utmb Health

SCSB
The Sealy Center for Structural Biology and Molecular Biophysics

Molecular Dynamics Flexible Fitting

NAMD MDFF
https://www.ks.uiuc.edu/Research/mdff/

VMD
https://www.ks.uiuc.edu/Research/vmd/

Cryo-EM Map

Atomic Coordinates – PDB File, Homology model,
https://www.rcsb.org/

Molecular Mechanics Force Field

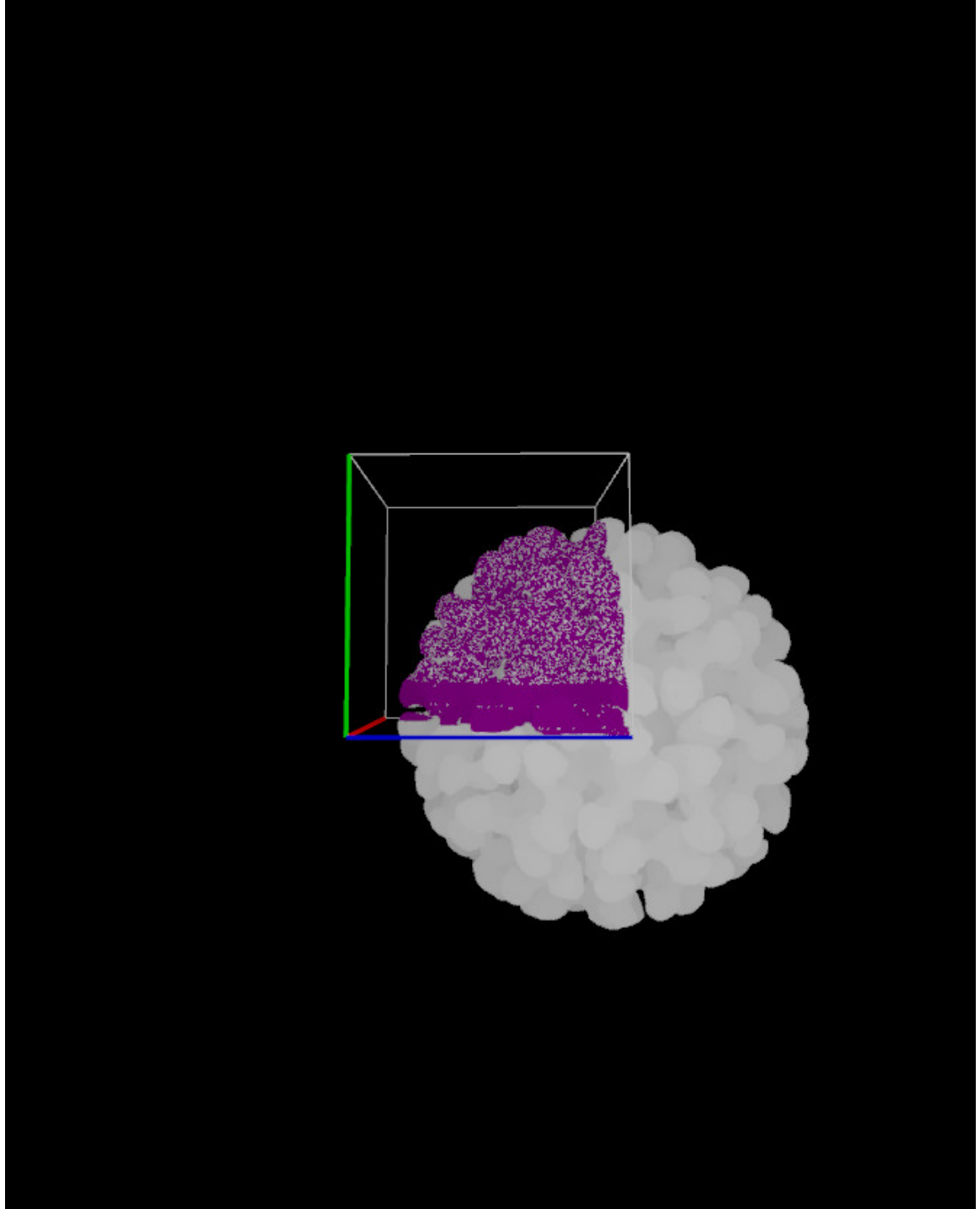
CHARMM36 - http://mackerell.umaryland.edu/charmm_ff.shtml

Amber - http://ambermd.org/AmberModels.php

$$U_{Total} = U_{bonded} + U_{nonbonded}$$
$$U_{bonded} = U_{bond} + U_{angle} + U_{dihedral}$$
$$U_{nonbonded} = U_{van\ der\ Waals} + U_{electrostatic}$$

