How to run an MD simulation

How to run an MD simulation

- Protocol for an MD simulation
- Initial Coordinates
  - X-ray diffraction or NMR coordinates from the Protein Data Bank
  - Coordinates constructed by modeling (homology)
- Treatment of non-bonded interactions
- Treatment of solvent
  - implicit
  - explicit
- If using explicit treatment of solvent
  - Periodic boundary conditions (PBC)
  - Solvation sphere
  - Active site dynamics

Molecular Modelling Software

- Commercial:
  - Cerius2, Insight II (from Accelrys)

- Academic:
  - MMTK
  - GROMACS
  - NAMD
  - CHARMM
  - AMBER

“If I were to rewrite MMTK today, I would use the exchange data formats accepted by the molecular simulation community”

But those formats don’t exist yet.

2013 – Konrad Hinsen

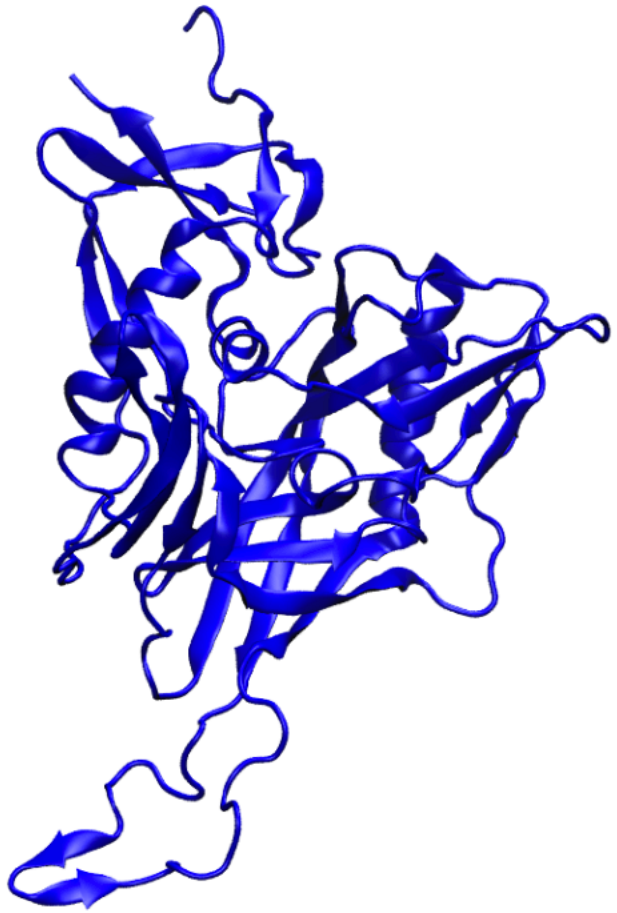
Molecular Visualisation Packages

- Many!
  - RasMol
  - PyMOL
  - Chimera
  - VMD

- Select one or two, become an expert ☺

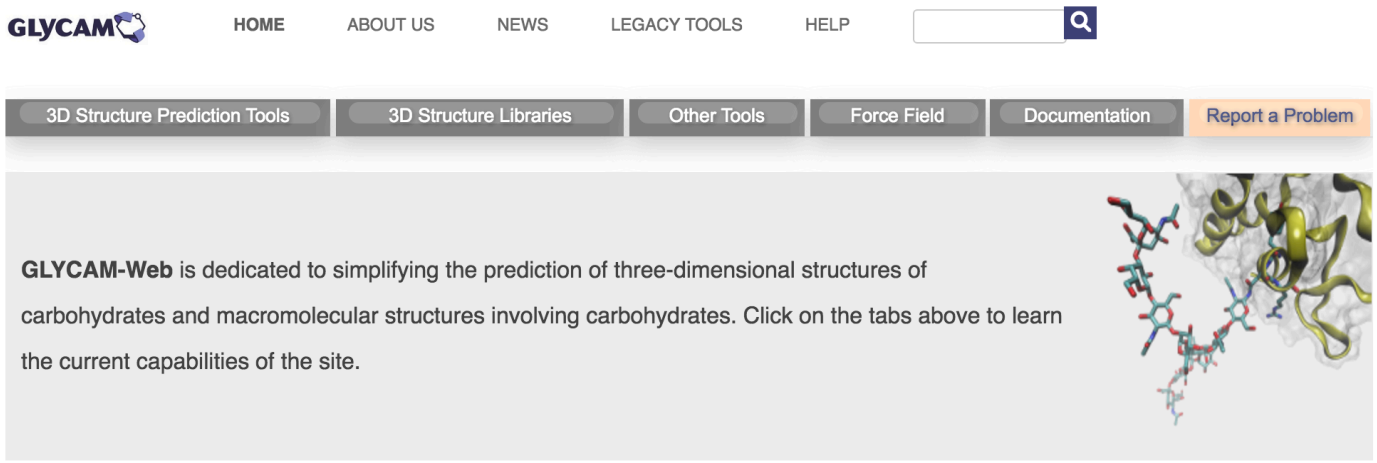
How to run an MD simulation

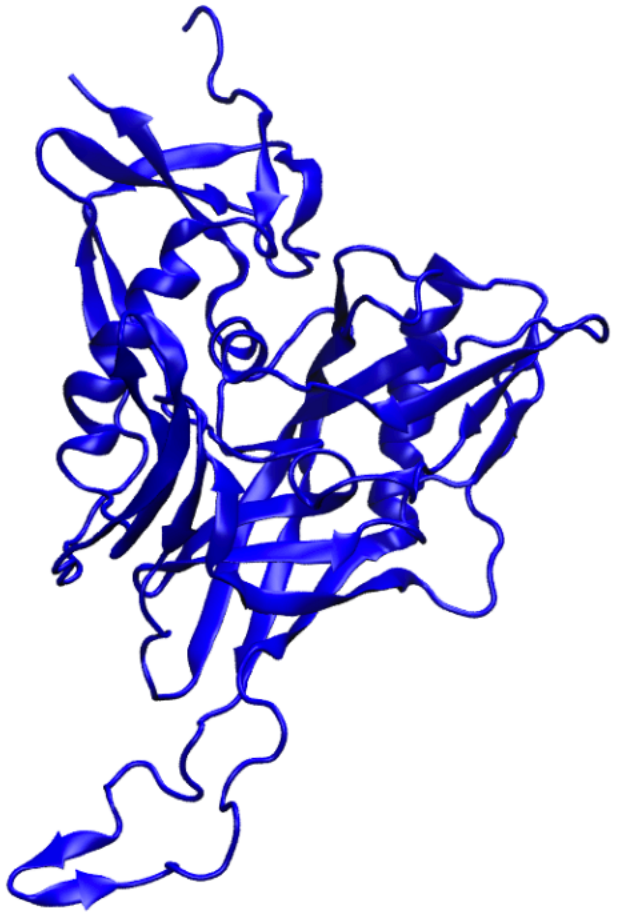
- Homology modelling
  - Modeller
  - Phyre2



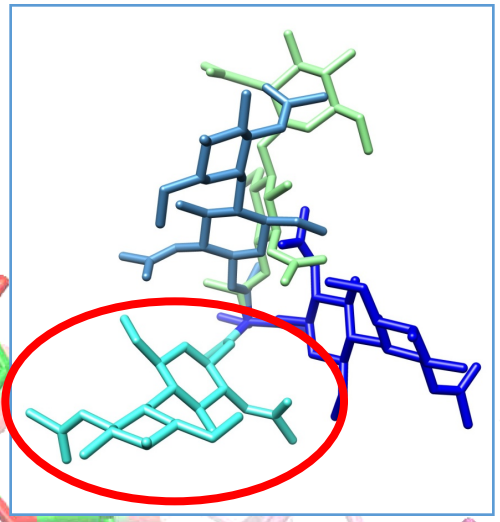
How to run an MD simulation

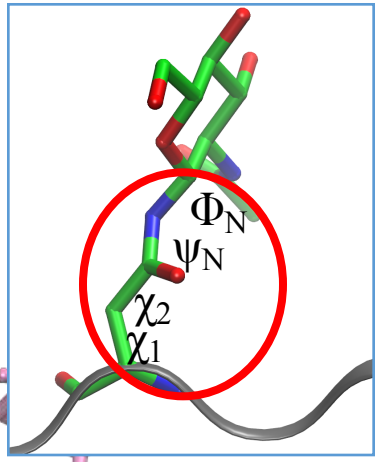
- Refine your structure
  - http://glycam.org/

