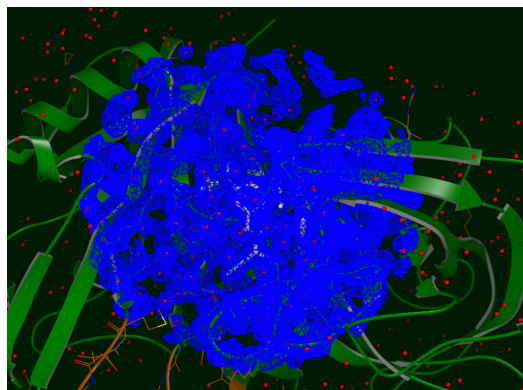
- Iridium classification for model quality analysis
- The quality of the structure data:
 - Give teams ability to understand quality of structures
 - Critical for managing modeling expectations
 - Key to understanding modeling results

Visualization of DesignUnits

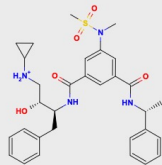
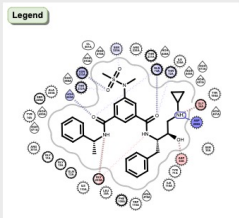
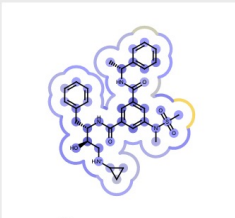

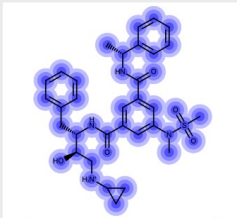
3D view



Electron density grid visible around binding site*



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

bound ligand	Active Site Depiction	B-Factor Depiction	du_title	Iridium Depiction	Ligand Density Depiction	pdb_code
Ligand from 3T... 			3TPP(A) > 5HA(... 		3tpp	

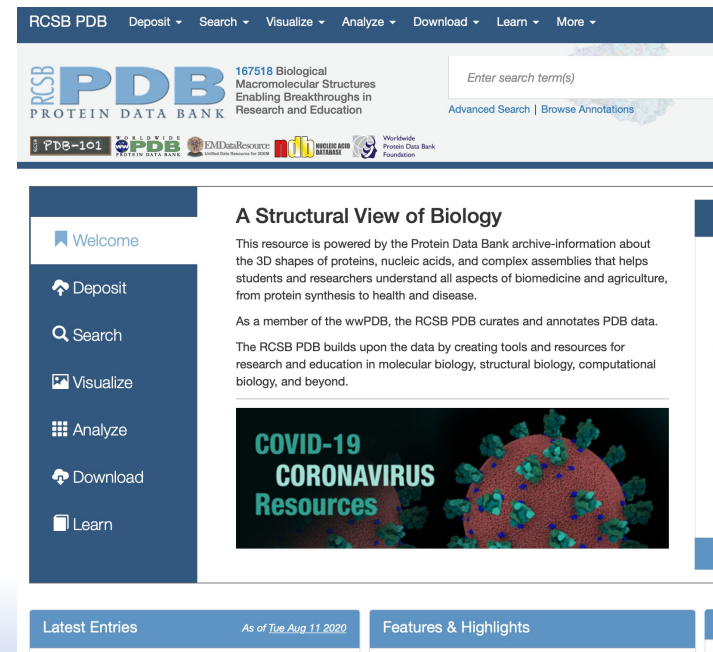
Spruce - Enabling structure-based modeling

