

High Performance Research Computing

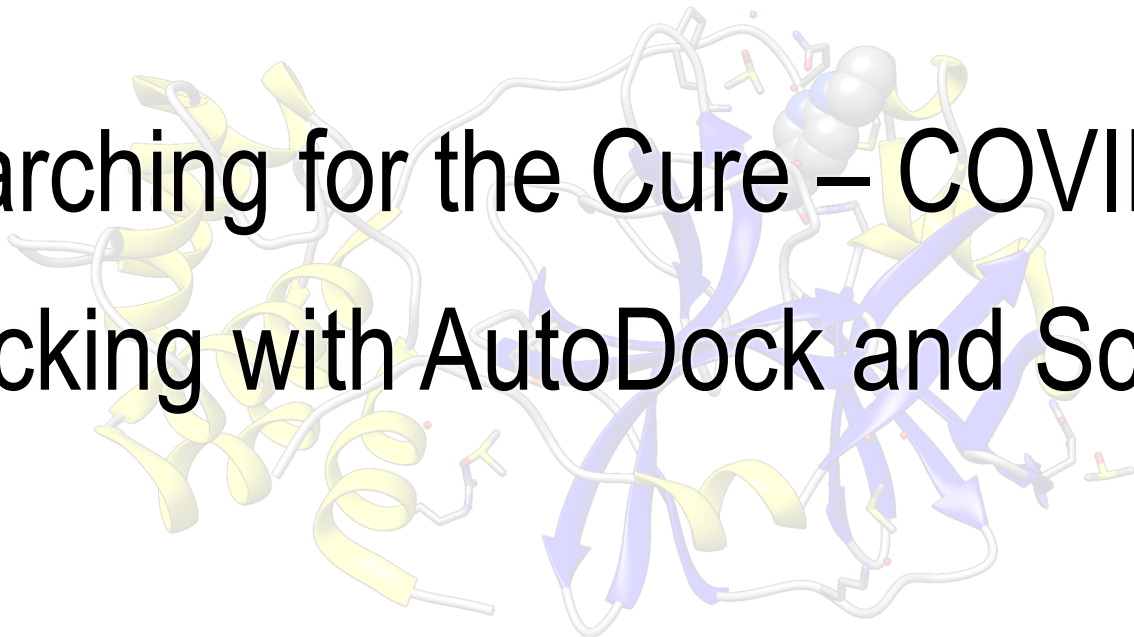
A Resource for Research and Discovery



TEXAS A&M
UNIVERSITY.

Searching for the Cure – COVID-19

Drug Docking with AutoDock and Schrödinger

A 3D ribbon diagram of a protein structure, likely a viral protein, rendered in yellow and blue. The structure is complex and multi-domain, with various loops and helices. It is centered in the background of the slide.

Texas A&M University

High Performance Research Computing

<https://hprc.tamu.edu>

Outline

1:30-2:00	Basic concepts for Drug Docking, Protein & Ligand Preparation, Grid Generation
2:00-2:45	Hands-on Session 1 – Preparing and running docking in Autodock, Glide and CovDock
2:45-3:00	Scoring functions
3:00-3:45	Hand-on Session 2 – Finish preparation and submission of docking if needed. Analyze results.
3:45-4:00	Wrap up lecture