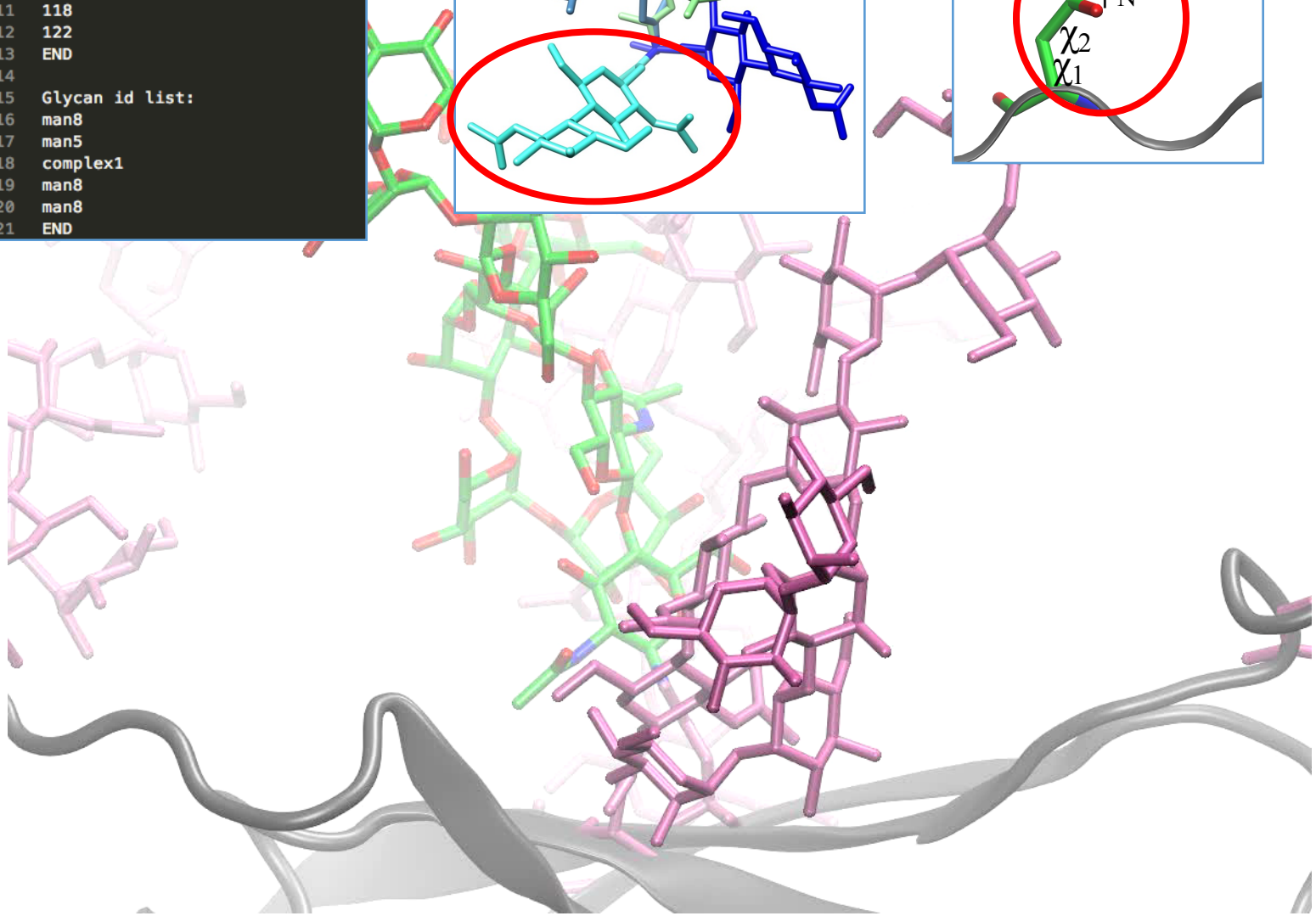




```
Protein:
protein.pdb

Glycans:
/home/natasha/WIGGLER/glycans/

Protein Residue list:
58
105
109
118
122
END

Glycan id list:
man8
man5
complex1
man8
man8
END
```

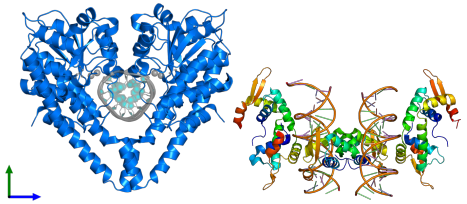






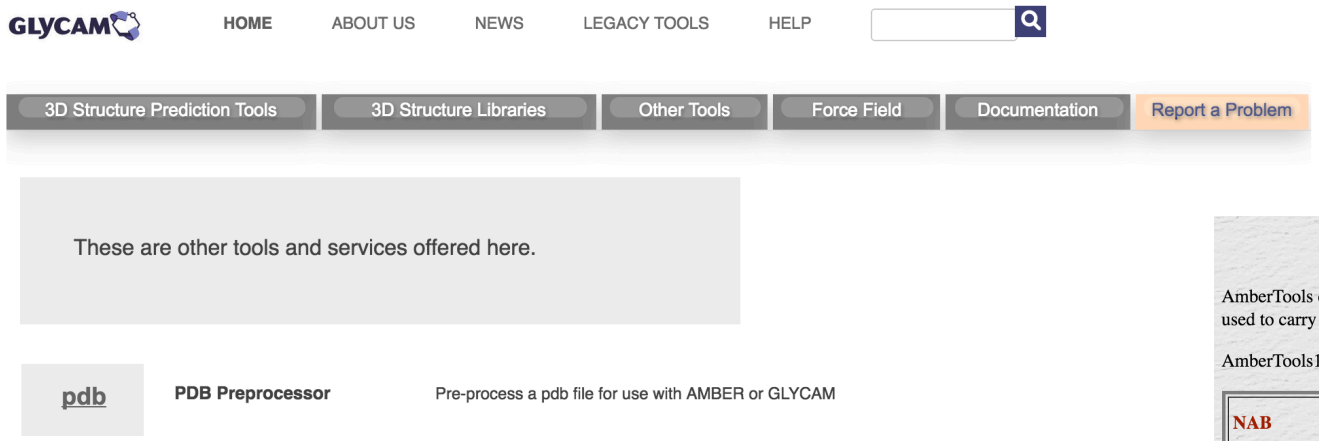
O Grant

How to run an MD simulation

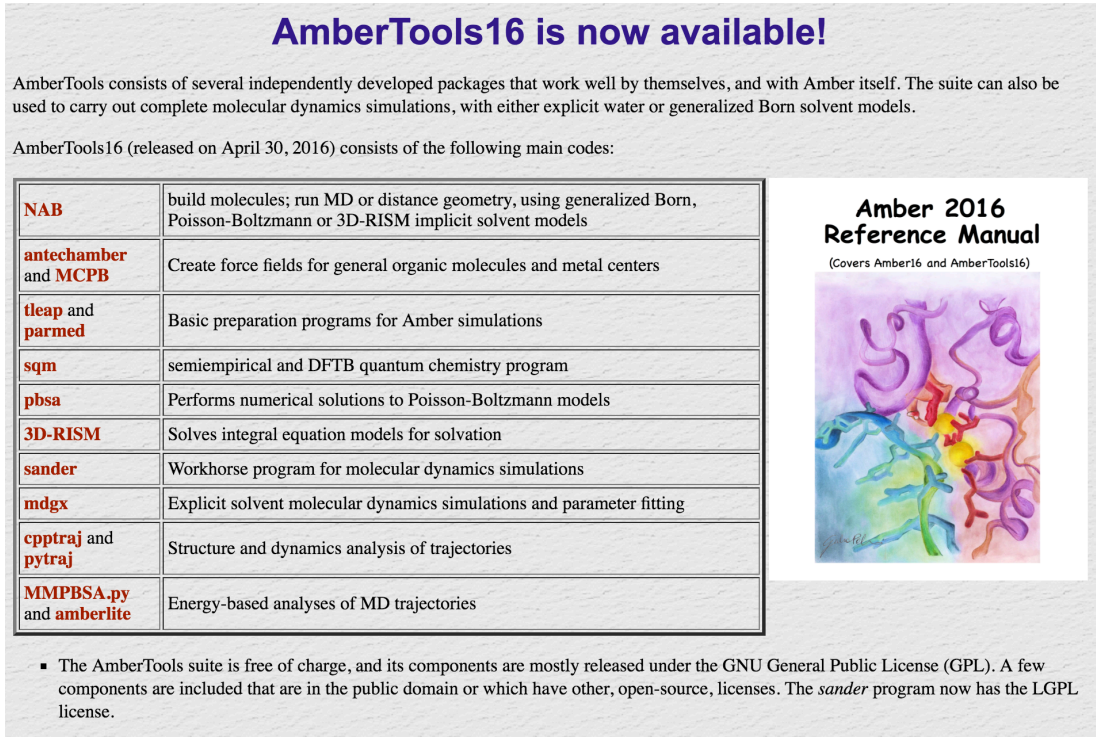


Topology and Coordinate file

How to run an MD simulation



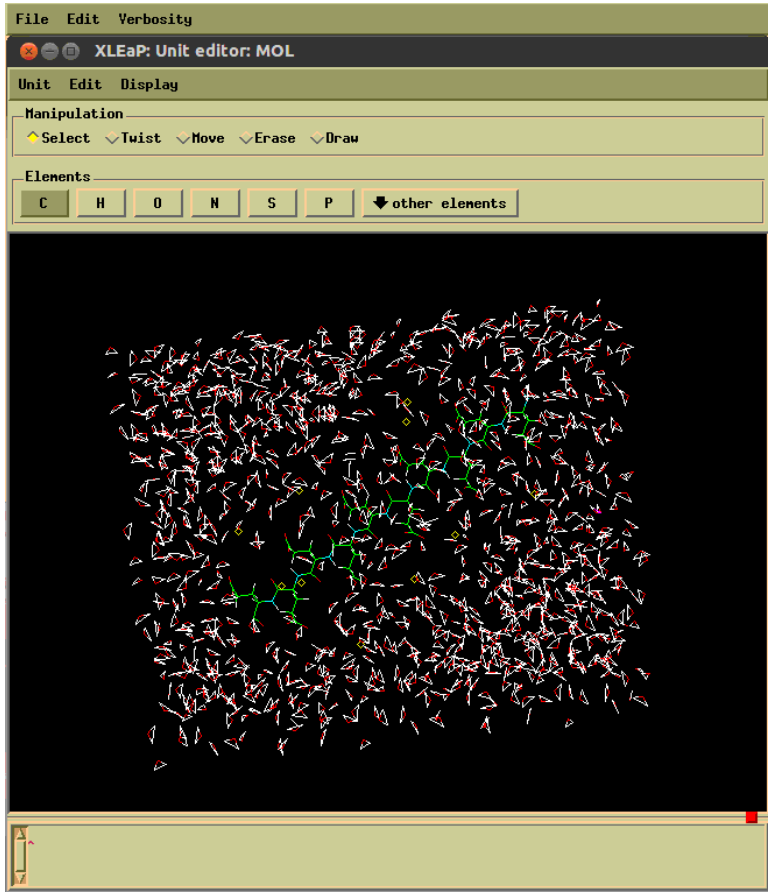
glycam.org



http://ambermd.org/

How to run an MD simulation

- AmberTools: LEaP




```
nwood$ tleap
-I: Adding /apps/chpc/chem/amber/14/dat/leap/prep to search path.
-I: Adding /apps/chpc/chem/amber/14/dat/leap/lib to search path.
-I: Adding /apps/chpc/chem/amber/14/dat/leap/parm to search path.
-I: Adding /apps/chpc/chem/amber/14/dat/leap/cmd to search path.

Welcome to LEaP!
(no leaprc in search path)
>
```