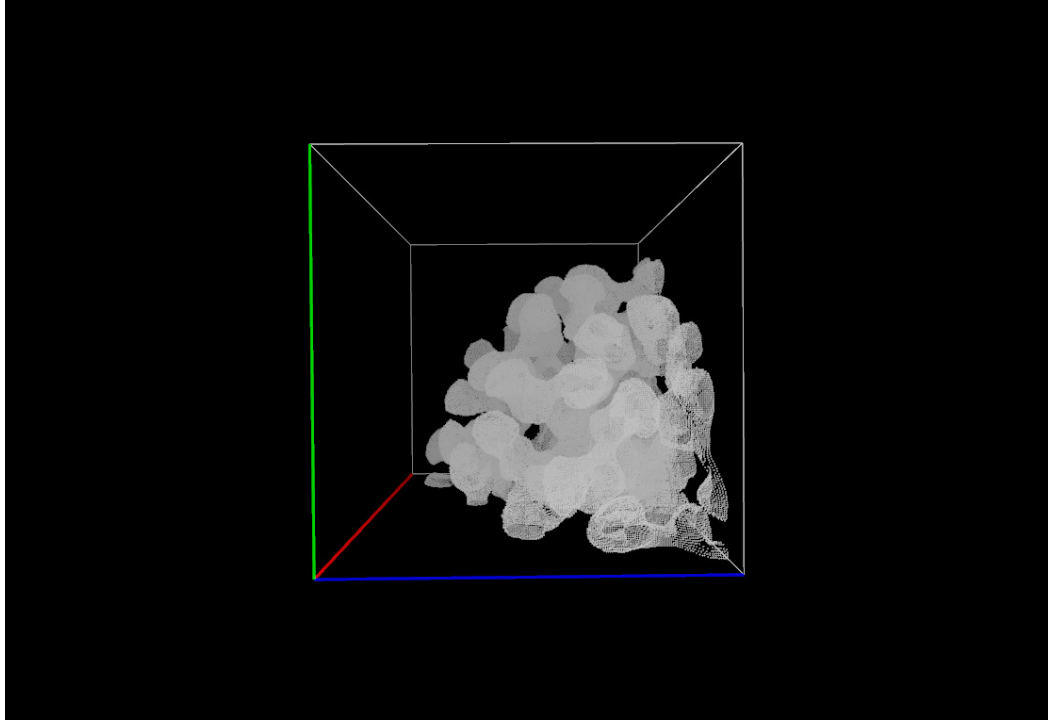
MDFF

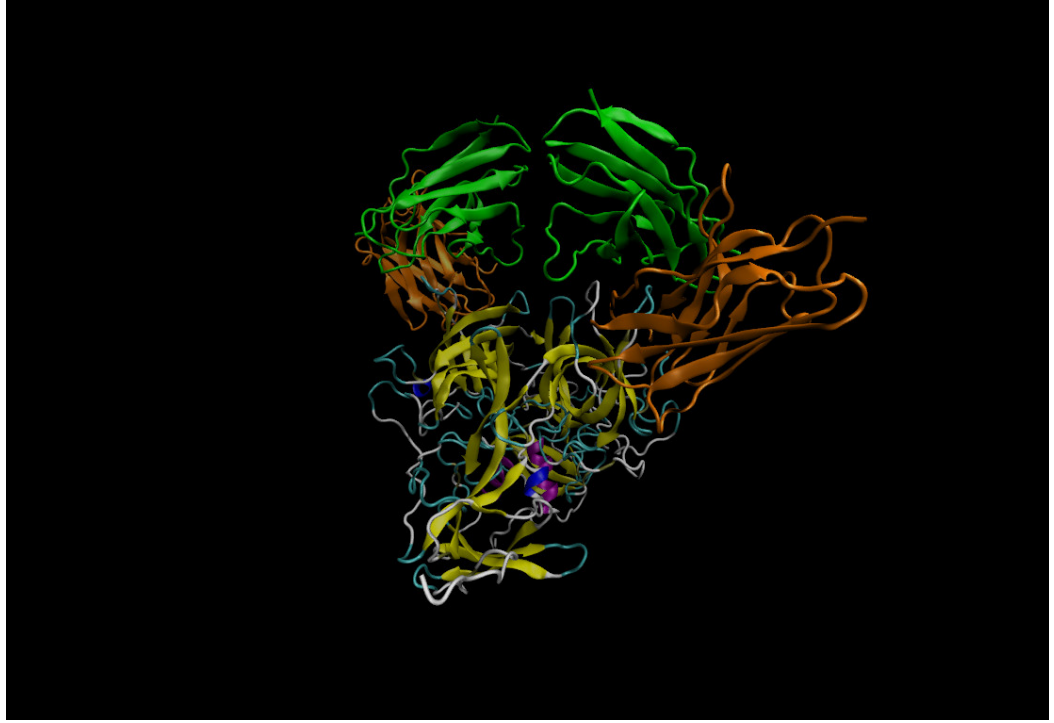
$$U_{Total} = U_{bonded} + U_{nonbonded} + U_{EM}$$