Cost of Drug Discovery

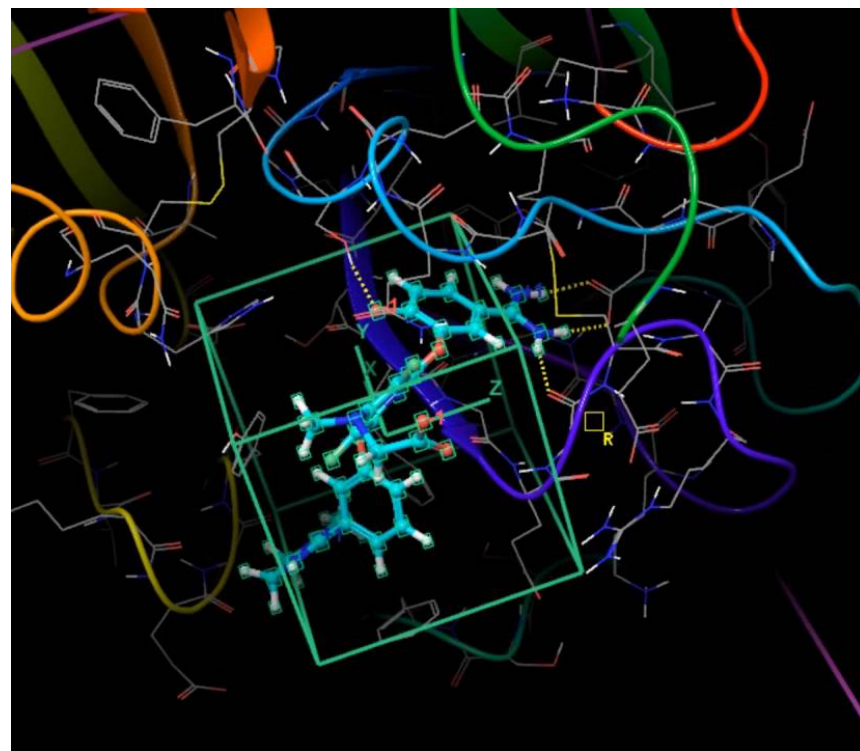
Pharmaceutical company	Number of drugs approved	Average R&D spending per drug (in \$ Millions)	Total R&D spending from 1997-2011 (in \$ Millions)
AstraZeneca	5	\$11,790.93	\$58,955
GlaxoSmithKline	10	\$8,170.81	\$81,708
Sanofi	8	\$7,909.26	\$63,274
Roche Holding	11	\$7,803.77	\$85,841
Pfizer	14	\$7,727.03	\$108,178
Johnson & Johnson	15	\$5,885.65	\$88,285
Eli Lilly & Co.	11	\$4,577.04	\$50,347
Abbott Laboratories	8	\$4,496.21	\$35,970
Merck & Co Inc.	16	\$4,209.99	\$67,360
Bristol-Meyers Squibb Co.	11	\$4,152.26	\$45,675
Novartis	21	\$3,983.13	\$83,646
Amgen Inc.	9	\$3,692.14	\$33,229

https://en.wikipedia.org/wiki/Cost_of_drug_development



Ligand Docking

- Procedure
 - Prepare the protein
 - Missing atoms/side chains
 - Protonation state
 - Flexible side chains
 - Prepare the ligand
 - Protonation state
 - Create a docking grid
 - Specify where to dock the ligand
 - Dock the ligand(s)
 - Scoring
 - Refinement

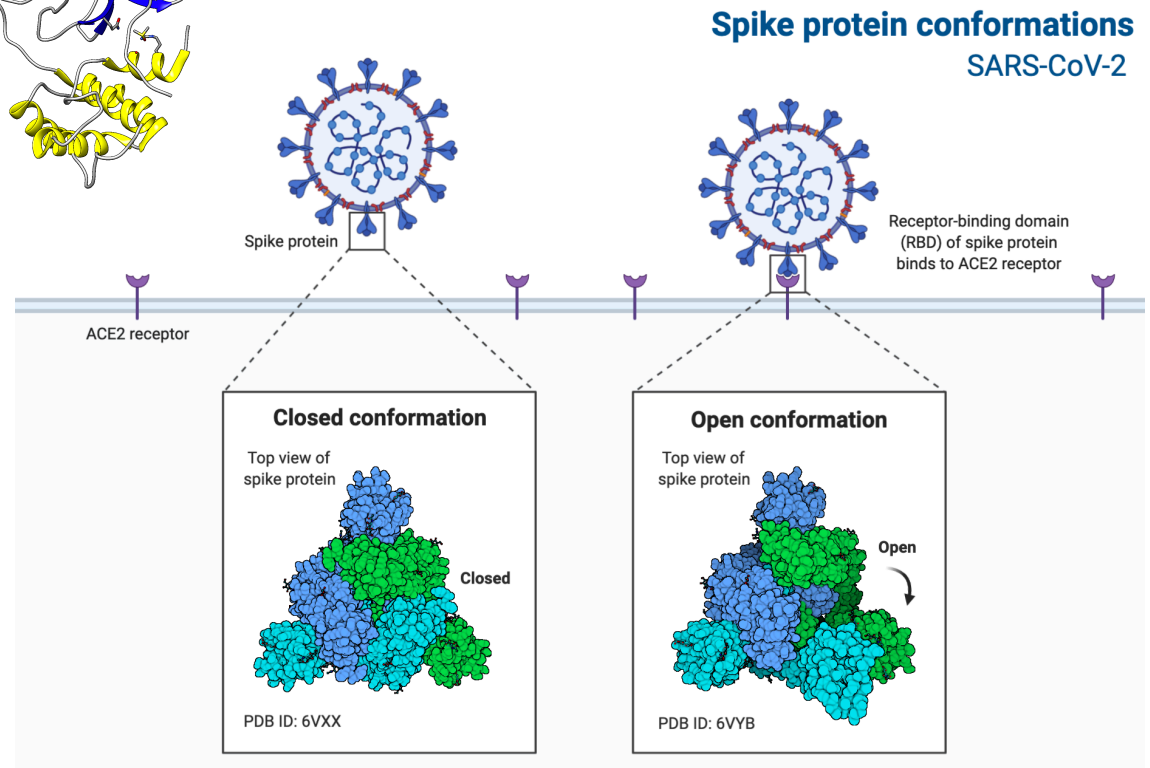
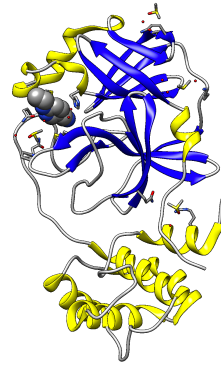


