MD II

Atomistic Modeling of Small-Angle Scattering Data Using SASSIE-web

September 21-23, 2016

Advanced Photon Source

Argonne National Laboratory, Argonne, IL

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Today: “Run, Analyze, Build”

9:00 AM - 10:00 AM: **MD II: NAMD MINIMIZATION to DYNAMICS & Analysis**

10:00 AM - 10:15 AM: Break

10:15 AM - Noon: Lab III

Noon - 1:00 PM: LUNCH & Group Photograph (1:00 PM)

1:00 PM - 1:30 PM: MMC & SASSIE Overview

1:30 PM - 3:00 PM: Lab IV: SASSIE-web Quick Start

3:00 - 3:15 PM: Break

3:15 - 5:00 PM: LAB V SASSIE-web Workflows

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Barriers: BUILD; EQUILIBRATE; PROPAGATE; ANALYZE

What software package(s) and force-fields do I use?

Starting structure?

How do I clean up the structure?

How do I set up a trajectory (**time** or space)?

How do I calculate scattering observables correctly?

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Overview

PDB + PSF + INPUT FILE : run a NAMD trajectory

Minimization (in vacuo)
Adding water & ions
PBC & PME
Fixed atom methods and control
Molecular dynamics parameters
IMD (link NAMD with VMD)
Restarting a simulation (continuation)

Output files

Analysis of MD & Connection to NS

Testing for equilibration
Neutron scattering (dynamics)
Connection MD trajectory to S(q,w)

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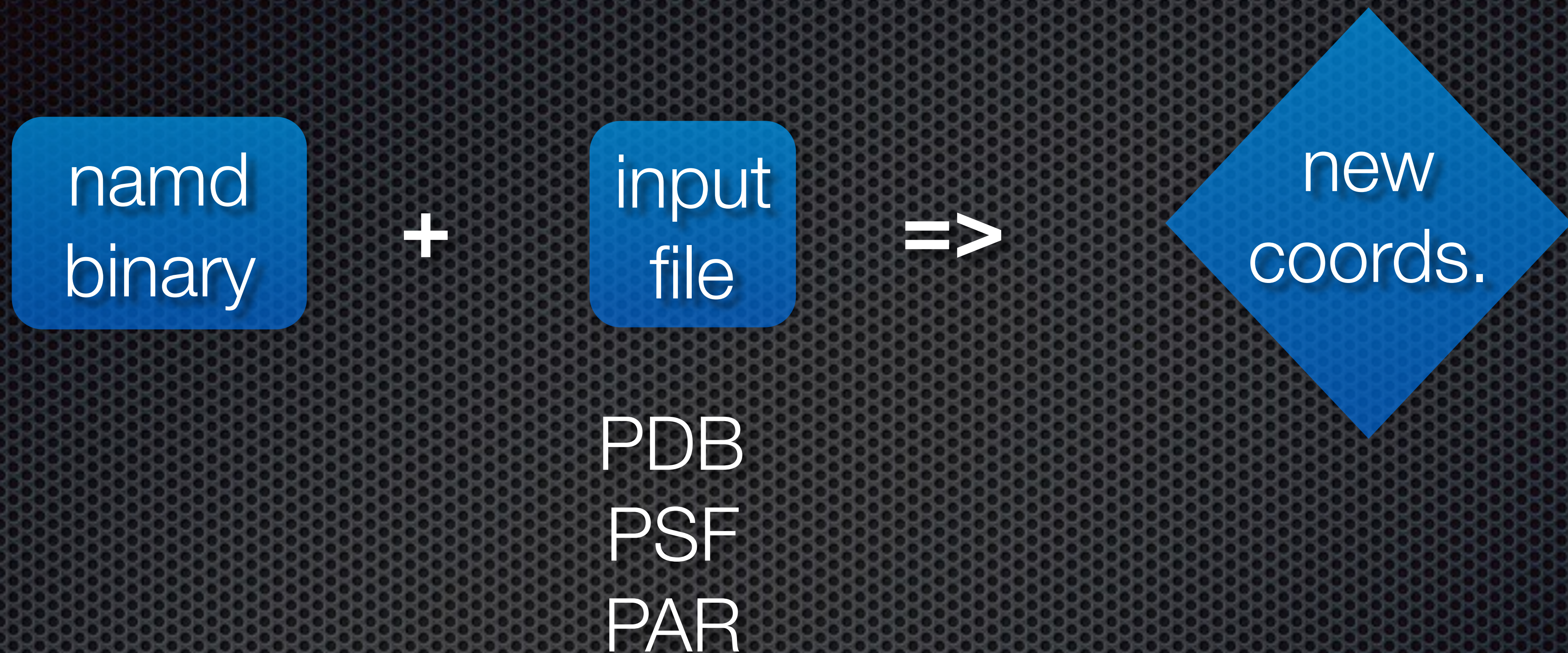
NAMD II