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

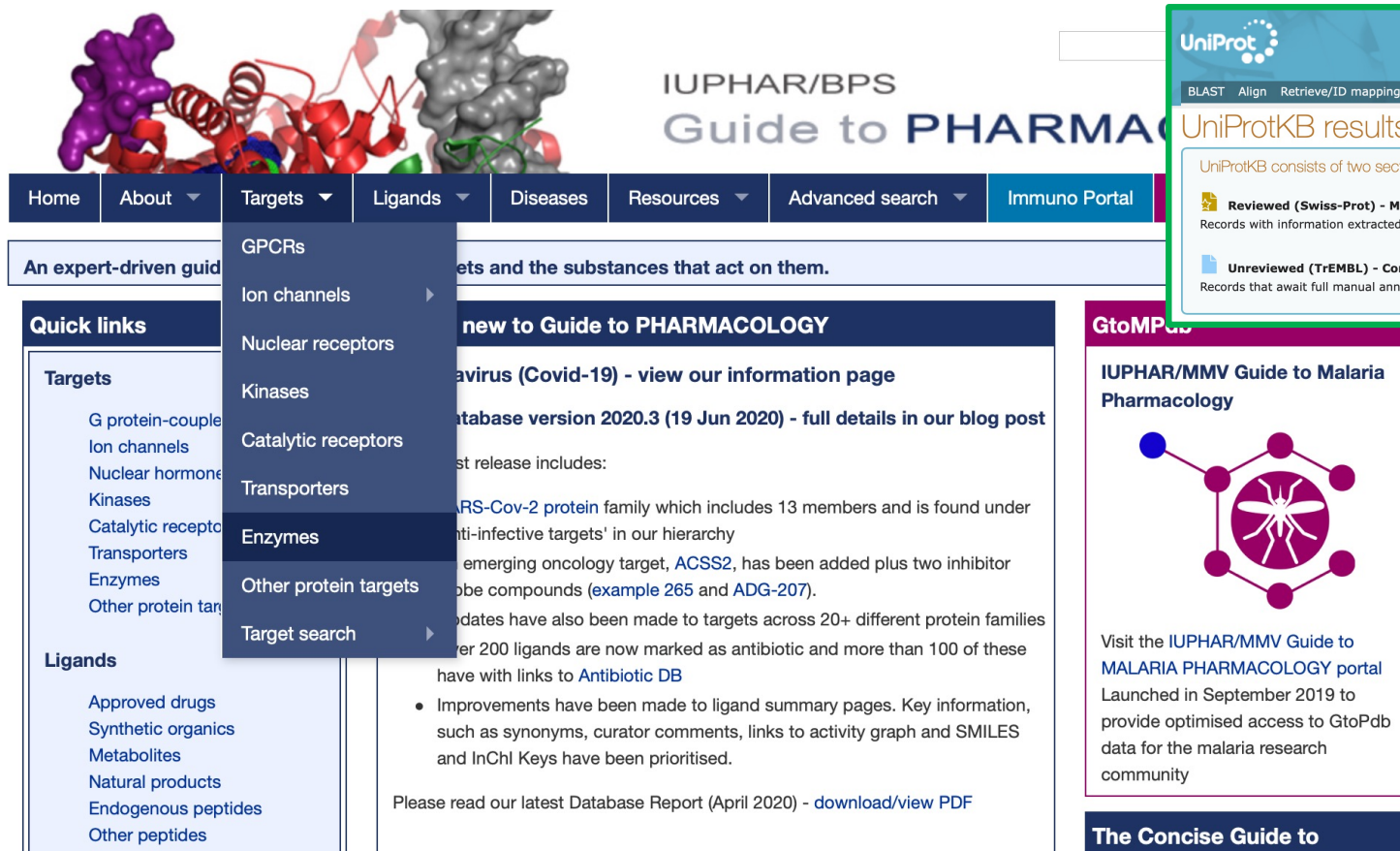
Prepared Structure Storage - MMDS

The Data

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



Guide to Pharmacology



The image shows the IUPHAR/BPS Guide to PHARMACOLOGY website. At the top, there is a 3D molecular model of a protein-ligand complex. The main navigation bar includes links for Home, About, Targets, Ligands, Diseases, Resources, Advanced search, and Immuno Portal. A dropdown menu for 'Targets' is open, showing categories like GPCRs, Ion channels, Nuclear receptors, Kinases, Catalytic receptors, Transporters, Enzymes, Other protein targets, and Target search. On the left, there are 'Quick links' for Targets and Ligands. The main content area features a 'new to Guide to PHARMACOLOGY' section with updates on the database version 2020.3 (19 Jun 2020) and mentions of the SARS-Cov-2 protein family and the ACSS2 target. A sidebar on the right highlights the 'GtoMPdb' and 'IUPHAR/MMV Guide to Malaria Pharmacology' portals.

IUPHAR/BPS
Guide to PHARMACOLOGY

Home About Targets Ligands Diseases Resources Advanced search Immuno Portal

An expert-driven guide to drug targets and the substances that act on them.

new to Guide to PHARMACOLOGY

SARS-Cov-2 protein family which includes 13 members and is found under 'anti-infective targets' in our hierarchy

emerging oncology target, [ACSS2](#), has been added plus two inhibitor probe compounds ([example 265](#) and [ADG-207](#)).

updates have also been made to targets across 20+ different protein families

over 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](#)

Quick links

Targets

- G protein-coupled receptors
- Ion channels
- Nuclear hormone receptors
- Kinases
- Catalytic receptors
- Transporters
- Enzymes
- Other protein targets

Ligands

- Approved drugs
- Synthetic organics
- Metabolites
- Natural products
- Endogenous peptides
- Other peptides

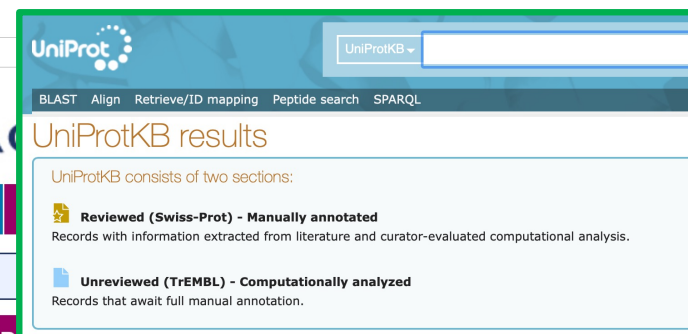
GtoMPdb

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



The image shows the UniProtKB results page. It features the UniProt logo and a search bar. Below the search bar, there are links for BLAST, Align, Retrieve/ID mapping, Peptide search, and SPARQL. The main heading is 'UniProtKB results'. Below this, it states 'UniProtKB consists of two sections:'. The first section is 'Reviewed (Swiss-Prot) - Manually annotated', which includes records with information extracted from literature and curator-evaluated computational analysis. The second section is 'Unreviewed (TrEMBL) - Computationally analyzed', which includes records that await full manual annotation.

UniProt

UniProtKB

BLAST Align Retrieve/ID mapping Peptide search SPARQL

UniProtKB results

UniProtKB consists of two sections:

- Reviewed (Swiss-Prot) - Manually annotated**
Records with information extracted from literature and curator-evaluated computational analysis.
- Unreviewed (TrEMBL) - Computationally analyzed**
Records that await full manual annotation.

Mapping key between
GtoP and RCSB is
UniprotKB accession #



OpenEye

SiteHopper

Data

3D

Analyze

FloE

Sources

System



MMDS - Macromolecular Data Service

Sessions

Projects

Experiments

▼ Expand

▲ Collapse

-	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](#)

© 2020 OpenEye Scientific Software, Inc. - MMDS v1.1.8



bob

OpenEye

BACE2

Data

3D

Analyze

Flow

Sources

System

1

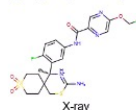
bob

?