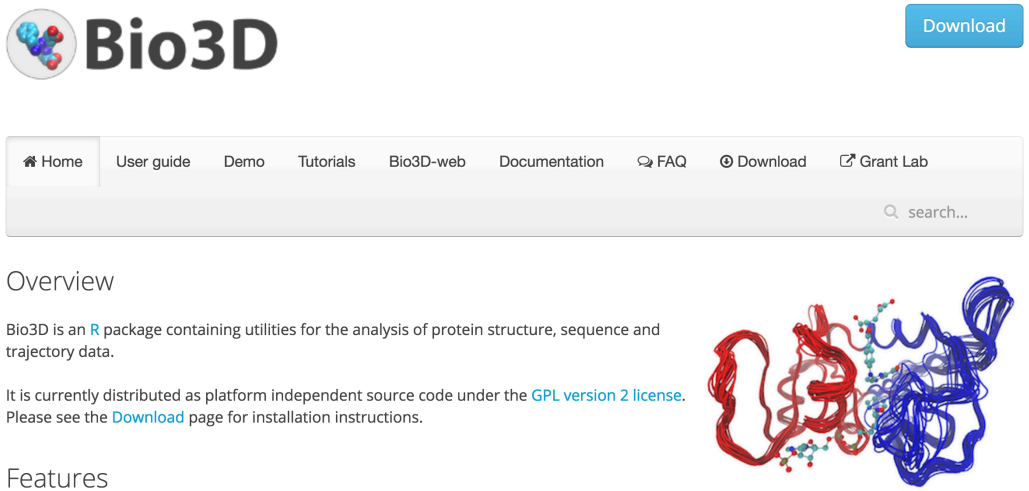
How to run an MD simulation

```
########## Set Defaults ###########################################
set default PBRadii mbondi2
####################################################################
########## Force Field Inputs ######################################
source /apps/chpc/chem/amber/14/dat/leap/cmd/leaprc.ff14SB
source /apps/chpc/chem/amber/14/dat/leap/cmd/leaprc.GLYCAM_06j-1
loadAmberParams frcmod.tip5p
####################################################################

########load Carb#################
mol=loadpdb structure.pdb

#BONDING
```

How to run an MD simulation

- Bond information

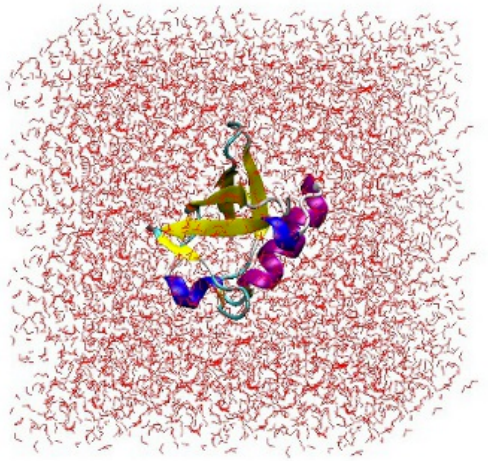
bond mol.1798.O4 mol.1799.C1
bond mol.1809.O4 mol.1810.C1
bond mol.1820.O4 mol.1821.C1



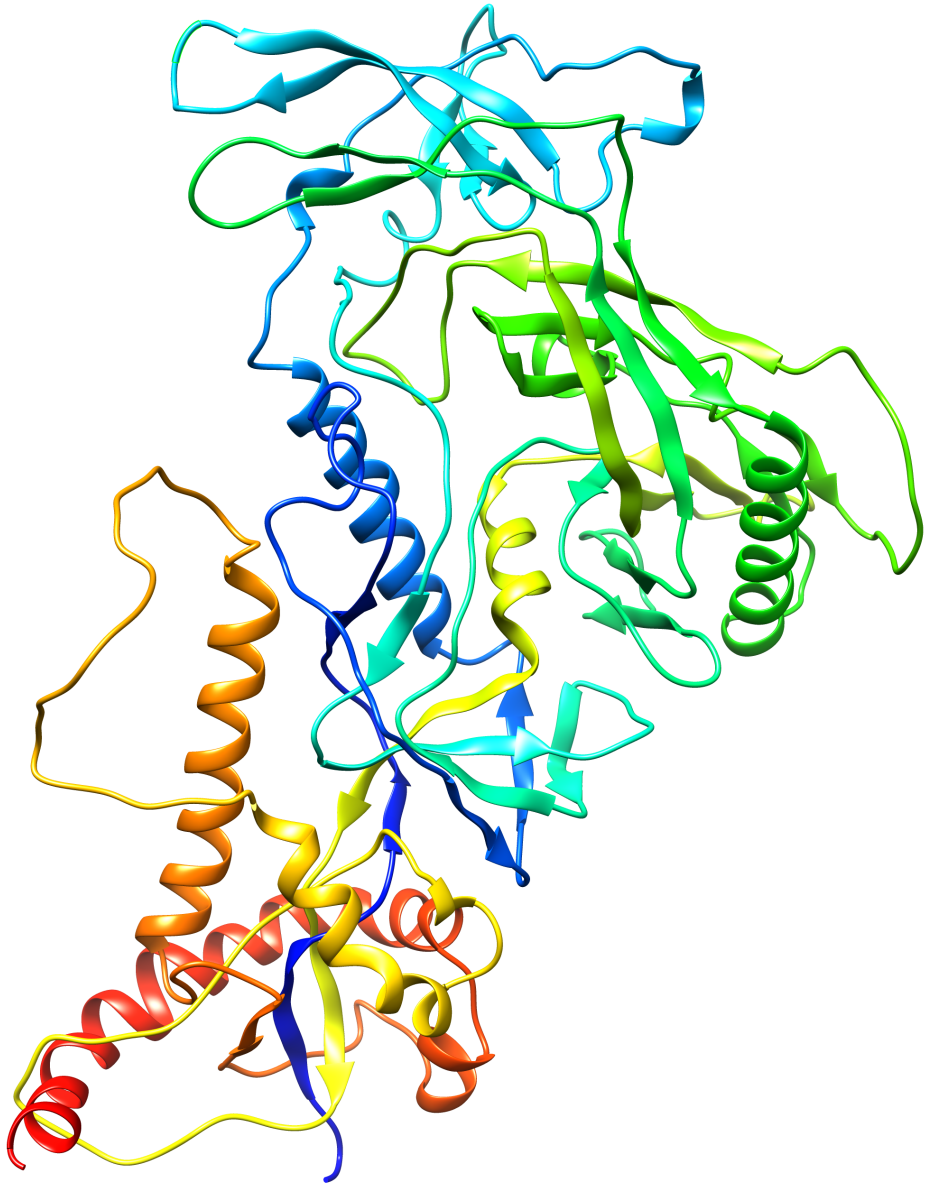
How to run an MD simulation

```
saveamberparm mol CPLX.prmtop CPLX.rst7
savepdb mol CPLX.pdb

##############Addions###############
addIons mol Na+ 0
addIons mol Cl- 0

saveamberparm mol CPLX_Neut.prmtop CPLX_Neut.rst7
savepdb mol CPLX_Neut.pdb

##############Solvate###############
solvatebox mol TIP5PBOX 10.0 1.0

saveamberparm mol CPLX_Neut_Sol.prmtop CPLX_Neut_Sol.rst7
savepdb mol CPLX_Neut_Sol.pdb

quit
```