MD parameters

1. Minimization
2. MD (time)
3. Directed MD

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NAMD INPUT FILE

```
# sample NAMD configuration file for Minimization

# molecular system
coordinates             output/new_icln.pdb
structure               output/new_icln.psf
temperature             300

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# output

outputname              output/min0
binaryoutput            no

# run control

minimize                1000
```

PDB

PSF

PAR

MD parameters

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RUNNING NAMD

USAGE (unix prompt):

Start a run:

>namd2 min0 >& min0.out &

Check status:

>tail -90f min0.out

Energy Minimization

run name	run_0		
reference pdb	Browse... dbd.pdb	or Browse server	*Local*: dbd.pdb
input filename (dcd or pdb)	Browse... dbd.pdb	or Browse server	*Local*: dbd.pdb
PSF file name	Browse... dbd.psf	or Browse server	*Local*: dbd.psf
output file name (dcd)	min_run_0.dcd		
number of minimization steps	100		
number of processors	1		
keep run output files	no		
DCD write frequency	20		
run type	minimization		

Advanced Input

Check Box for Advanced Input

Submit   Reset to default values

Multi-processor run:

>charmrun ++local ++p 2 /usr/local/bin/namd/namd2 min0 >& min0.out &

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NAMD OUTPUT (MIN.)

```
. . .

BRACKET: 0.00207889 7.0816 -1821.94 1646.18 8572.11
TIMING: 1000  CPU: 24.2692, 0.0240947/step  Wall: 24.3809, 0.0241311/step, 0
hours remaining, 650704 kB of memory in use.
ETITLE:      TS           BOND          ANGLE          DIHED          IMPRP
ELECT            VDW       BOUNDARY           MISC        KINETIC
TOTAL           TEMP         TOTAL2         TOTAL3        TEMPAVG
PRESSURE      GPRESSURE         VOLUME       PRESSAVG      GPRESSAVG

ENERGY:     1000      4561.4004      3396.5872       881.8814        15.2681
-148982.9533     16811.5791         0.0000         0.0000         0.0000
-123316.2371         0.0000   -123316.2371   -123316.2371         0.0000
-4162.6459     -4161.2347    366289.0000     -4162.6459     -4161.2347


WRITING EXTENDED SYSTEM TO OUTPUT FILE AT STEP 1000
WRITING COORDINATES TO OUTPUT FILE AT STEP 1000
WRITING VELOCITIES TO OUTPUT FILE AT STEP 1000
==========================================
WallClock: 302.991364  CPUTime: 309.270966  Memory: 690456 kB
```

Plotting (Lab III)

Check status:

>tail -90f min0.out | grep TOL

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MINIMIZATION NOTES

Large negative energies (especially electrostatic and VDW)

Local minimum ...

“Minimized structures” often fail when you use min. coords for MD runs

Topologically unlikely structures can be minimized

Cycle of minimization and short MD (with constraints) may be neccessary

Some convergence issues could indicate a poor structure (coor or PSF).

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SOLVATE

Many tools (GUI & scripts) are available to automatically "dunk" your bio-molecule into a water-box. ---> VMD

The VMD plugin requires that you have a **PSF/ PDB** of your system.

The VMD plugin will generate NEW a PDB/ PSF pair automatically.