griddx
gridpdb

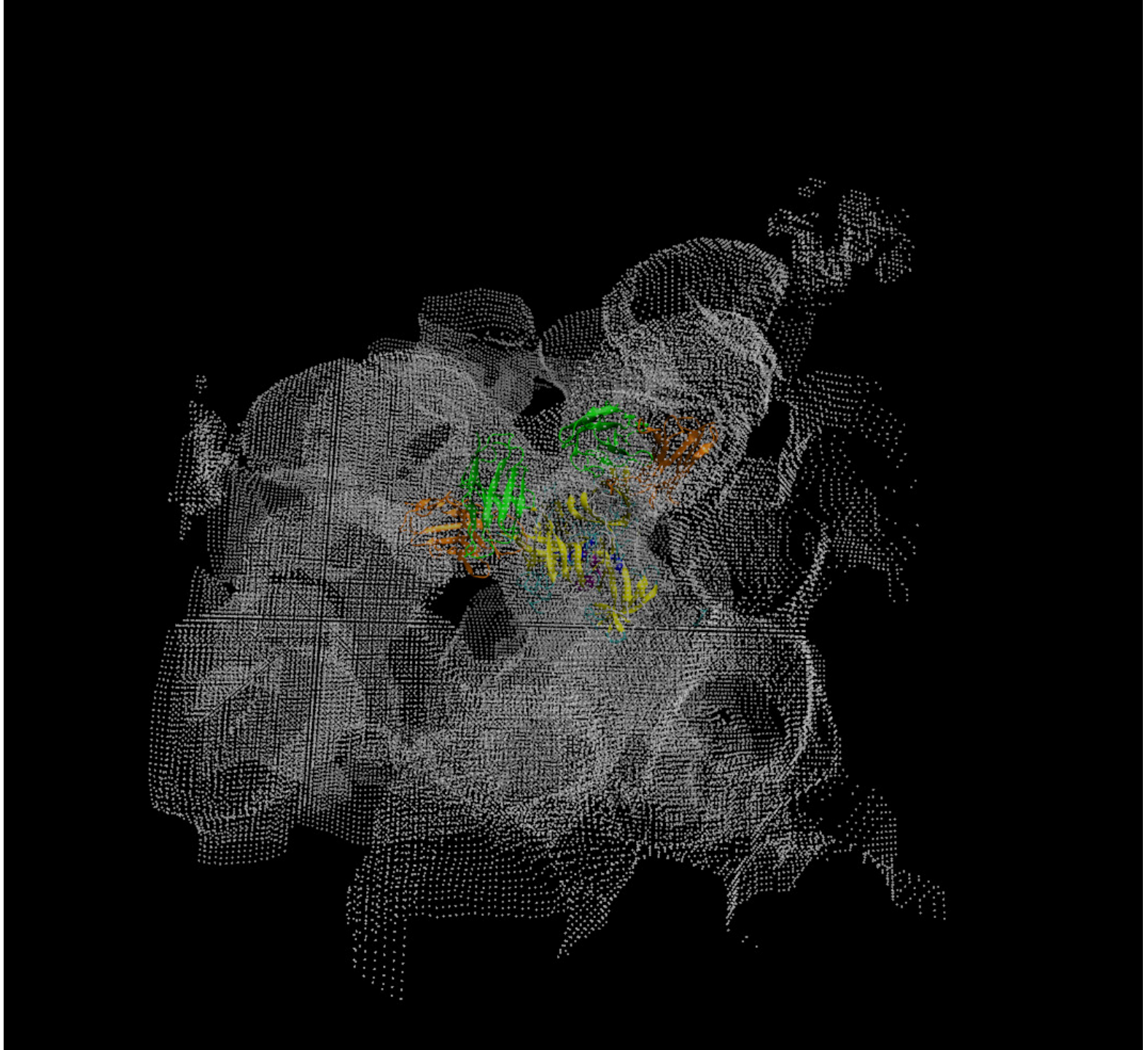
U_{em}





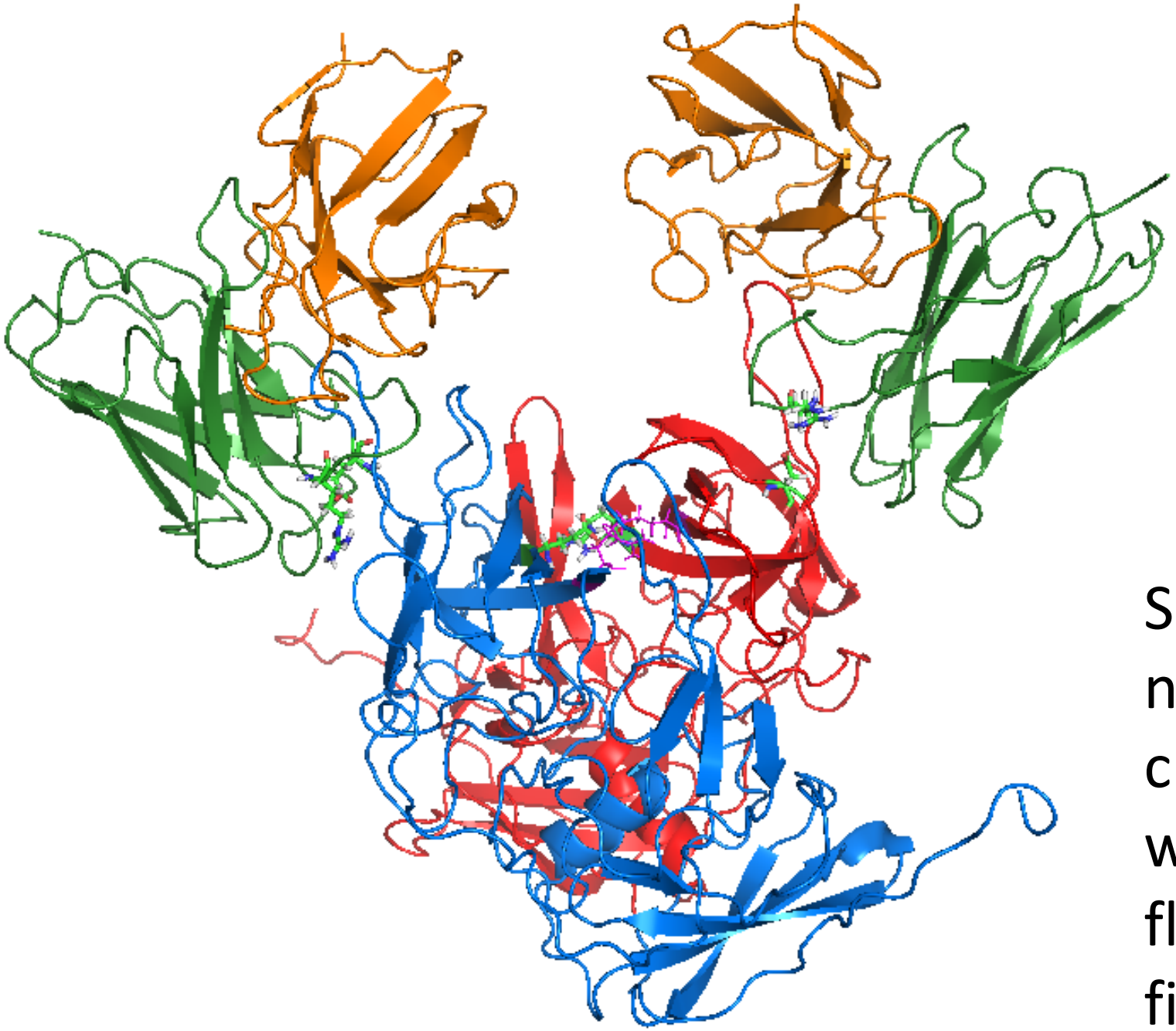
Rigid body fit with Situs
https://situs.biomachina.org/fguide.html