How to run an MD simulation

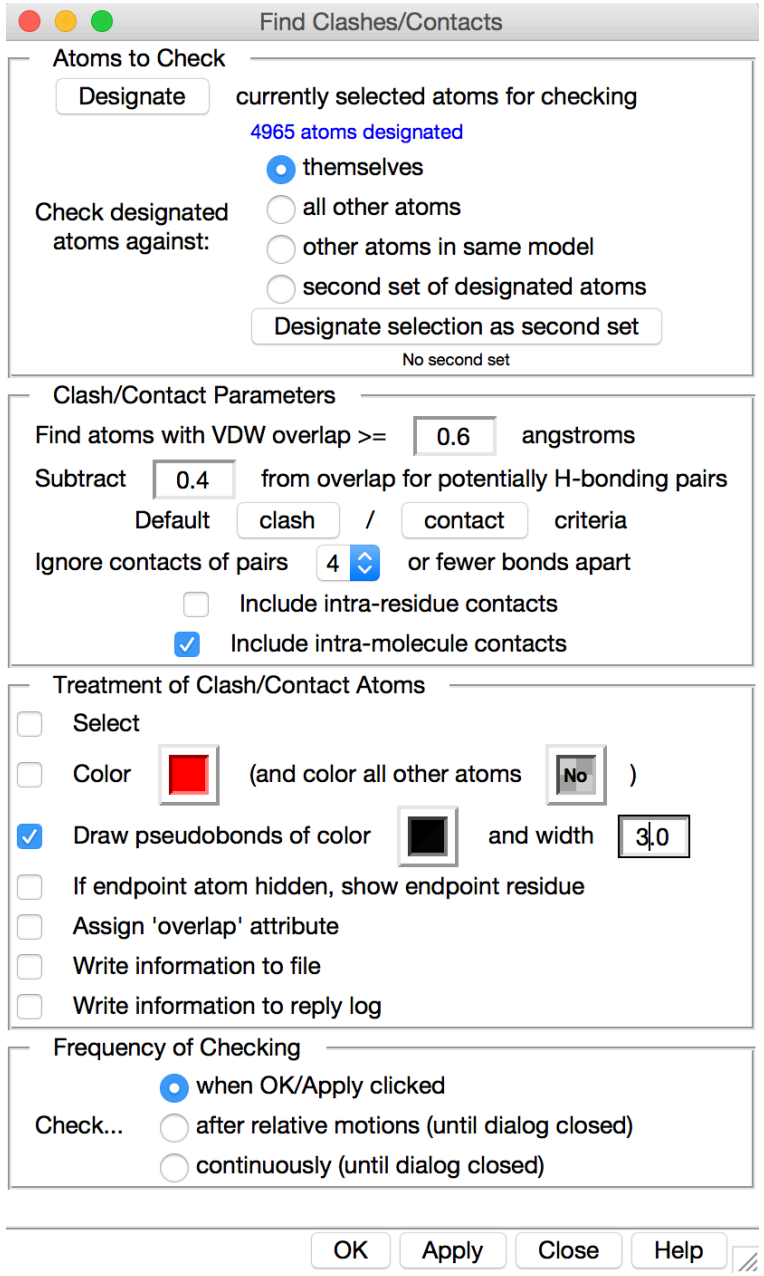


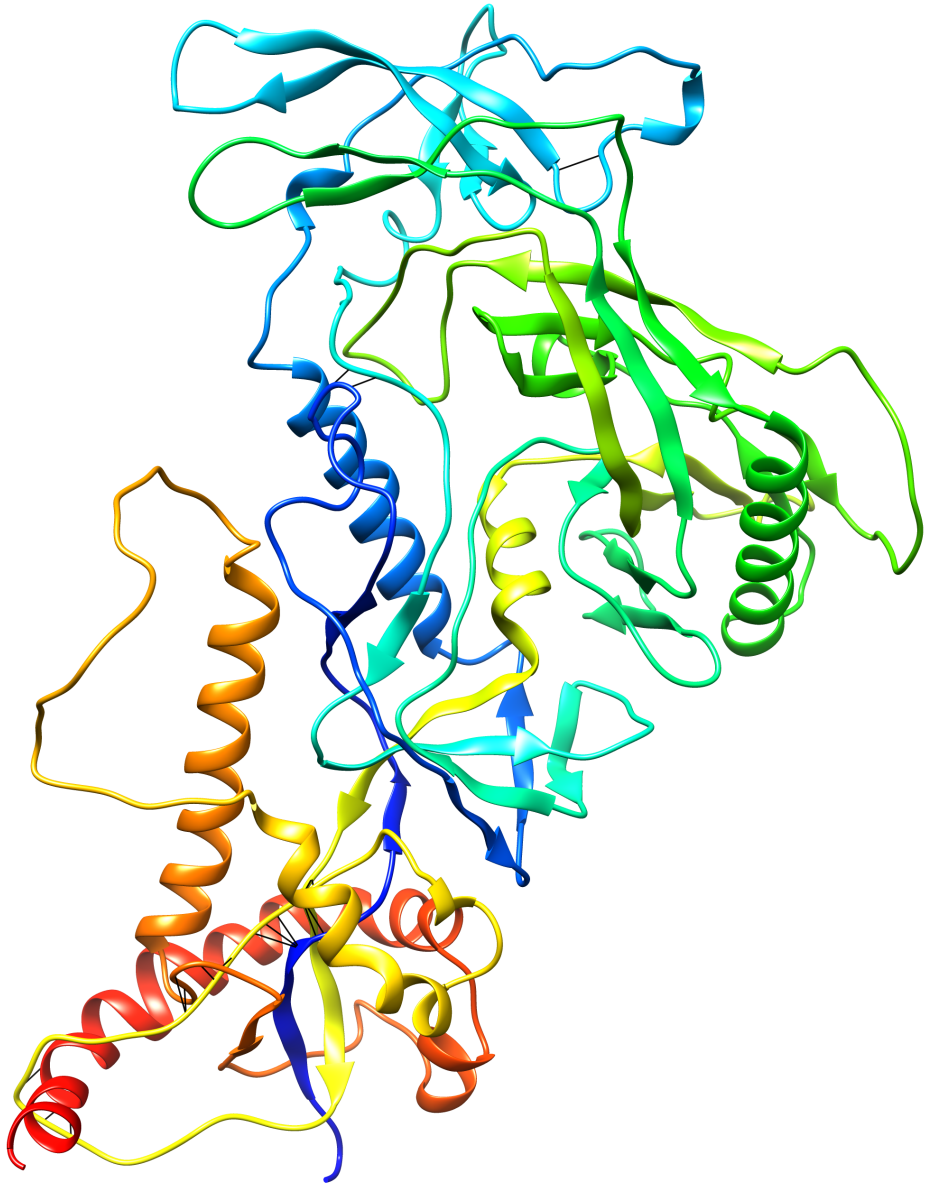
Minimisation:
remove bad contacts between non-bonded neighbouring atoms



Chimera:

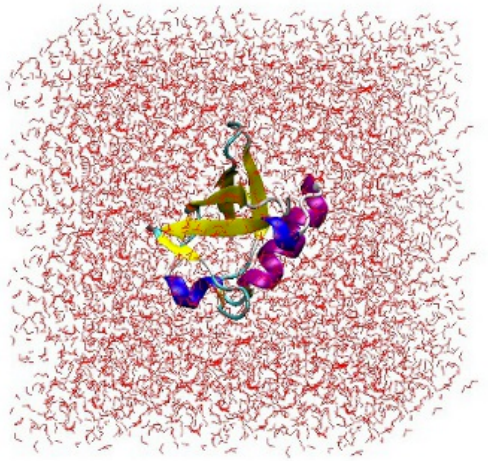
find clashes/contacts






KA-POW!

How to run an MD simulation



Minimisation:
remove bad contacts between non-bonded neighbouring atoms

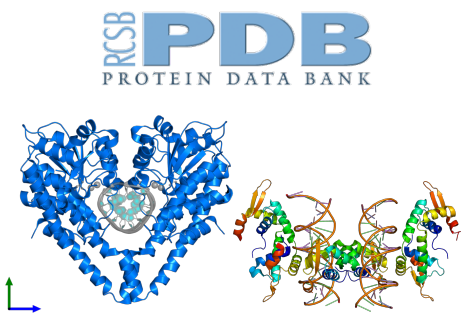
How to run an MD simulation

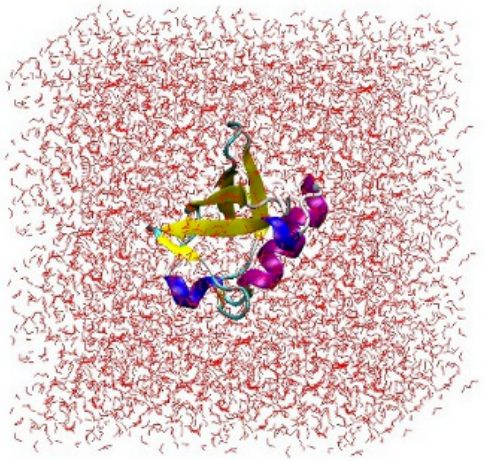
```
Constant Volume Minimization
 # Control section
 &cntrl
  imin=1,
  dielc = 1, cut = 10.0,
  ntb = 1,
  maxcyc = 20000, dx0 = 0.01, drms = 0.0001,
  ntmin = 1, ncyc = 10000,
  ntp = 0,
  ntr = 1,
  irest = 0,
 /
Restraints kcal/mol
5.0
```

Minimisation:
Amber input file

Input files available online, eg: http://ambermd.org/tutorials/advanced/tutorial8/loop1.htm

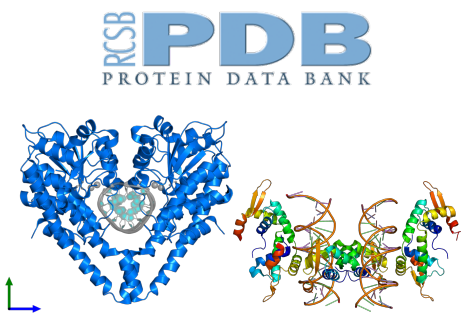
How to run an MD simulation

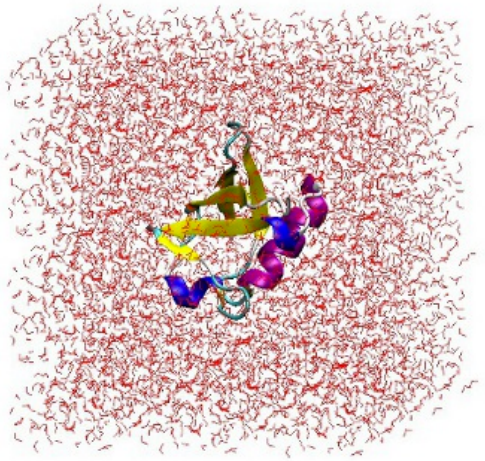




Minimisation:
remove bad contacts between non-bonded neighbouring atoms

How to run an MD simulation



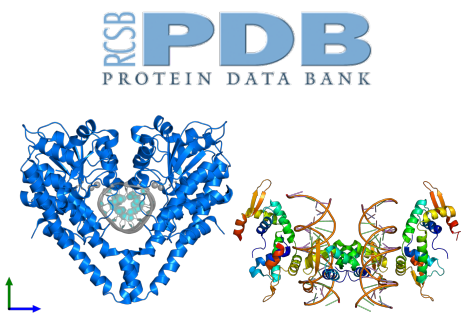


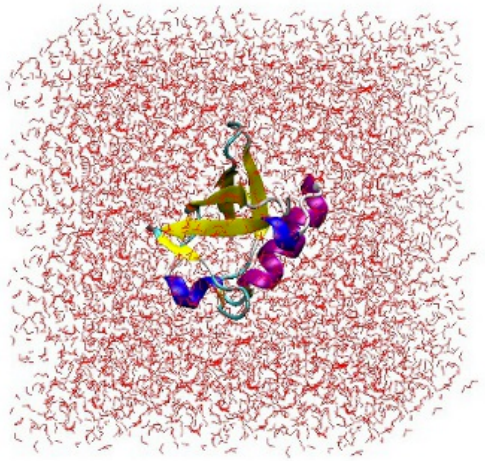
Minimisation:
remove bad contacts between non-bonded neighbouring atoms