Solvate

Input

PSF: /Users/curtisj/tmppp/new_complex.psf Browse

PDB: /Users/curtisj/tmppp/new_complex.pdb Browse

Waterbox Only

Rotate to minimize volume Rotation Increment (deg): 10

Selection for Rotation: all

Output

solvate Browse

Segment ID Prefix: WT

Boundary: 2.4

Box Size:

Min: x: y: z:

Max: x: y: z:

Use Molecule Dimensions

Box Padding:

Min: x: 0 y: 0 z: 0

Max: x: 0 y: 0 z: 0

Use nonstandard solvent

Solvent box PDB:

Solvent box PSF:

Solvent box topology:

Solvent box side length:

Solvent box key selection:

Solvate

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SOLVATE II

Solvate

Input
PSF: new_protein.psf [Browse]
PDB: new_protein.pdb [Browse]
Waterbox Only
Rotate to minimize volume — Rotation Increment (deg): 10
Selection for Rotation: all

Output
solvated_protein [Browse]

Segment ID Prefix: WT
Boundary: 2.4

Box Size:
Min: x: -30 y: -35 z: -32
Max: x: 30 y: 35 z: 32
Use Molecule Dimensions

Box Padding:
Min: x: y: z:
Max: x: y: z:

Use nonstandard solvent
Solvent box PDB:
Solvent box PSF:
Solvent box topology:
Solvent box side length:
Solvent box key selection:

Solvate

path to topology file

path to PDB file

name & path to OUTPUT FILES

YOU pick a segment name

YOU pick MIN dimensions

YOU pick MAX dimensions

Write these down

Measure dimensions w/ VMD and add ~12 Ang. pad (x,y,z +/- 12)

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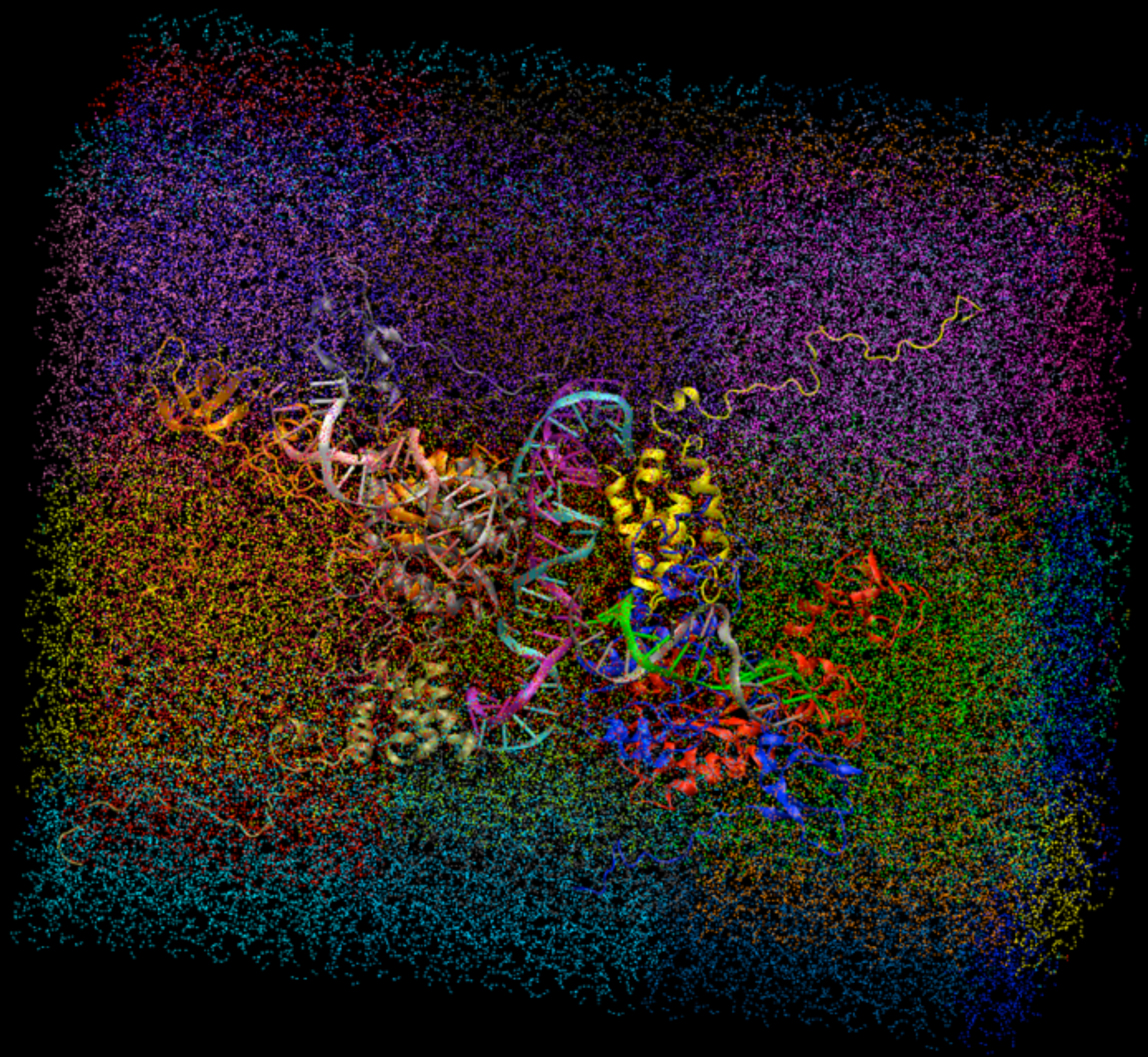
CHRNS NIST