VMD ssrestraints – extra bonds to maintain secondary structure



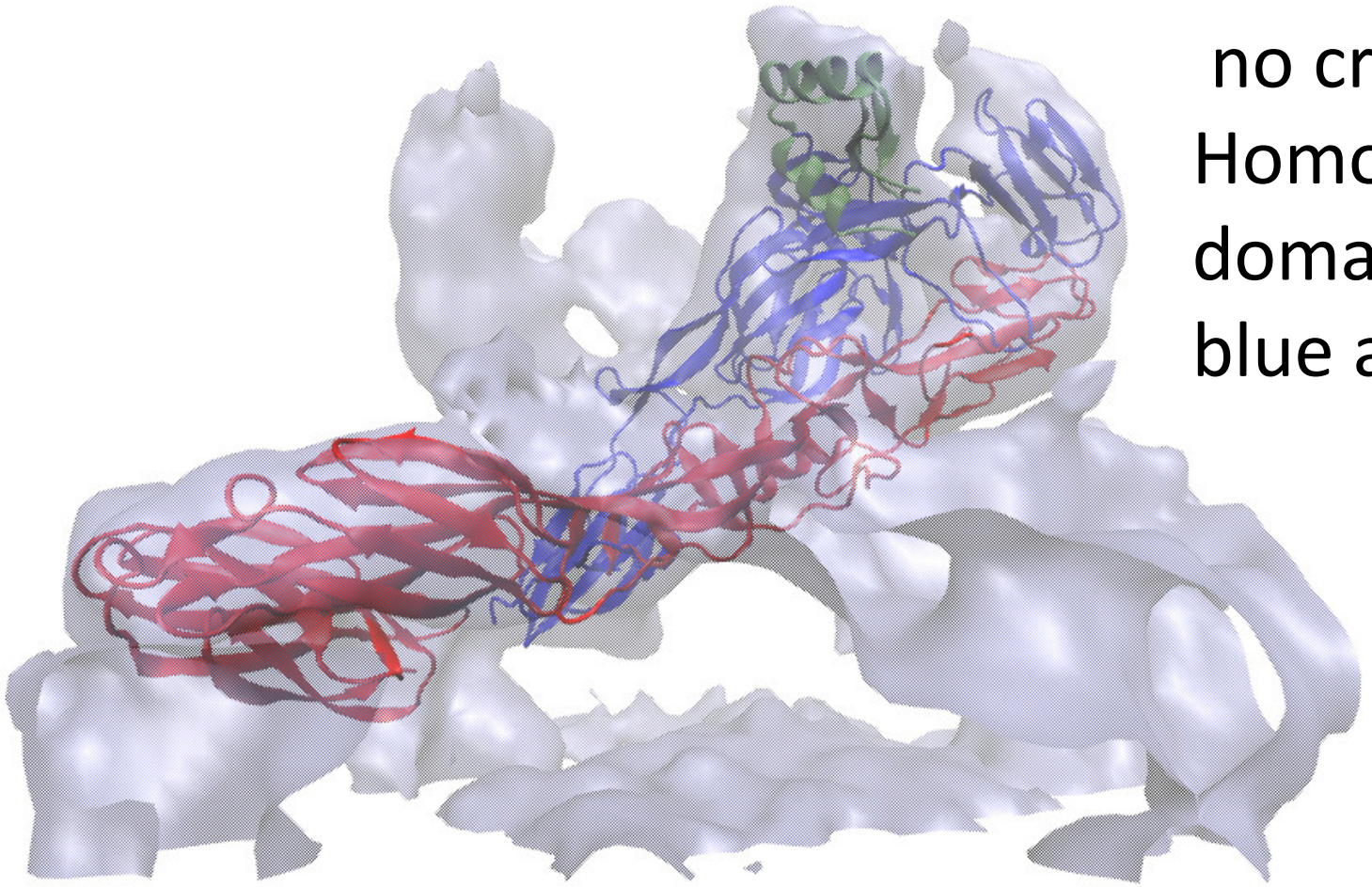
3D grid of the mrc file

PDB ID: 3lq6