MMDS Load View Selection Tools Help

BACE2 (beta-secretase 2)

6JSZ(AD) > C7O(A-401)



6JSZ

C7O

counter ions

solvent

surface

2Fo-Fc

Fo-Fc

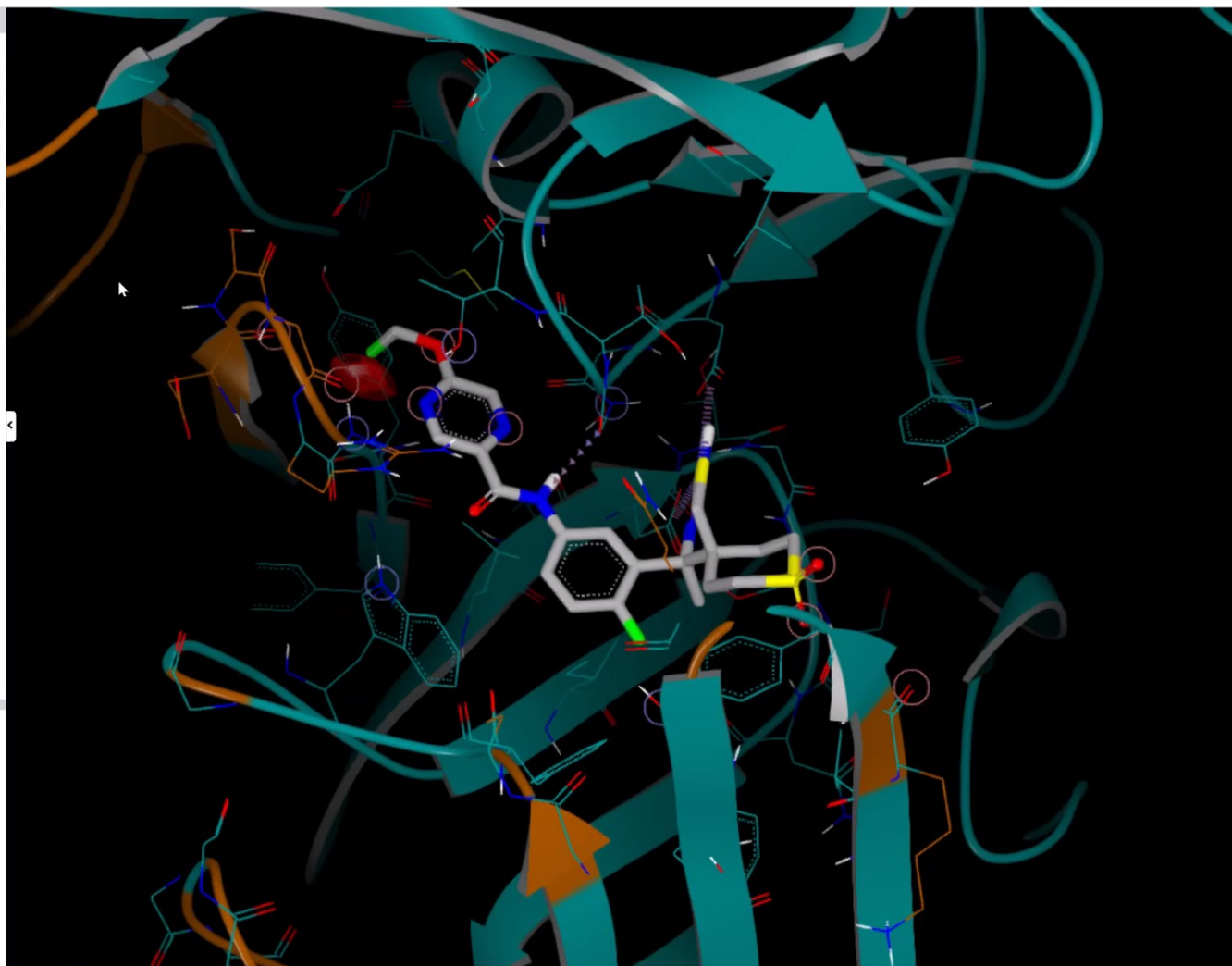
packing residues

- > 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 13A 63A

6JSZ(AD) > C7O(A-401) - ANFLAMVDNLQGDSSGRGYYLEMLIGTPPQKLQILVDTGSSNFAVAGTPHYSYIDTYFDTERSSSTYRSKGFEDVTVKYTQGSWTGFVGEDLVTIPKGFNTS