NCNR

SOLVATE II

Solvate

Input

PSF: /Users/curtisj/Desktop/summer_school/ [Browse] ← path to topology file

PDB: /Users/curtisj/Desktop/summer_school/ [Browse] ← path to PDB file

☐ Waterbox Only

☐ Rotate to minimize volume — Rotation Increment (deg): 10

Selection for Rotation: all

Output

solvated_proteinII [Browse] ← name & path to OUTPUT FILES

Segment ID Prefix: WT ← YOU pick a segment name

Boundary: 2.4

Box Size:

	x	y	z
Min:	-30	-35	-32
Max:	30	35	32

☑ Use Molecule Dimensions

Box Padding:

	x	y	z	
Min:	12	12	12	← YOU pick MIN padding
Max:	14	14	14	← YOU pick MAX padding

☐ Use nonstandard solvent

Solvent box PDB:

Solvent box PSF:

Solvent box topology:

Solvent box side length:

Solvent box key selection:

[Solvate]

Write these down

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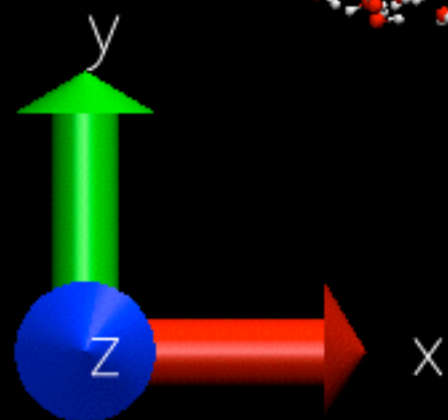
CHRNS NIST


y
z
x

Measure dimensions of final box ("2") graphically via VMD

OR

Use the VMD Console:

```
vmd > set everyone [atomselect top all]
atomselect32
vmd > measure minmax $everyone
{-9.961199989319 -10.5780000687 -14.7969999313}
{59.4099998474 55.422000885 60.5979995728}
```

dx ~ 70
dy ~ 66
dz ~ 76

ADD IONS

Autoionize

Autoionize randomly places ions (NaCl/KCl) in a previously solvated system.

Input

PSF: solvated_proteinII.psf [Browse] ← path to topology file

PDB: solvated_proteinII.pdb [Browse] ← path to PDB file

Output prefix: ionized_solvated_proteinII ← name & path to OUTPUT FILES

Ionic Concentration (defined as (#Na + #Cl)/V)

☐ Concentration (mol/L): 0.5

☐ User defined # Na: 0 # Cl: 0

☑ Neutralize ← choose neutralize

Min. distance from molecule (A): 5

Min. distance between ions (A): 5

Segment ID: ION

☐ Switch to KCl instead of NaCl

[Autoionize]