Protein Target

- Crystal structure
- NMR
- Homology Model
- cryoelectron microscopy (cryo-EM)

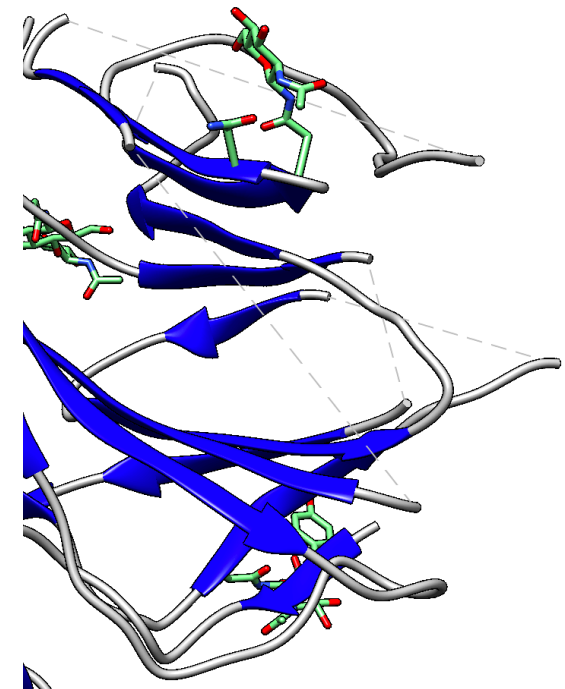
RCSB Protein Data Bank (PDB)
<https://www.rcsb.org/>

<https://pdb101.rcsb.org/learn/guide-to-understanding-pdb-data/>



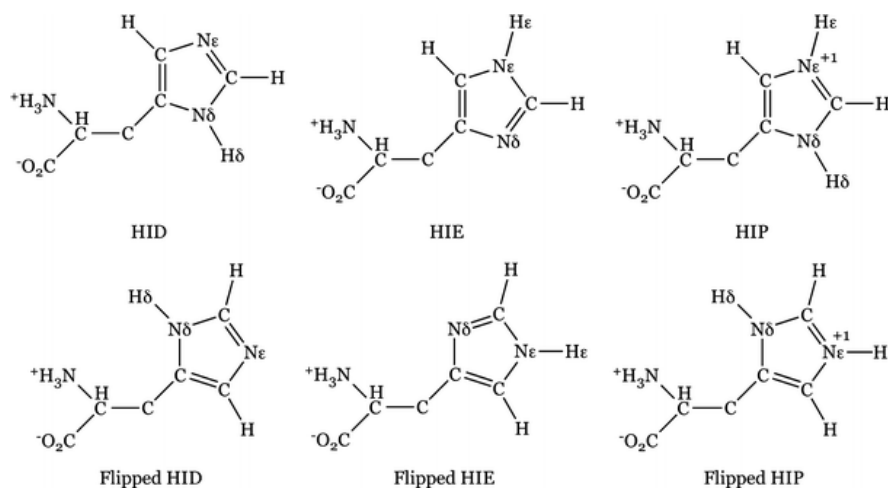
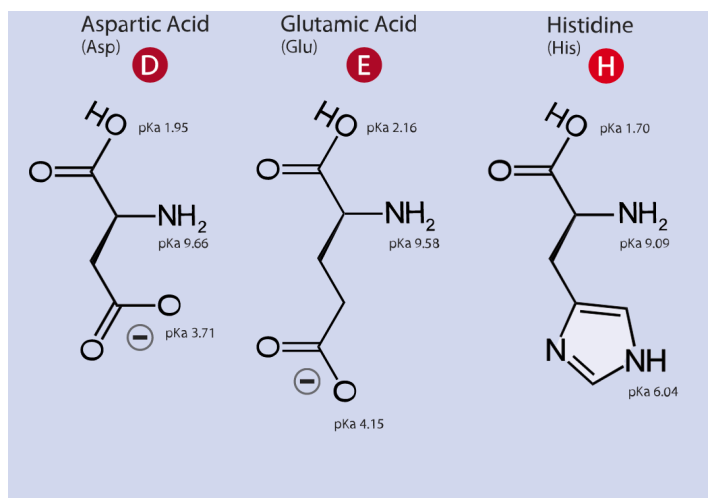
Protein Preparation – Missing atoms