Two mutation sites shown as yellow and mauve balls that affect binding



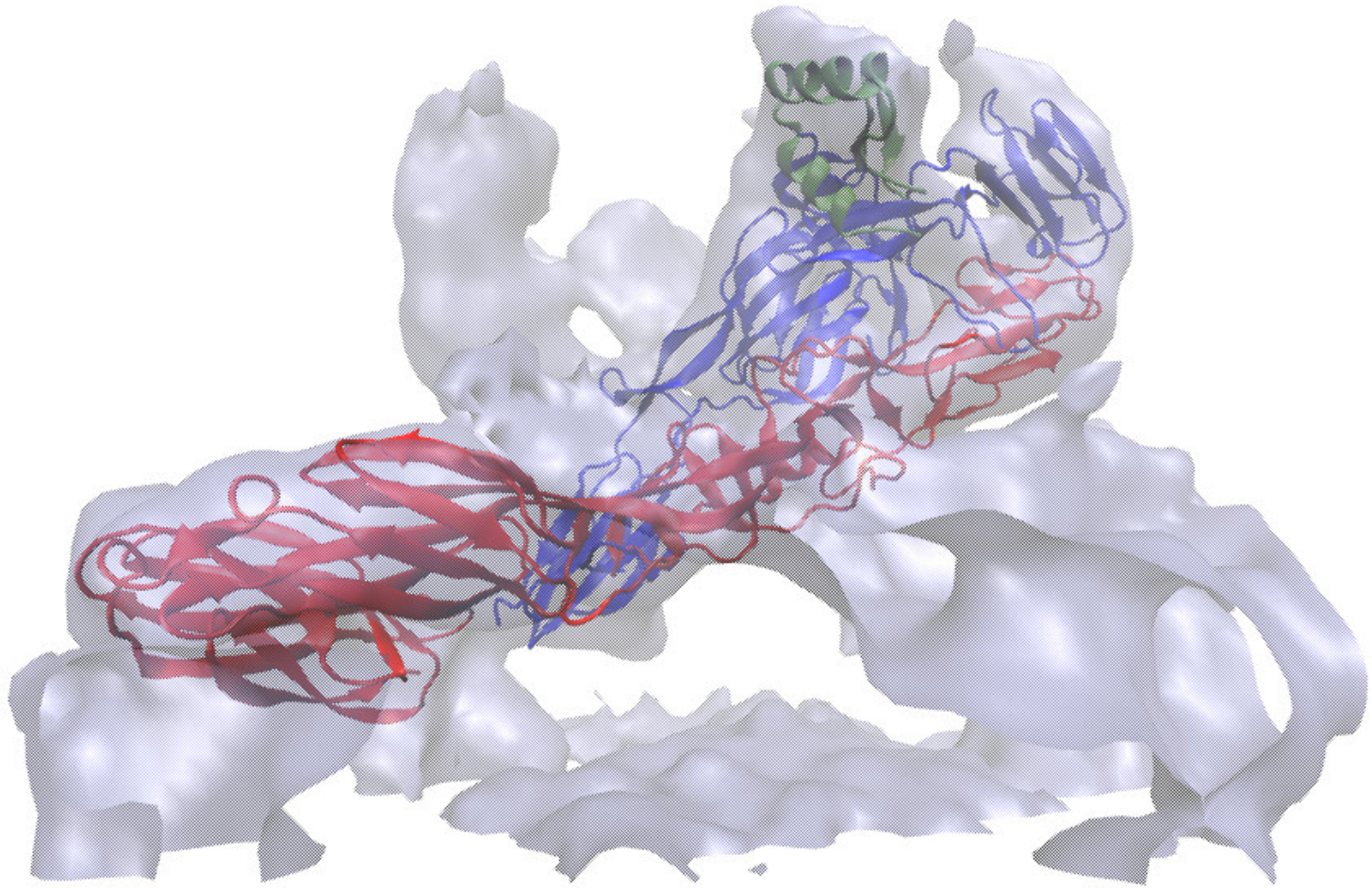
Salt bridge network changes with flexible fitting