Equilibration:
heating the system to room temperature

Production:
run our simulation at constant pressure and temperature

How to run an MD simulation





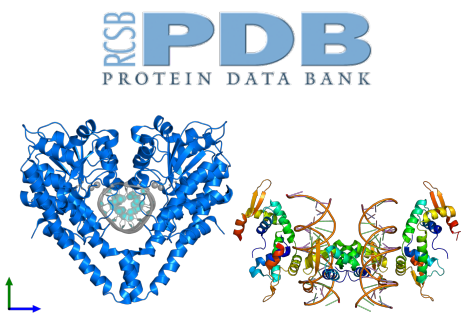
Minimisation:
remove bad contacts between non-bonded neighbouring atoms

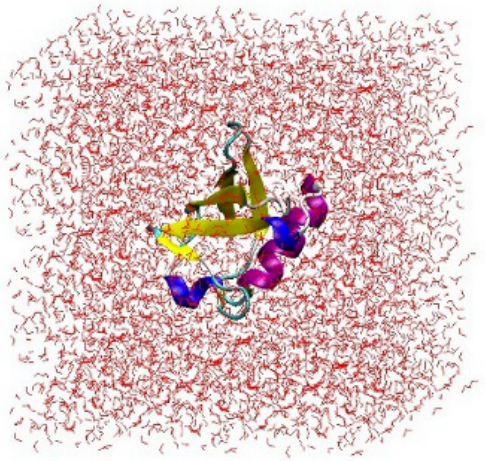
Equilibration:
heating the system to room temperature

Temp

constant volume

How to run an MD simulation





Minimisation:
remove bad contacts between non-bonded neighbouring atoms

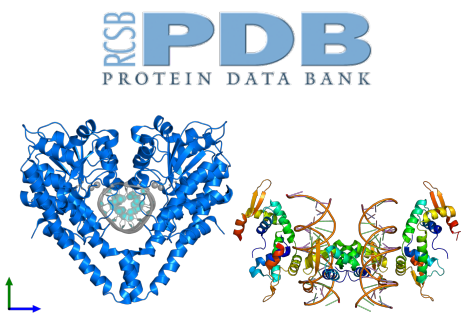
Equilibration:
heating the system to room temperature