- Missing atoms
 - Hydrogens are not included
 - Entire side chains may be missing
 - There are a number of utilities to fill in missing atoms/sidechain
- Missing segments
 - More complicated to fix
 - Normally requires homology modeling to obtain reasonable results if more than a few residues are missing



Protein Preparation – Protonation states

- ASP, GLU and HIS

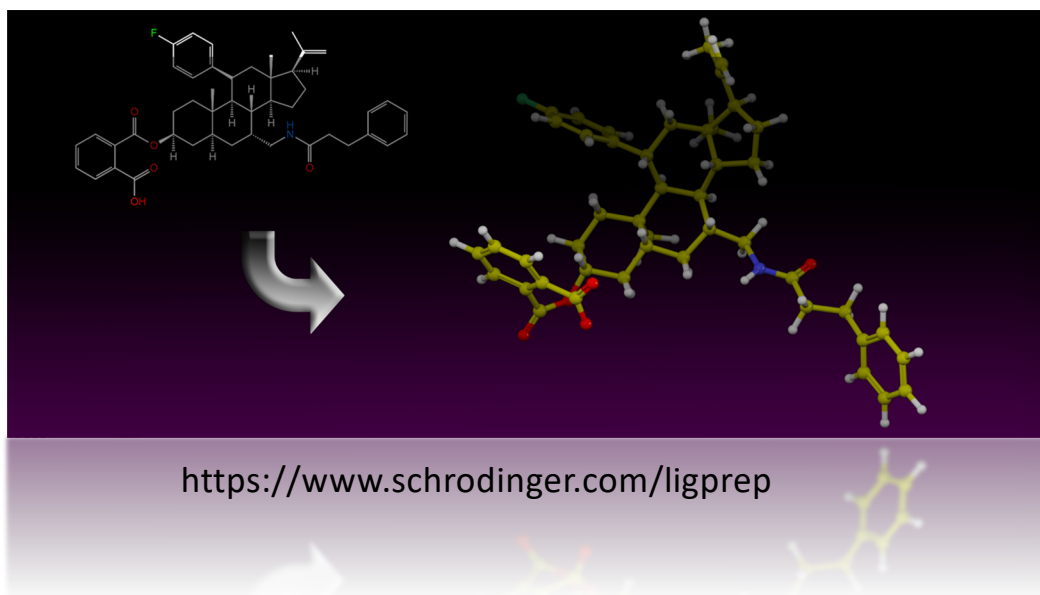


Adapted from https://commons.wikimedia.org/wiki/File:Amino_Acids.svg
 Dancojocari / CC BY-SA (<https://creativecommons.org/licenses/by-sa/3.0>)