Write this down

Other options available

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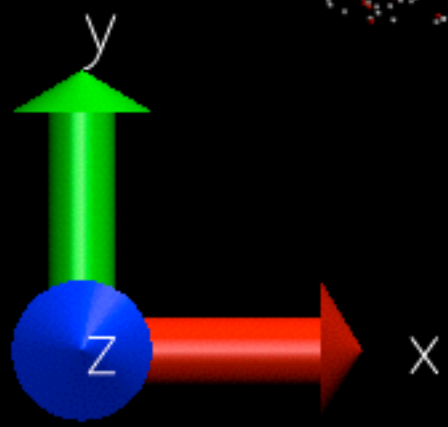
CHRNS NIST



y
z
x

MINIMIZATION NOTES II

Example steps for a solvated protein:

0. **Minimize vacuum structure (w/ restraints?) Then BUILD solvated system.**

1. **Restrain protein atoms (let waters/ions relax)**
2. **Restrain protein backbone (let side-chains and waters/ions relax)**
3. **Restrain secondary structure elements (let loops, etc. relax)**
4. **No restraints**

5. **Start short MD run (10 ps or so)   [[[does it run?]]]**

Number of steps is something YOU need to monitor (1000 to 10000+ steps)

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NAMD INPUT FILE

Now, we need to add to our NAMD input file to handle:

(1) Periodic boundary conditions

(2) Particle Mesh Ewald (PME) for PBC electrostatics

(3) Fixed atoms (for systematic “relaxation” and future needs)

--> TCL/PYTHON/PERL/MDTOOLS . . .

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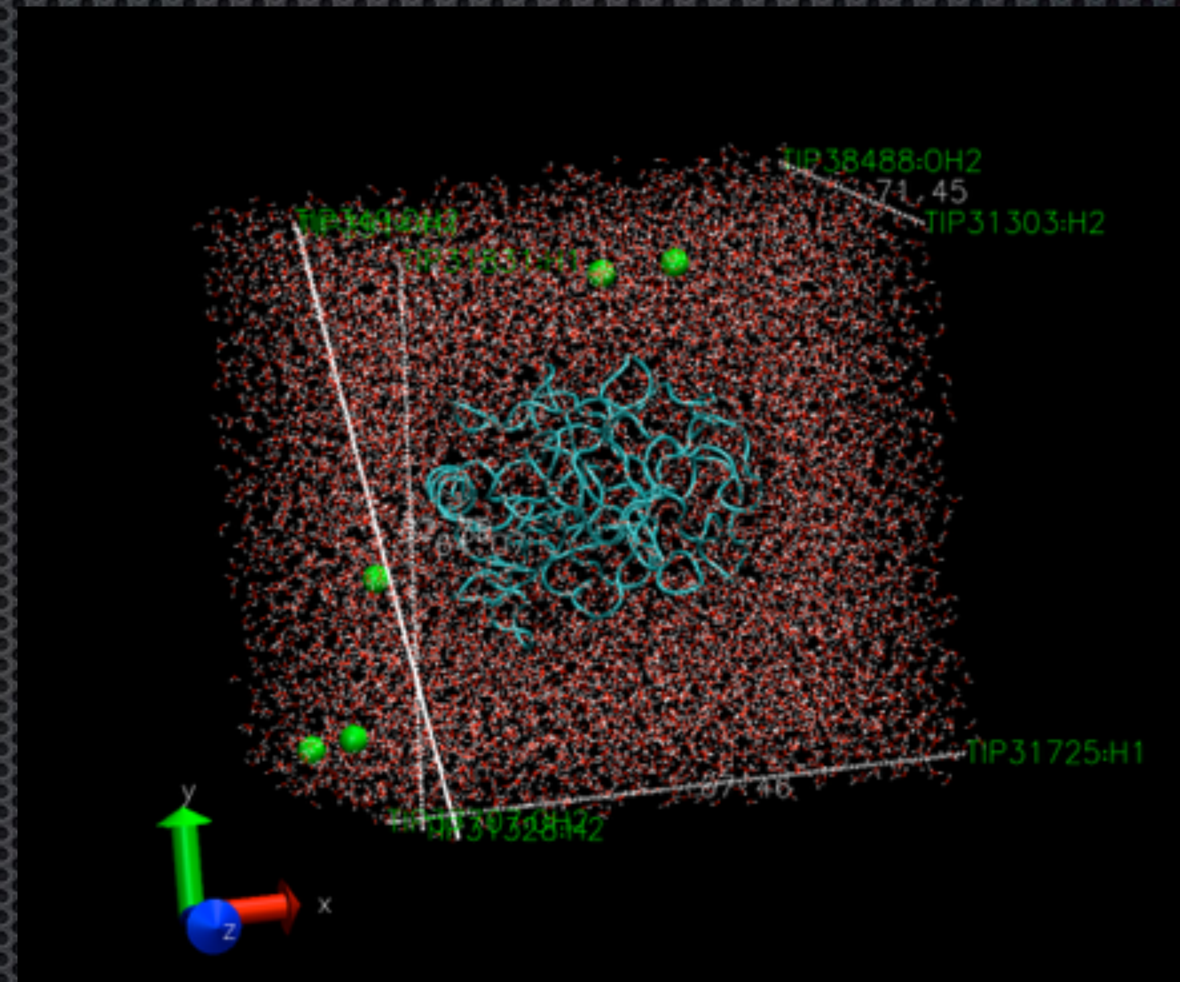
PBC