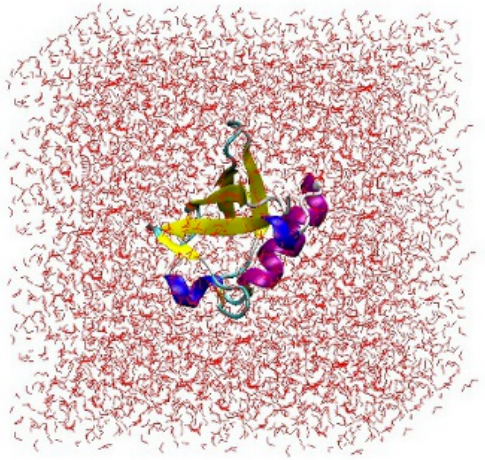
Temp

constant volume

constant pressure

How to run an MD simulation





Minimisation:
remove bad contacts between non-bonded neighbouring atoms

Equilibration:
heating the system to room temperature

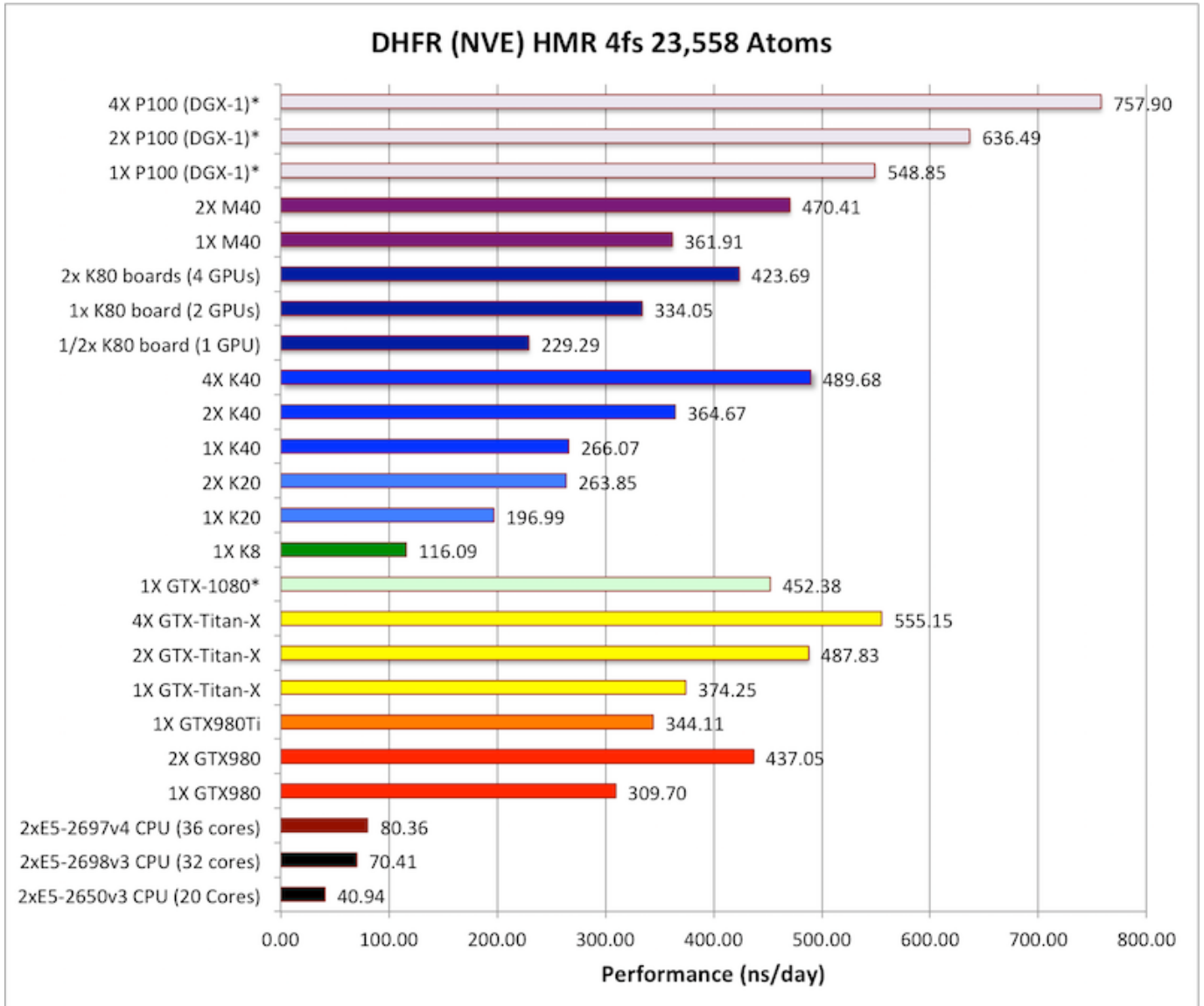
Temp

constant volume

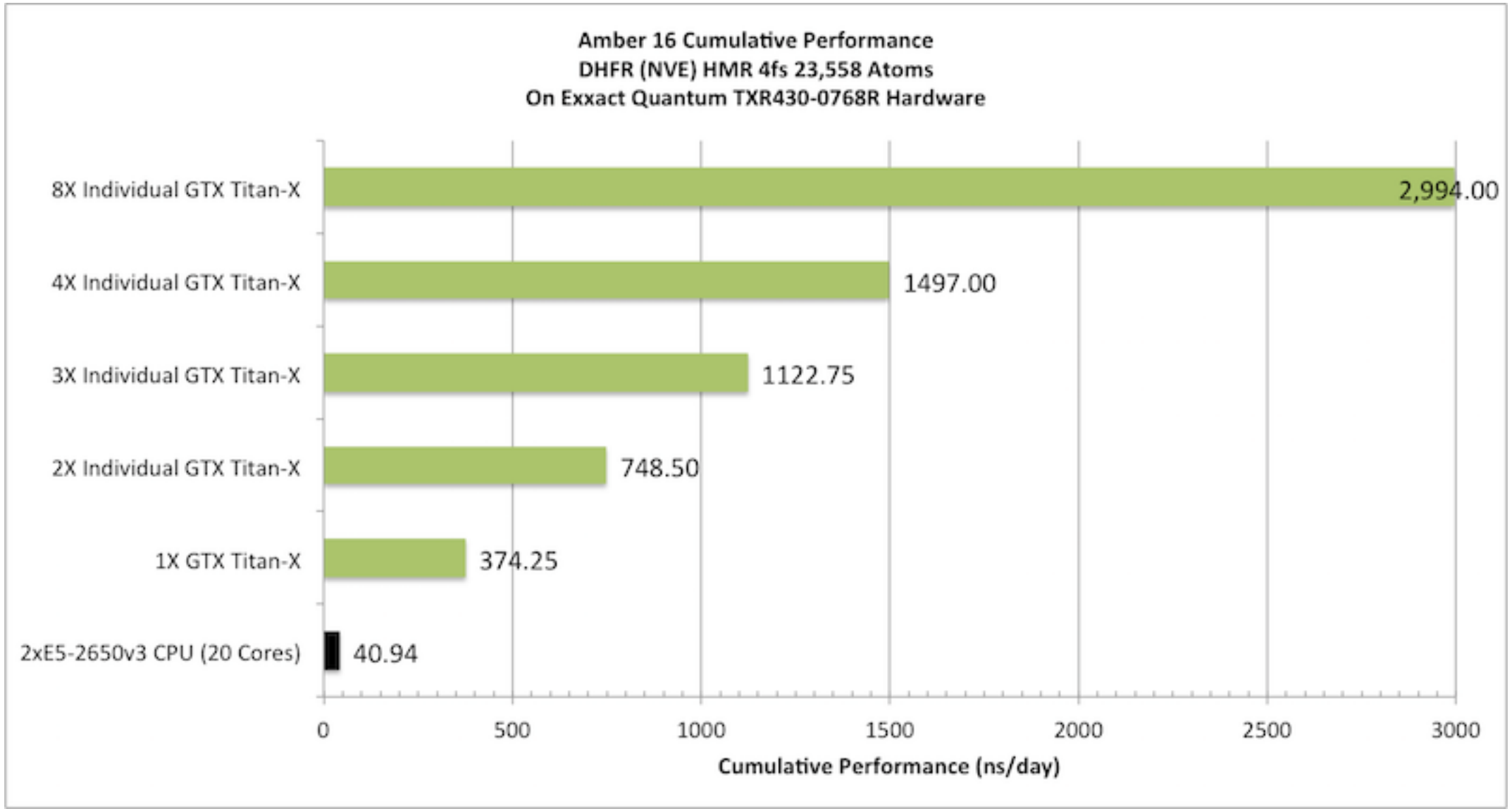
constant pressure

Production:
run our simulation at constant pressure and temperature

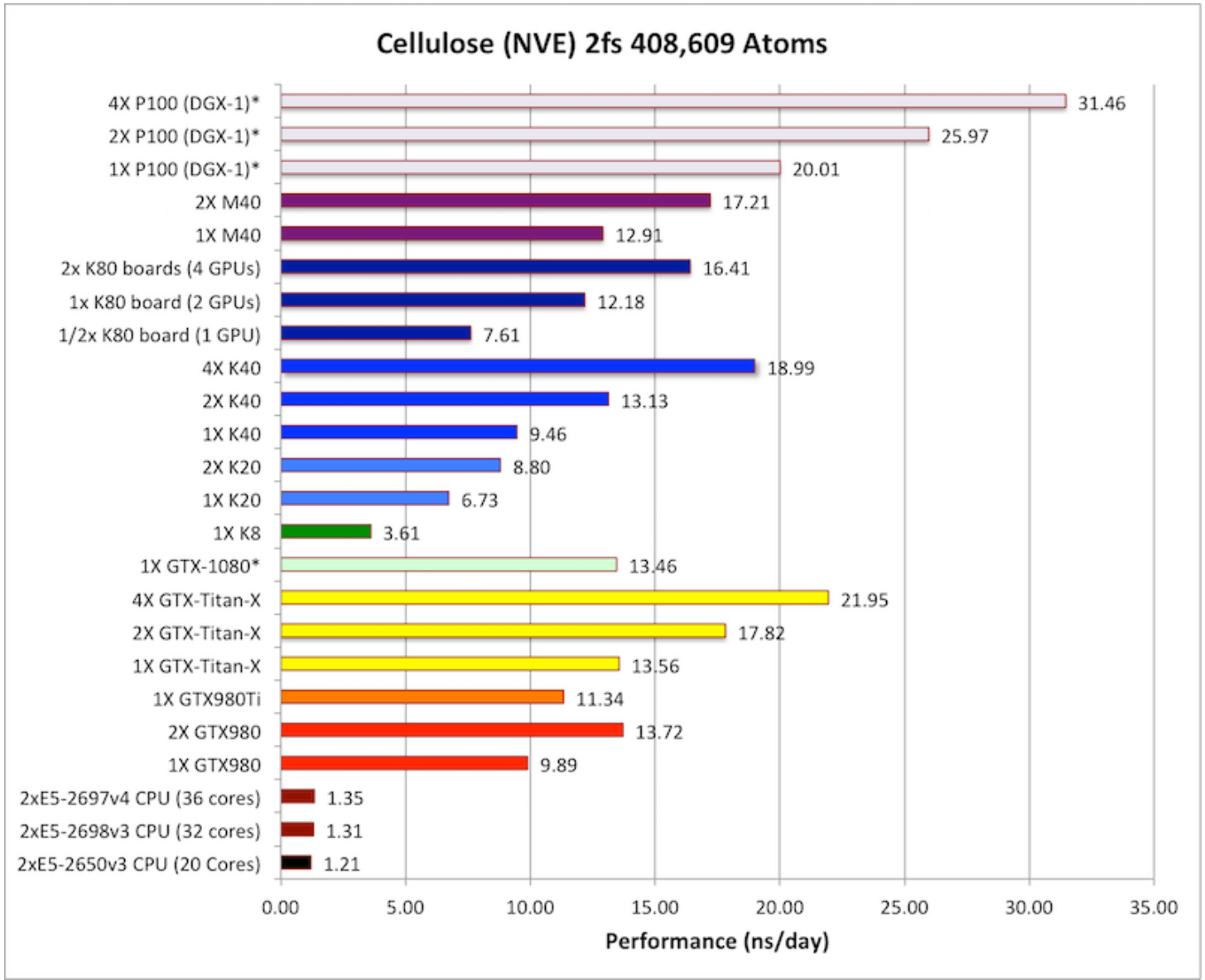
Benchmarks - Amber



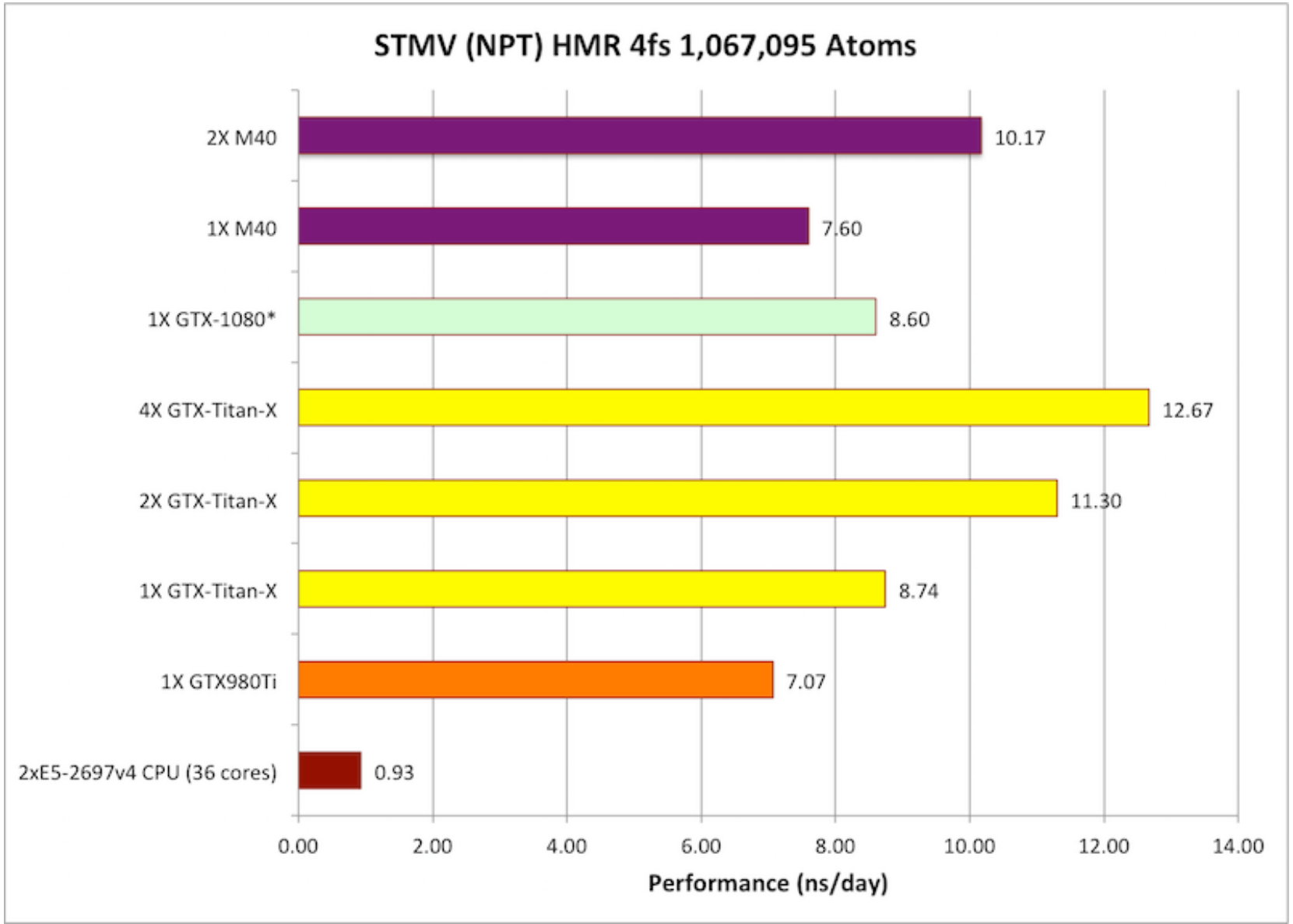
Benchmarks - Amber



Benchmarks - Amber



Benchmarks - Amber



Tutorial

Run your own MD simulation

Analyse an MD run: H-bonds over time

Manipulate your pdb file

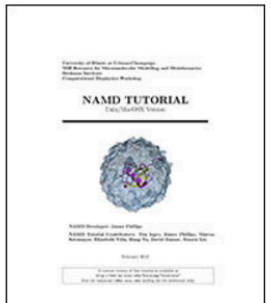
Run your own Interactive MD simulation

- VMD http://www.ks.uiuc.edu/Research/vmd/
- NAMD http://www.ks.uiuc.edu/Research/namd/
- Tutorial http://www.ks.uiuc.edu/Research/vmd/imd/tutorial/

VMD
Visual Molecular Dynamics

NAMD Tutorials

These tutorials focus on NAMD specifically, although many others utilize it as well. Be sure you have the latest version of **NAMD**.