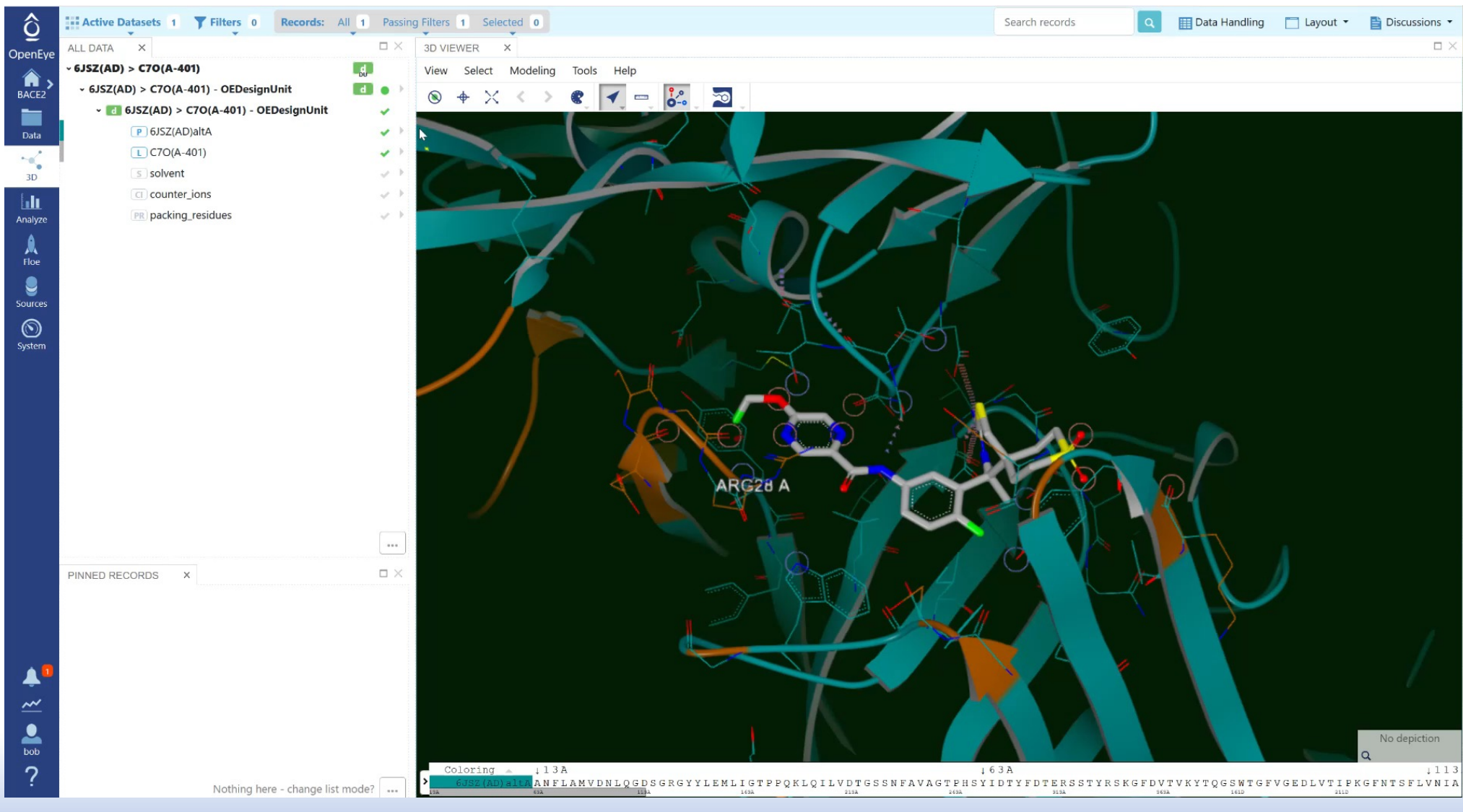
MMDS

- Prepared DesignUnit storage
- Organized by Family and Project
- Structures ready for calculations in Orion