Chain A	Chain B	Cryo-EM reconstruction	MDFF Fitted R Å	V339I Fitted R Å
A:ARG 231[OD2]	B:ARG228[N]			
A:ARG 238[NE]	B:ASP 313[OD2]	3.32		
A:ARG 238[NH1]	B:ASP 313[OD2]		3.7	
A:ASP 255[OD1]	B:LYS 345[NZ]			3.97
A:ASP 313[OD1]	B:ARG 238[NH1]			
A:ASP 313[OD2]	B:ARG 238[NE]	3.14		
A:ASP 313[OD2]	B:ARG 238[NH1]	3.28		
A:ASP 313[OD2]	B:ARG 238[NH2]	3.93		
A:GLU 338[OE1]	B:ARG 396[NE]			
A:GLU 338[OE1]	B:ARG 396[NH1]	2.76		
A:GLU 338[OE1]	B:ARG 396[NH2]	3.65		
A:GLU 338[OE2]	B:ARG 396[NH1]	2.63		
A:GLU 338[OE2]	B:ARG 396[NH2]	3.12		3.44
A:GLU 338[OE2]	B:ARG 437[NH2]	2.75		
A:LYS 349[NZ]	B:ASP 440[OD2]			3.98
A:ARG 396[NH1]	B:GLU 338[OE1]	2.85		3.92
A:ARG 396[NH1]	B:GLU 338[OE2]	3.16		3.31
A:ARG 396[NH2]	B:GLU 338[OE2]	2.58		3.57
A:ARG 396[NH2]	B:GLU 338[OE1]	3.81	2.98	
A:ARG 396[NE]	B:GLU 338[OE2]			



Second system
no crystal structure
Homology model of 3 domain shown in red, blue and green

Order of rigid body fit matters. If this structure is fitted first it could go anywhere in the map and not in the volume where it should be located