NAMD Tutorial:

- Participants learn how to use NAMD to set up basic molecular dynamics simulations, and to understand typical NAMD input and output files, with an emphasis on such files for protein energy minimization and equilibration in water. Tutorial versions available for Windows, or Mac and Unix/Linux platforms.
- Instructions: [**html for Unix/Mac**] [**pdf for Unix/Mac**, 8.0M] [**html for Windows**] [**pdf for Windows**, 6.5M]
- Required tutorial files (all platforms): [**.tar.gz**, 148M], [**.zip**, 148M], **individual files (all platforms)**

Run your own MD simulation

- Chimera - https://www.cgl.ucsf.edu/chimera/docs/ContributedSoftware/md/md.html

- File → Fetch by ID → 1zik

Chimera Animations

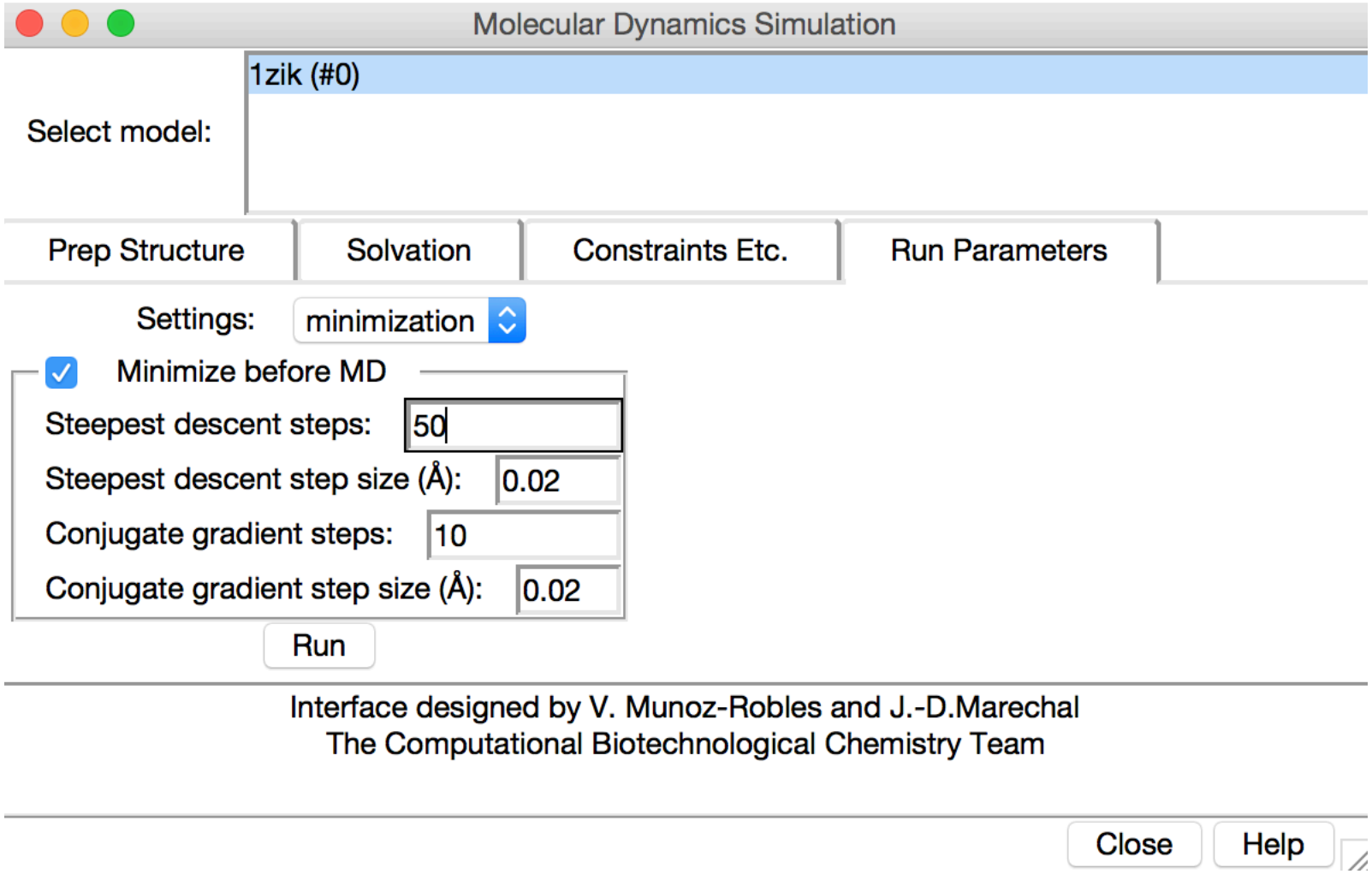
- movie record ; turn y 3 120 ; wait 120 ; movie stop ; movie encode output ~/Desktop/turn.mov bitrate 10000

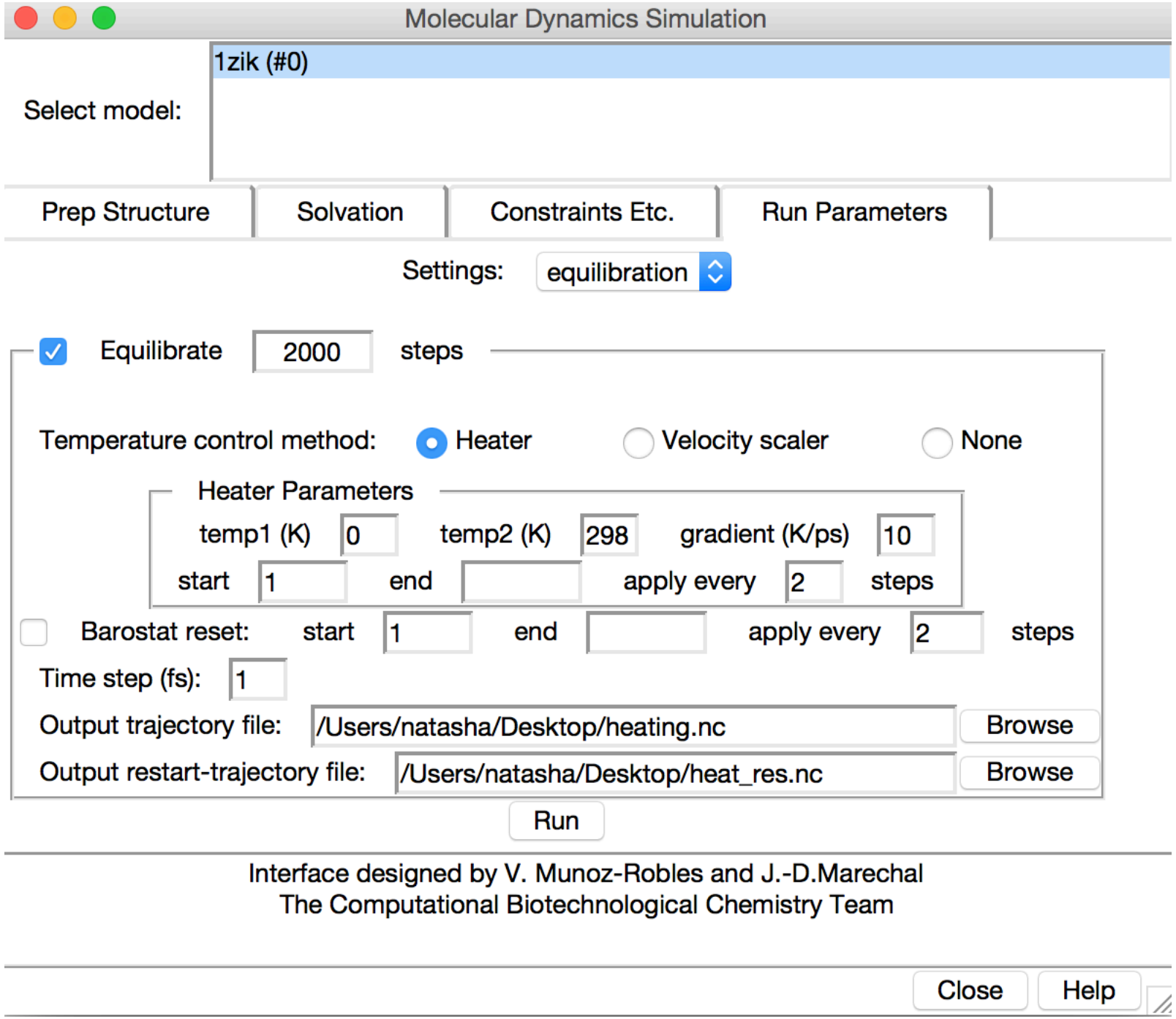
- movie record ; rock y 4 68 ; wait ; rock x 4 68 ; wait ; movie stop ; movie encode output ~/Desktop/rock.mov