Interactive 3D Modeling

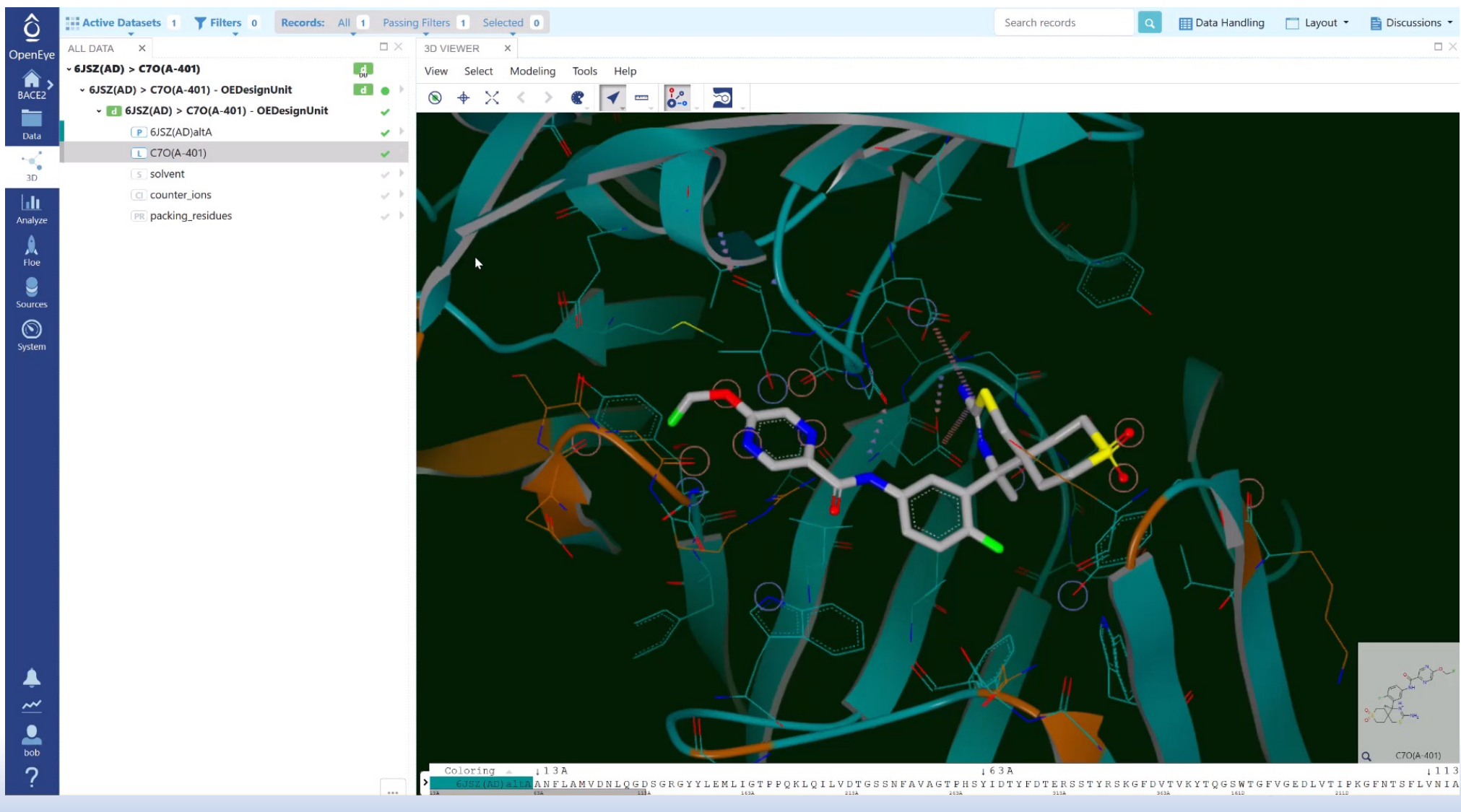
3D interactive editing

- Duplicate the current OEDesignUnit
- Ligand
 - Edit
 - Minimize in context of protein
 - Save back to OEDesignUnit
- Protein
 - Select a residue
 - Mutate
 - Save back to OEDesignUnit



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



Interactive 3D modeling

- Edit ligand in context of the protein
- Generate analogs
- Protein editing for last step prep for modeling/MD

3D Workflows

Browse Workflows:

OpenEye Classic Floes 0.8.0b2

All

My Floes

Favorites

Analyze-enabled

3D Modeling-enabled

Recently Used

classic

Select All

Classic Szybki Ligand in Fixed Protein

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic Brood

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic Szybki Ligand in Flexible Protein

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic EON

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic FreeForm Conformer Energies

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic FreeForm Solvation Energies

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic FreeForm Restriction Energies

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic Szybki Free Ligand

Package: OpenEye Classic Floes v0.8.0b2

Owner: OpenEye Org Administrator

[Show description](#)

Classic Gameplan

Package: OpenEye Classic Floes v0.8.0b2

Large selection of QM workflows

OpenEye

BACE2

Data

3D

Analyze

Floe

Sources

System

FloesJobsEditorPackages

Browse Workflows:

OpenEye QM Floes 0.5.0b4

AllMy FloesFavoritesAnalyze-enabled3D Modeling-enabledRecently Used

search

Select All

Psi4 QM Property Calculation
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

Psi4 QM Geometry Optimization
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

Psi4 QM Conformer Ensemble
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

Psi4 QM Local Minima Search
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

Psi4 QM Complete Molecule Torsion Scan
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

Psi4 HF3c Dipole Moment
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

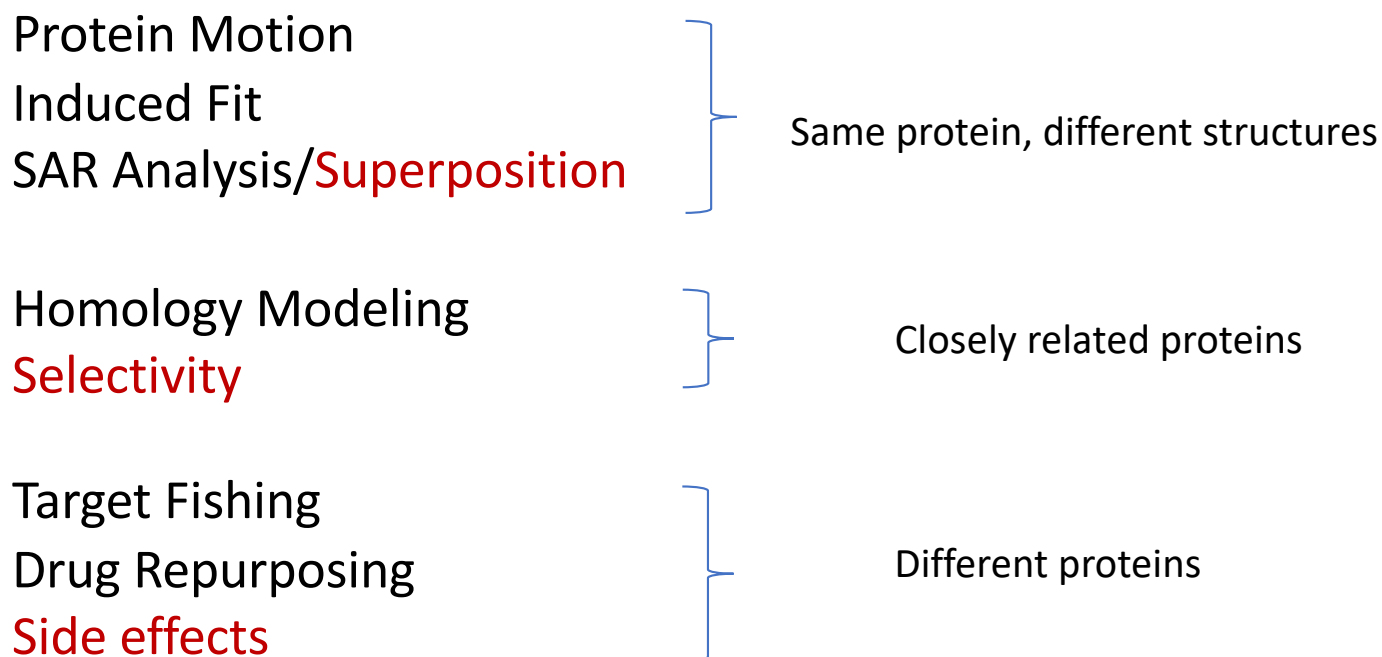
Psi4 QM Fragmentation and Torsion Scanning
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