Measure box (x,y,z)
add values to the diagonal

```
. . .

# pbc

cellBasisVector1          71.0 0.0 0.0
cellBasisVector2          0.0 67.0 0.0
cellBasisVector3          0.0 0.0 77.0

. . .

# run control

minimize                  1000
```



It is generally prudent to add 1-2 Angstroms in each dimension . . . NPT

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PME

```
Our test-case box (ionized_solvated_proteinII):

cellBasisVector1        68.0 0.0 0.0
cellBasisVector2        0.0 65.0 0.0
cellBasisVector3        0.0 0.0 72.0
```

```
. . .

# pme

PME                     on
PMEGridSpacing          1.0

. . .

# run control

minimize                 1000
```

Particle mesh is a 3D grid which the system charge is distributed. From this charge, F (and U) are calculated.

Grid spacing should be > 1/Angstrom

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Fixed Atoms

```
. . .

# restraints

fixedAtoms              on
fixedAtomsForces        on
fixedAtomsFile          output/fixed_protein_atoms.pdb
fixedAtomsCol           B


. . .

# run control

minimize                1000
```

These specific commands:

(1) apply fixed atoms “on”

(2) instruct forces to be included FROM these atoms

(3) define the file that is used to tell NAMD which atoms are fixed

(4) define the COLUMN in the file that defines the fixed atoms:

1.00 == FIXED
0.00 == NOT FIXED

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Fixed Atoms

```
. . .

# restraints

fixedAtoms                    on
fixedA
fixedA  File    put/fixed_pr  n_at    pdb
fixedA  sCol

. . .

# run control

minimize                      1000
```

```
REMARK original generated coordinate pdb file
ATOM      1   OH2  TIP3   0      0.000    0.000    0.000   0.00   1.00      TIP3  O
ATOM      2   H1   TIP3   0      1.000    0.000    0.000   0.00   0.00      TIP3  H
ATOM      3   H2   TIP3   0     -0.326    0.946    0.000   0.00   0.00      TIP3  H
END
```

OCC. BETA

These specific commands:

(1) apply fixed atoms “on”

(2) instruct forces to be included FROM these atoms

(3) define the file that is used to tell NAMD which atoms are fi

(4) define the COLUMN in the file that defines the fixed atoms:

1.00 == FIXED
0.00 == NOT FIXED

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Fixed Atoms III

OCC. BETA

```
REMARK original generated coordinate pdb file
ATOM      1  OH2 TIP3    0       0.000   0.000   0.000  0.00  1.00      TIP3 O
ATOM      2  H1  TIP3    0       1.000   0.000   0.000  0.00  0.00      TIP3 H
ATOM      3  H2  TIP3    0      -0.326   0.946   0.000  0.00  0.00      TIP3 H
END
```

The PDB files that "we" have created so far have not specifically done anything to the "beta" (or "occupancy") fields.