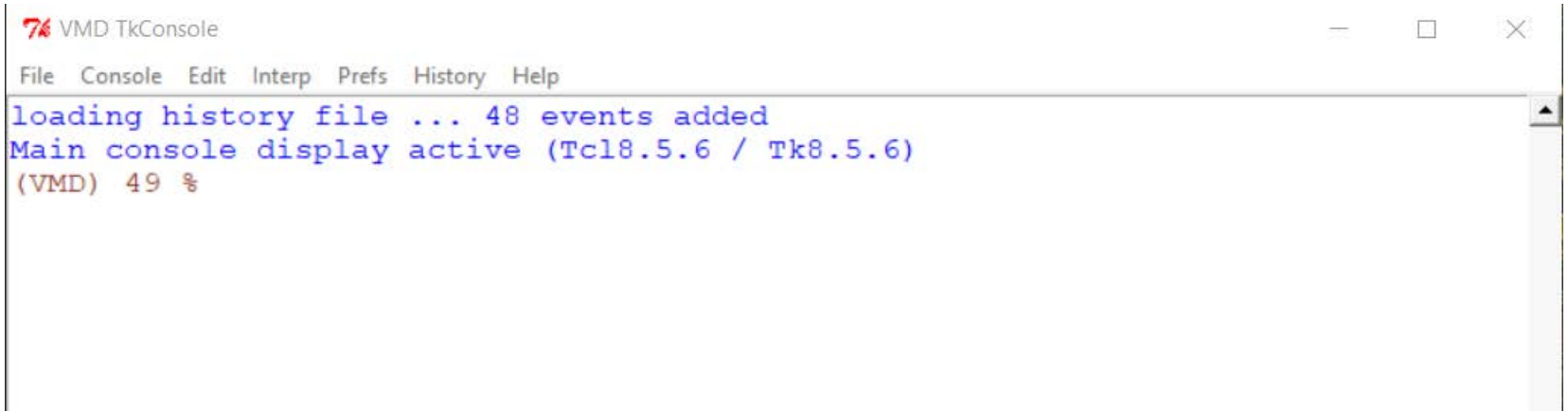


Norovirus MNV Example

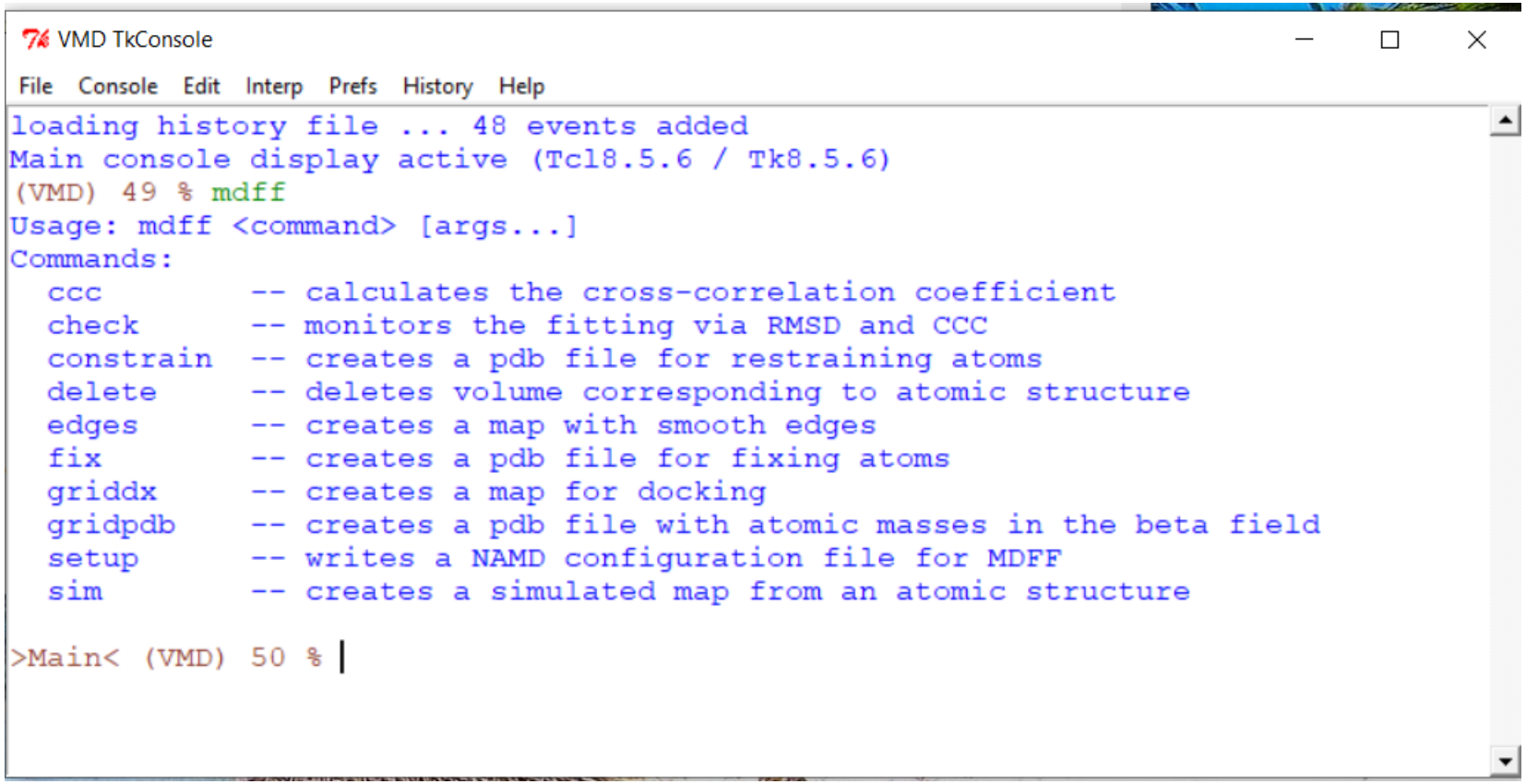
RCSB PDBID: 3lq6

Cryo-EM Map – MNV-Fab-trimmed.mrc

Commands will be executed in VMD's Tk console



VMD – use mdff griddx to generate 3D grid of map

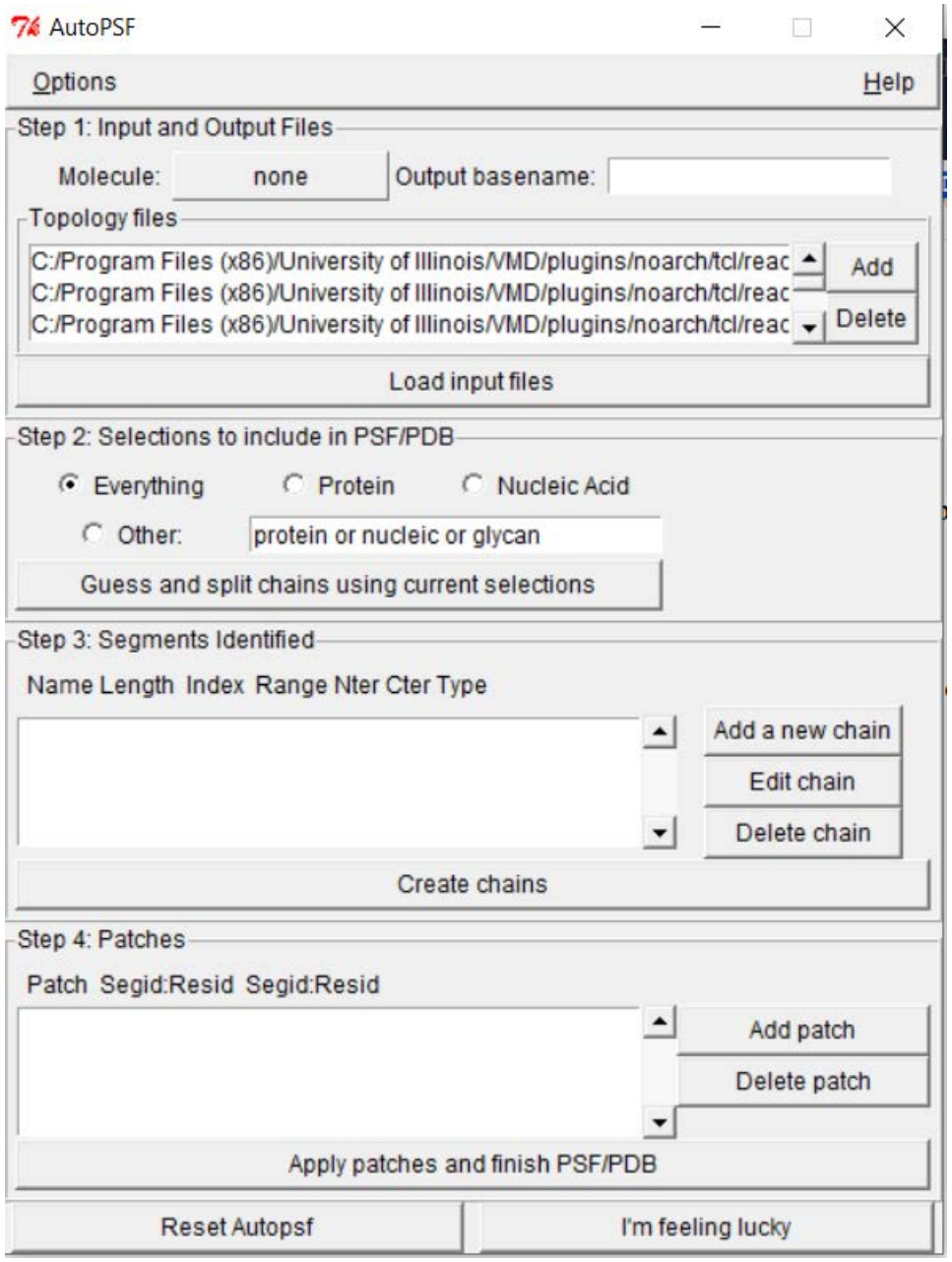


Type the following command in the Tk console

mdff griddx –i MNV-Fab-trimmed.mrc –o MNV-Fab-trimmed.dx

Use VMD to add hydrogens to the starting structure and generate a PSF file

3lq6-psf.pdb
3lq6-psf.psf



Rigid body fit the PDB to the map

If using Situs:

```
colores MNV-Fab-trimmed.mrc 3lq6-psf.pdb –res 9.0 –powell
```

Rename the best structure

```
cp col_best_001.pdb 3lq6-psf-docked.pdb
```

Use VMD - Prepare the initial structure and files

PDB file containing the per-atom scaling factors for U_{EM}

```
mdff gridpdb –psf 3lq6-psf.psf –pdb
3lq6-psf-docked.pdb –o 3lq6-grid.pdb
```

Use VMD - Prepare the initial structure and files

Define secondary structure restraints

ssrestraints –psf 3lq6-psf.psf –pdb 3lq6-psf-docked.pdb –o 3lq6-extrabonds.txt -hbonds

Use VMD - Prepare the initial structure and files

Retain peptide bonds to cis/trans configuration as well as chiral centers

First – need to load the pdb and psf files