Psi4 QM Interaction Energy
Package: OpenEye QM Floes v0.5.0b4
Owner: OpenEye Org Administrator
Show description

Psi4 QM SMARTS Torsion Scan
Package: OpenEye QM Floes v0.5.0b4

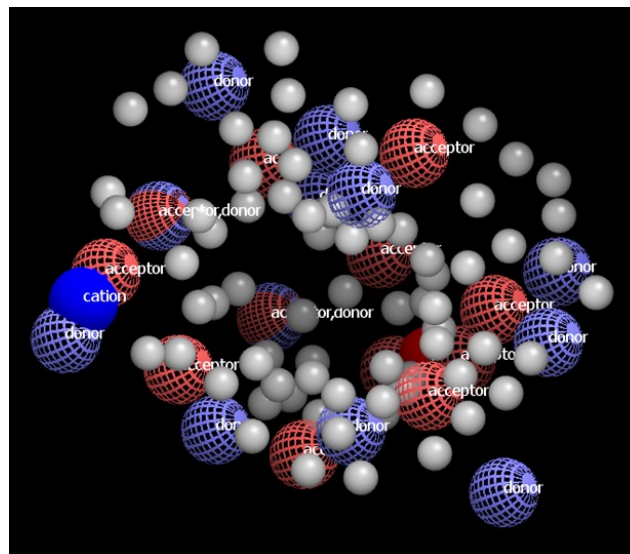
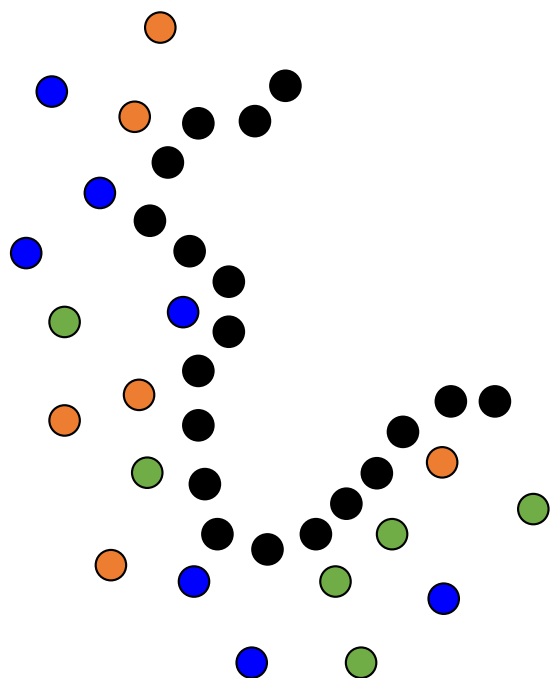
Binding Site Search - SiteHopper

Why compare binding sites?