<https://link.springer.com/article/10.1007/s10822-013-9643-9>

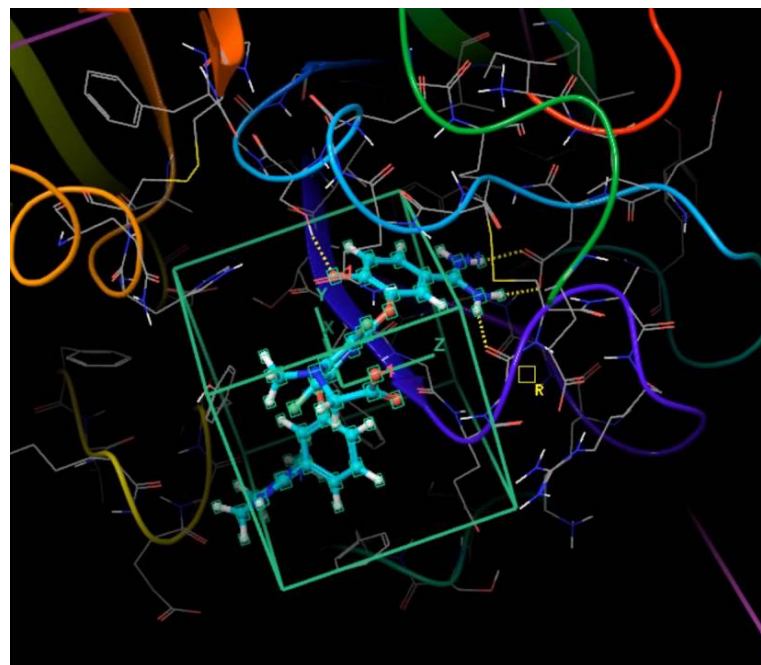
Ligand Preparation

- Generate reasonable atomic coordinates for a ligand dataset
- tautomeric states
- ionization states
- ring conformations
- stereoisomers
- conformers



Binding Pocket – Grid Generation

- Utilities to suggest binding sites – such as Schrödinger's SiteMap
- Use binding site from crystal structures with a bound ligand
- Binding Pocket Grid
 - Bounding box where docking is performed
 - Too small
 - ligands won't dock
 - miss good ligands
 - Too big
 - increase computational cost substantially
 - miss good binding poses
- Is the binding pocket rigid or flexible?
 - Molecular dynamics simulations can be used to investigate the stability of the binding pocket



Hands-on Session 1

Preparing and running docking in
Autodock, Glide and CovDock

45 minutes



Scoring Functions

- Do not correlate with IC_{50} , K_d , EC_{50} , etc
- Do not provide a rank-ordering of ligands
- Are optimized to give good enrichment
 - Separate good from bad ligands
 - Limit the number of ligands that need to be investigated further
- More negative the score, the better



Glide Scoring Functions

- SP – 5-20 sec/molecule
 - First pass virtual screening on large databases
 - Seeks to minimize false negatives
- XP – 3-5 min/molecule
 - Refinement for a smaller dataset for lead optimization
 - Seeks to minimize false positives



Glide Docking SP

$$\text{GScore} = 0.05 \cdot \text{vdW} + 0.15 \cdot \text{Coul} + \text{Lipo} + \text{Hbond} + \text{Metal} + \text{Rewards} + \text{RotB} + \text{Site}$$

Component	Description
vdW	Van der Waals energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Coul	Coulomb energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Lipo	Lipophilic term, which is a pairwise term in SP but is derived from the hydrophobic grid potential for XP. Rewards favorable hydrophobic interactions.
HBond	Hydrogen-bonding term. This term is separated into differently weighted components that depend on whether the donor and acceptor are neutral, one is neutral and the other is charged, or both are charged.
Metal	Metal-binding term. Only the interactions with anionic or highly polar acceptor atoms are included. If the net metal charge in the apo protein is positive, the preference for anionic or polar ligands is included; if the net charge is zero, the preference is suppressed.
Rewards	Rewards and penalties for various features, such as buried polar groups, hydrophobic enclosure, correlated hydrogen bonds, amide twists, and so on. This category covers all terms other than those explicitly mentioned.
RotB	Penalty for freezing rotatable bonds.
Site	Polar interactions in the active site. Polar but non-hydrogen-bonding atoms in a hydrophobic region are rewarded.