```
mol new 3lq6-psf.psf

mol addfile 3lq6-psf-docked.pdb
```

Use VMD - Prepare the initial structure and files

Use cispeptide plugin to restrain cis peptide bonds to current cis/trans config.

```
cispeptide restrain –o 3lq6-extrabonds-cispeptide.txt
```

Use VMD - Prepare the initial structure and files

Use chirality plugin to restrain chiral centers

chirality restrain –o 3lq6-extrabonds-chirality.txt

Use VMD - Prepare the initial structure and files

Generate NAMD mdff configuration file. For this simple example only 5000 steps will be used and a grid scale of 0.3

```
mdff setup –o 3lq6 –psf 3lq6-psf.psf
-pdb 3lq6-psf-docked.pdb
-griddx MNV-Fab-trimmed.dx
-gridpdb 3lq6-grid.pdb
-extrab {3lq6-extrabonds.txt 3lq6-extrabonds-
cispeptide.txt 3lq6-extrabonds-chirality.txt}
-gscale 0.3 –numsteps 5000
```

Two files will be created:

`3lq6-step1.namd`

`mdff-template.namd`

Run the mdff calculation with NAMD

```
namd2 3lq6-step1.namd >& 3lq6-step1.log
```

Use VMD to view results

The final structure will be in the file named 3lq6-step1.coor. Compare the 2 structures

```
mol new 3lq6-psf.psf

mol addfile 3lq6-step1.coor type namdbin

mol new 3lq6-psf-docked.pdb
```


TACC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