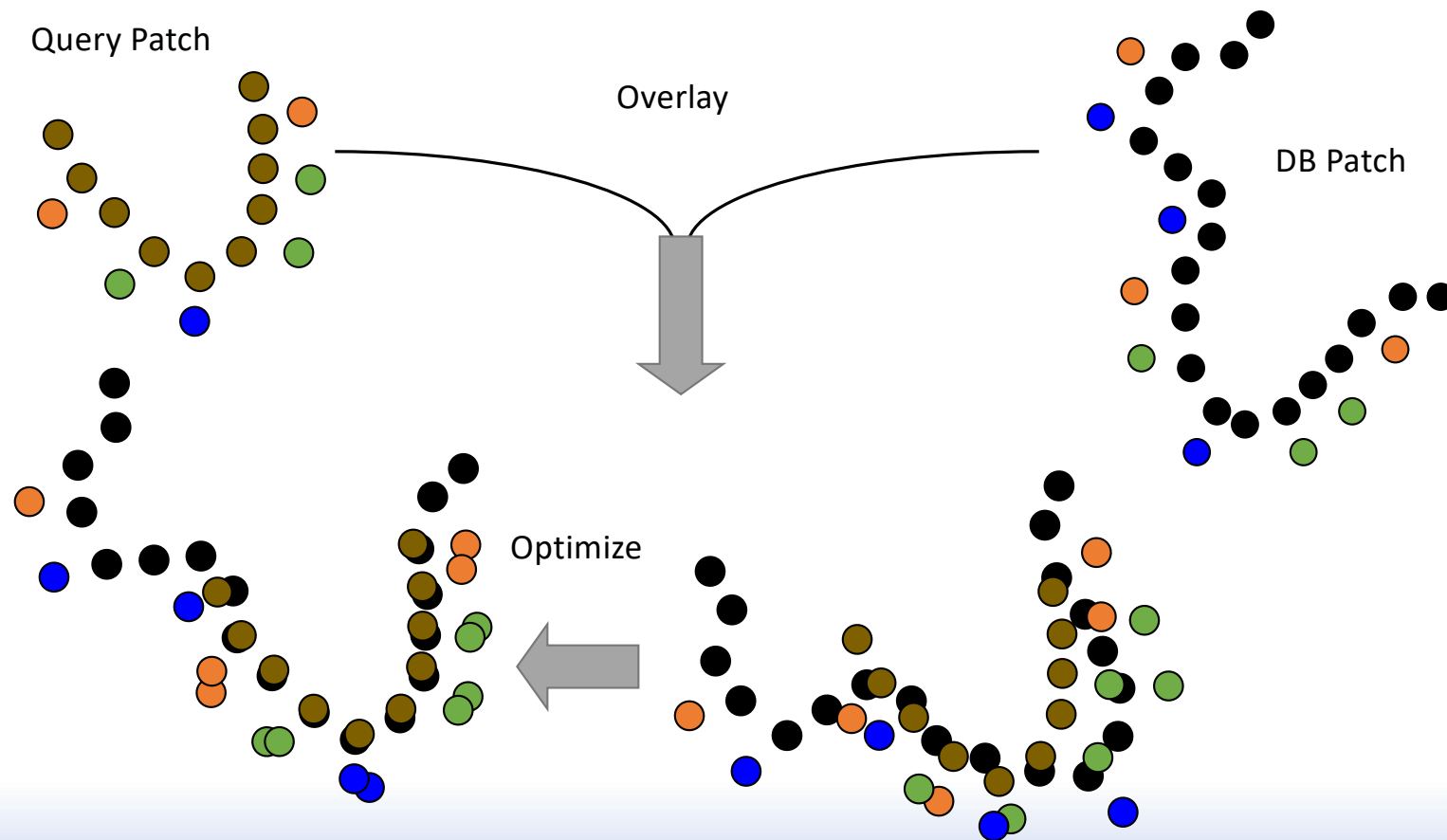


...

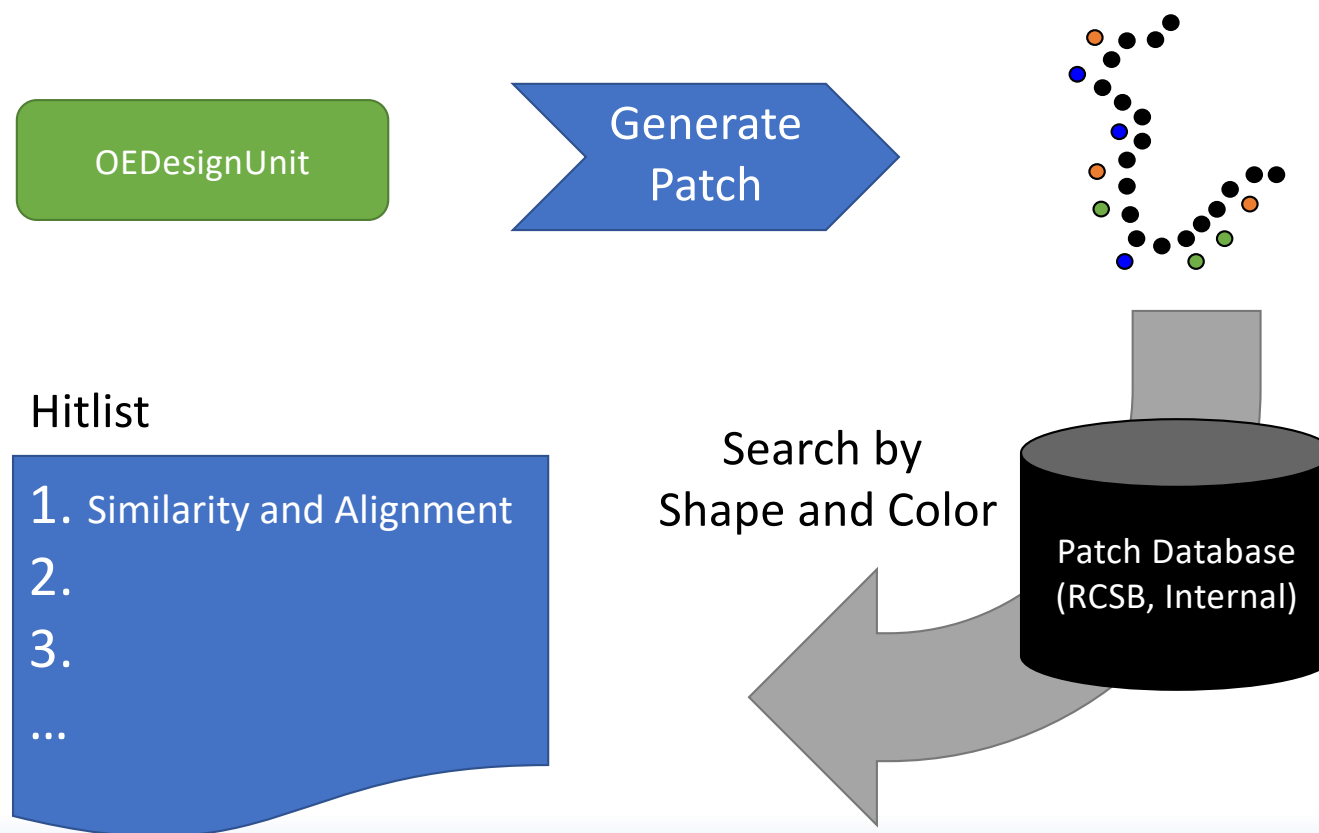
Patch: Shape atoms + color atoms



Overlay and alignment: SiteHopper TK



SiteHopper: How it works



SiteHopper results in Orion

OpenEye
SiteHopper Demo
Data
3D
Analyze
Floe
Sources
System

Active Datasets 1 Filters 0 Records: All 201 Passing Filters 201 Selected 1

ALL DATA x

- > 2VIQ(A) > D55(A-1246)
- > 6QHC(A)altA > 135(A-302)
- > 6QHA(A)altA > J2Q(A-303)
- > 2F9P(ABCD) > F-301-ACE-LL-AR7-304
- > 4QS4(A) > B-1-G-81R-ALGRGCENHRCL-NH2-15
- > 6QHC(B)altA > 135(B-302)
- > 6SKB(C)altA > LH5(C-302)
- > 1GJ8(B) > 133(B-251)
- > 2ZEB(ABCD) > 11M(C-244)
- > 4FUH(A)altB > 1U2(A-301)
- > 4JYV(ABHL)altA > 1OJ(A-301)
- > 1LO6(A)altA > BEN(A-299)
- > 1W13(U) > SM1(U-1245)
- > 1GJ9(B)altB > 134(B-251)
- > 3NCL(A) > CCZ(A-500)