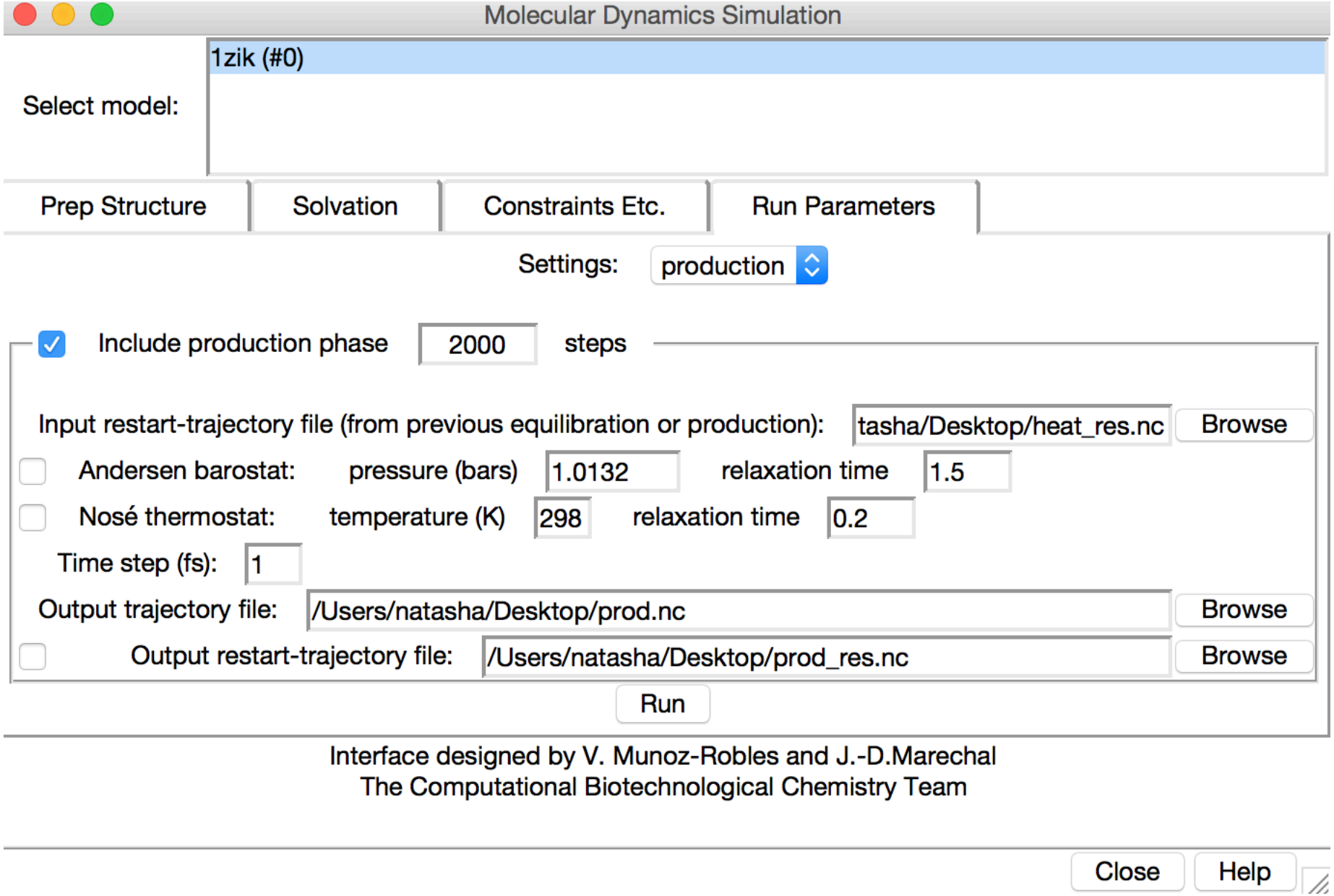
Run your own MD simulation

- Chimera - https://www.cgl.ucsf.edu/chimera/docs/ContributedSoftware/md/md.html

- File → Fetch by ID → 1zik
- Tools → MD/Ensemble Analysis → Molecular Dynamics Simulation


Molecular Dynamics Simulation
Select model:
1zik (#0)
Prep Structure
Solvation
Constraints Etc.
Run Parameters
Settings:
minimization
Minimize before MD
Steepest descent steps:
50
Steepest descent step size (Å):
0.02
Conjugate gradient steps:
10
Conjugate gradient step size (Å):
0.02
Run
Interface designed by V. Munoz-Robles and J.-D.Marechal
The Computational Biotechnological Chemistry Team
Close
Help


Molecular Dynamics Simulation
Select model:
1zik (#0)
Prep Structure
Solvation
Constraints Etc.
Run Parameters
Settings:
equilibration
Equilibrate
2000
steps
Temperature control method:
Heater
Velocity scaler
None
Heater Parameters
temp1 (K)
0
temp2 (K)
298
gradient (K/ps)
10
start
1
end
apply every
2
steps
Barostat reset:
start
1
end
apply every
2
steps
Time step (fs):
1
Output trajectory file:
/Users/natasha/Desktop/heating.nc
Browse
Output restart-trajectory file:
/Users/natasha/Desktop/heat_res.nc
Browse
Run
Interface designed by V. Munoz-Robles and J.-D.Marechal
The Computational Biotechnological Chemistry Team
Close
Help


Molecular Dynamics Simulation
Select model:
1zik (#0)
Prep Structure
Solvation
Constraints Etc.
Run Parameters
Settings:
production
Include production phase
2000
steps
Input restart-trajectory file (from previous equilibration or production):
tasha/Desktop/heat_res.nc
Browse
Andersen barostat:
pressure (bars)
1.0132
relaxation time
1.5
Nosé thermostat:
temperature (K)
298
relaxation time
0.2
Time step (fs):
1
Output trajectory file:
/Users/natasha/Desktop/prod.nc
Browse
Output restart-trajectory file:
/Users/natasha/Desktop/prod_res.nc
Browse
Run
Interface designed by V. Munoz-Robles and J.-D.Marechal
The Computational Biotechnological Chemistry Team
Close
Help

Run your own MD simulation

- Chimera - https://www.cgl.ucsf.edu/chimera/docs/ContributedSoftware/md/md.html

- File → Fetch by ID → 1zik
- Tools → MD/Ensemble Analysis → Molecular Dynamics Simulation

- Use defaults!

- Run parameters → Run
  - Add hydrogens - OK
  - Assign charges for minimize - OK

Analyse an MD run: H-bonds over time

- Chimera

Chimera Tutorials Index

space

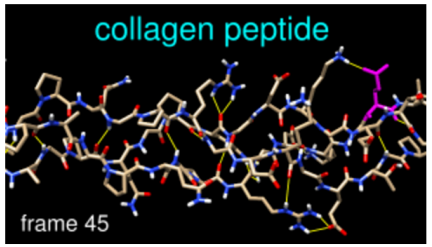
Trajectory and Ensemble Analysis Tutorial

This tutorial focuses on visualization and analysis of molecular dynamics (MD) trajectories and other structural ensembles with the **MD Movie** tool. Part 1 uses an MD trajectory of a collagen peptide, and Part 2 uses an NMR ensemble of Met-enkephalin.

Part 1 - Collagen Peptide

We will view an MD trajectory of the nonmutant collagen peptide described in:

> Severity of osteogenesis imperfecta and structure of a collagen-like peptide modeling a lethal mutation site. Radmer RJ, Klein TE. *Biochemistry*. 2004 May 11;43(18):5314-23.



(Thanks to the authors for providing the data!) To follow along, download the data files:

- leap.top - **Amber** parameter/topology file
- md01.crd - **Amber** trajectory file
- collagen.meta - metafile specifying these input files for **MD Movie**

On **Windows/Mac**, click the **chimera** icon; on **UNIX**, start Chimera from the system prompt:

```
unix: chimera
```

- https://www.cgl.ucsf.edu/chimera/current/docs/UsersGuide/tutorials/ensembles2.html

Analyse an MD run: H-bonds over time

"A better understanding of the details of collagen structure, dynamics, and hydrogen bond networks will improve our ability to predict the physicochemical properties that contribute to the stability of collagen molecules, or lack thereof, and the severity of a single-point mutation."

Biochemistry **2004,** *43,* 5314−5323

Severity of Osteogenesis Imperfecta and Structure of a Collagen-like Peptide Modeling a Lethal Mutation Site†

Randall J. Radmer and Teri E. Klein*

Department of Genetics, School of Medicine, Stanford University, Stanford, California 94305

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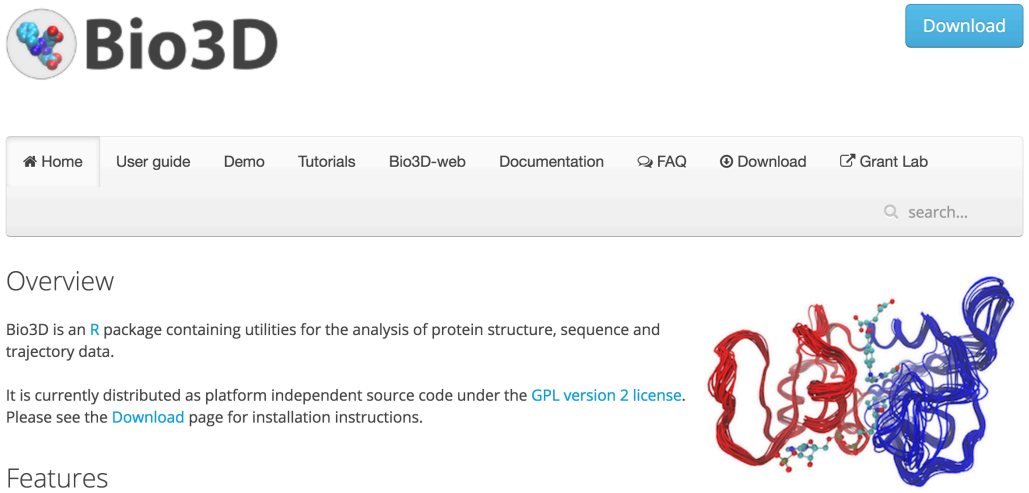
ABSTRACT: We show that there are correlations between the severities of osteogenesis imperfecta (OI) phenotypes and changes in the residues near the mutation site. Our results show the correlations between the severity of various forms of the inherited disease OI and alteration of residues near the site of OI causing mutations. Among our many observed correlations are particularly striking ones between the presence of nearby proline residues and lethal mutations, and the presence of nearby alanines residues and nonlethal mutations. We investigated the possibility that these correlations have a structural basis using molecular dynamics simulations of collagen-like molecules designed to mimic the site of a lethal OI mutation in collagen type I. Our significant finding is that interchain hydrogen bonding is greatly affected by variations in residue type. We found that the strength of hydrogen bond networks between backbone atoms on different chains depends on the local residue sequence and is weaker in proline-rich regions of the molecule. We also found that an alanine at a site near an OI mutation causes less structural disruption than a proline, and that residue side chains also form interchain hydrogen bonds with frequencies that are dependent on residue type. For example, arginine side chains form strong hydrogen bonds with the backbone of the subsequent peptide chain, while lysine and glutamine less frequently form similar hydrogen bonds. This decrease in the observed hydrogen bond frequency correlates with a decrease in the experimentally determined thermal stability. We contrasted general structural properties of model collagen peptides with and without the mutation to examine the effect of the single-point mutation on the surrounding residues.

Manipulate your pdb file

- RStudio - https://www.rstudio.com/products/rstudio/download/
- Bio3D - http://thegrantlab.org/bio3d/tutorials/installing-bio3d

- Tutorial: http://thegrantlab.org/bio3d/tutorials/structure-analysis
- -renumbering, changing chain identifiers, identify binding site residues



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