Glide Docking XP (Extra Precision)

- Increase computational cost
- Anchor fragments of the docked ligand, typically rings, are chosen from the set of SP poses and the molecule is re-grown bond by bond from these anchor positions
- Glide SP with additional Extra Precision terms
- Rewards occupancy of well-defined hydrophobic pockets by hydrophobic ligand groups which is often under-estimated
- Includes improvements to the scoring of hydrogen bonds as well as detection of buried polar groups, and detection of pi-cation and pi-pi stacking interactions



AutoDock Vina Scoring

$$\Delta G_{\text{binding}} = \Delta G_{\text{gauss}} + \Delta G_{\text{repulsion}} + \Delta G_{\text{hbond}} + \Delta G_{\text{hydrophobic}} + \Delta G_{\text{tors}}$$

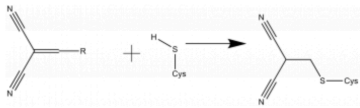
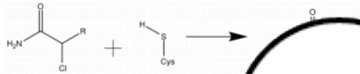

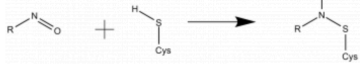

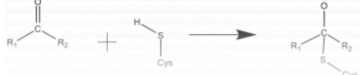
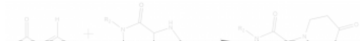
- ΔG_{gauss} Attractive term for dispersion, two gaussian functions
- $\Delta G_{\text{repulsion}}$ Square of the distance if closer than a threshold value
- ΔG_{hbond} Ramp function - also used for interactions with metal ions
- $\Delta G_{\text{hydrophobic}}$ Ramp function
- ΔG_{tors} Proportional to the number of rotatable bonds

- Calibrated with 1,300 complexes from PDB-Bind
- Standard error = 2.85 kcal/mol



Schrödinger CovDock

Custom Covalent Reactions

Index	Reaction	Ligand SMARTS	Receptor SMARTS	CDOCK File
1		<chem>[C,c]=[C,c]-[C,c]#[N,n]</chem>	<chem>[C]-[S,O;H1,-1]</chem>	Download
2		<chem>[C;H1]([Cl])-[C]=[O]</chem>	<chem>[S]-[C;H2]</chem>	Download
3				
4		<chem>[N]=[O,S]</chem>	<chem>[C,c]-[S,O;H1,-1]</chem>	Download
5		<chem>[N]=[C]=[S]</chem>	<chem>[#6]-[S;H1]</chem>	Download
6		<chem>[C,c]=[O,S]</chem>	<chem>[C,c]-[S,O;H1,-1]</chem>	Download
7		<chem>[C]=[C]-[C]=[O]</chem>	<chem>[C](=[O])-[C]-[C]</chem>	Download

<https://www.schrodinger.com/newsletters/introducing-covdock-covalent-docking>

Mutate reactive residue to ALA

Sample ligand conformations with ConfGen

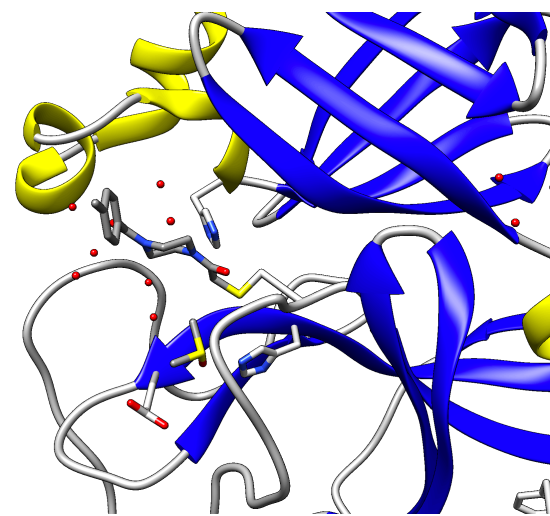
Glide docking with positional constraint

Apply pose selection criteria

Covalently link ligand & attachment residue

Optimize ligand poses and residue geometry with Prime VSGB2.0

Rank poses using VSGB2.0 and compute binding affinity



<https://www.rcsb.org/structure/5rgl>



Hands-on Session 2

Finish preparation and submission of docking
if needed. Analyze results.

45 minutes



Illustrative Applications & Training

Schrödinger <https://www.schrodinger.com/training>

MOE https://www.chemcomp.com/Research-Current_Journals.htm



Need Help? Contact the HPRC Helpdesk

Website: hprc.tamu.edu

Email: help@hprc.tamu.edu

Telephone: (979) 845-0219

Help us, help you -- we need more info

- Which Cluster (Terra, Ada, Curie)
- NetID (NOT your UIN)
- Job id(s) if any
- Location of your jobfile, input/output files
- Application used if any
- Module(s) loaded if any
- Error messages
- Steps you have taken, so we can reproduce the problem