PINNED RECORDS x

- > 1G3D(A) > 108(A-601)
- > 1G3D(A)
- > 108(A-601)
- > cofactors
- > solvent
- > packing_residues
- > excipients
- > other_cofactors
- > SiteHopper patch

3D VIEWER x

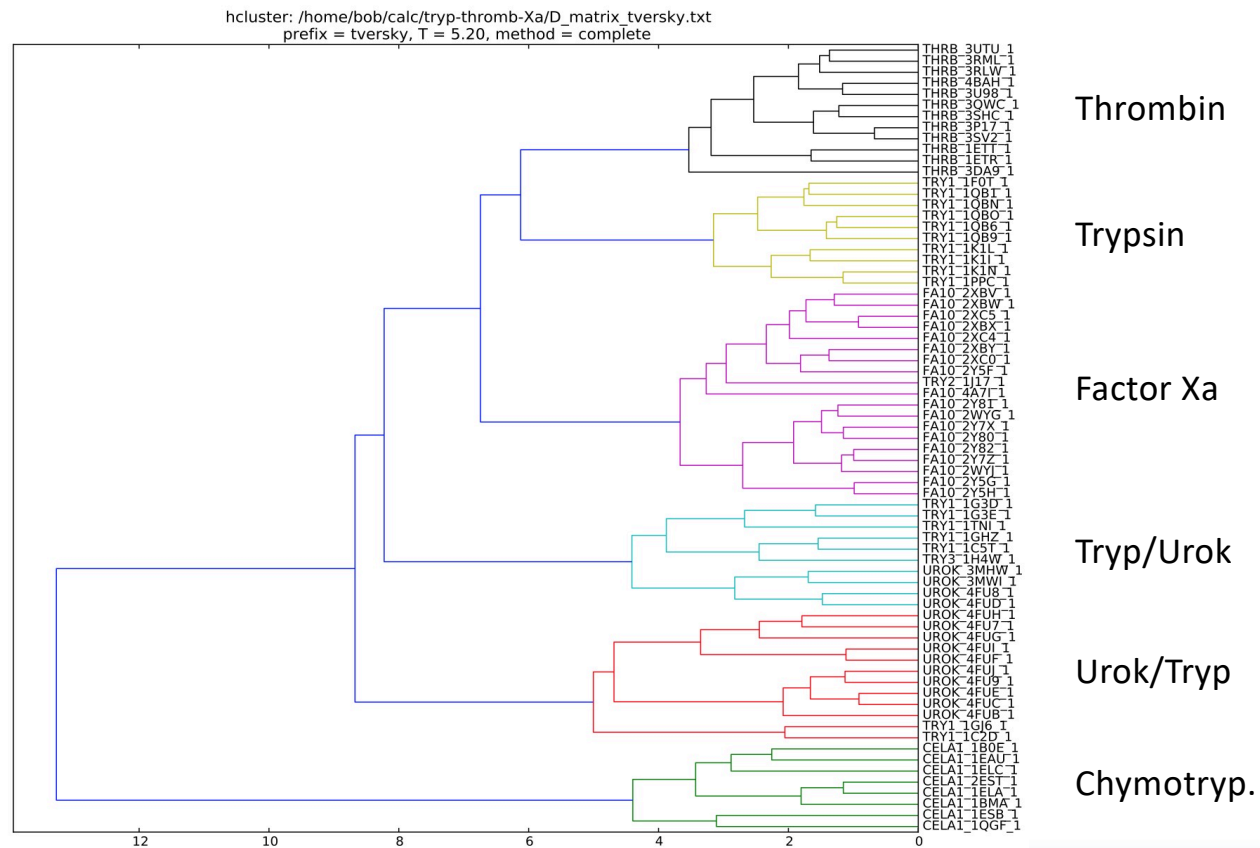
View Select Modeling Tools Help

Field: Active Site Depiction
4QS4(A) ...

Coloring

1G3D(A) I V G G Y T C G A N T V P Y Q V S L N S G Y H F C G G S L I N S Q W V V S A A H C Y K S G I Q V R L G E D N I N V V E G N E Q F I S A S K S I V H P S Y N S N T L N D I M L I K L S A A S L N S R V A S I S L P T S C A S A
4054(A) I G G E F T T I E N Q P W F A A I Y R R H R G G S V T Y C G G S L I S P C W V I S A T H C F I D Y P K K E D Y I V Y L G R S R L N S N T Q G E M K F E V E N L I L H K D Y S A D T L A H N D I A L L K I R S K E G R C A Q P

SiteHopper clustering



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

A full-page background image of a starry night sky with the Milky Way galaxy visible. A person's silhouette is standing on the right side, looking up at the stars. The word "Questions?" is written in white text in the center of the image.

Questions?

For more information, please contact:

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www.eyesopen.com

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