Ways to alter the field (all protein atoms, side-chains, backbone, etc.):

(1) by hand or via clever unix command-line scripting (grep/sed/awk etc.)

(2) using a interpretative language using stand-alone script (python, tcl, perl)

(3) using other open source tools

(4) tcl within VMD (python with VMD is an option)

Useful in MANY ways!

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Tangent . . . tcl & vmd

Steps WE are going to take:

(1) Open ionized_solvated_proteinII.pdb (hydrolayse in water box + 6 CLA)

(2) Set all BETA values -> 0.00

(3) Set all protein atoms BETA values -> 1.00 then save coords to a new PDB file (**fixed_protein_atoms.pdb**) ; reset all BETA -> 0.00

(4) Set all backbone protein atoms BETA values -> 1.00 then save coords to a new PDB file (**fixed_backbone_atoms.pdb**) ; reset all BETA -> 0.00

(5) Set all alpha helix AND beta sheet and backbone protein atoms BETA values -> 1.00 then save coords to a new PDB file (**fixed_secondary_structure_atoms.pdb**)

THREE SPECIFIC PDB FILES FOR SUCCESSIVE MINIMIZATION RUNS

only BETA is used from these files

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New PDB I

With the **ionized_solvated_proteinII.pdb** file open in VMD . . . at the console type:

```
vmd > set everyone [atomselect top all]
atomselect32

vmd > $everyone set beta 0.00

vmd > set sel1 [atomselect top "protein"]
atomselect33

vmd > $sel1 set beta 1.00

vmd > $everyone writepdb fixed_protein_atoms.pdb

Info) Opened coordinate file fixed_protein_atoms.pdb for writing.
Info) Finished with coordinate file fixed_protein_atoms.pdb.
```

New PDB I

With the **ionized_solvated_proteinII.pdb** file open in VMD . . . at the console type:

```
vmd > set everyone [atomselect top all]
atomselect32

vmd > $everyone set beta 0.00

vmd > set sel1 [atomselect top "protein"]
atomselect33

vmd > $sel1 set beta 1.00

vmd > $everyone writepdb fixed_protein_atoms.pdb

Info) Opened coordinate file fixed_protein_atoms.pdb for writing.
Info) Finished with coordinate file fixed_protein_atoms.pdb.
```

```
. . .
ATOM   3159 HD21 ASN H 245       6.667  19.714  34.439  1.00  1.00      HYDR H
ATOM   3160 HD22 ASN H 245       7.401  21.295  34.329  1.00  1.00      HYDR H
ATOM   3161  OH2 TIP3W   1      50.279  45.432  40.650  1.00  0.00      WT1  O
ATOM   3162  H1  TIP3W   1      51.097  45.825  40.462  1.00  0.00      WT1  H
. . .
```

New PDB II

Now, lets only restrain the backbone atoms . . . continuing (not starting over) . . . at the console type:

```
vmd > $everyone set beta 0.00

vmd > set sel2 [atomselect top "protein and backbone"]
atomselect34

vmd > $sel2 set beta 1.00

vmd > $everyone writepdb fixed_backbone_atoms.pdb

Info) Opened coordinate file fixed_backbone_atoms.pdb for writing.
Info) Finished with coordinate file fixed_backbone_atoms.pdb.
```

New PDB II

Now, lets only restrain the backbone atoms . . . continuing (not starting over) . . . at the console type:

```
vmd > $everyone set beta 0.00

vmd > set sel2 [atomselect top "protein and backbone"]
atomselect34

vmd > $sel2 set beta 1.00

vmd > $everyone writepdb fixed_backbone_atoms.pdb

Info) Opened coordinate file fixed_backbone_atoms.pdb for writing.
Info) Finished with coordinate file fixed_backbone_atoms.pdb.
```

```
. . .

ATOM     38  N   GLY H  18      38.970  21.537  14.910  1.00  1.00      HYDR N
ATOM     39  HN  GLY H  18      39.749  21.183  15.426  1.00  0.00      HYDR H
ATOM     40  CA  GLY H  18      39.254  22.674  14.040  1.00  1.00      HYDR C
ATOM     41  HA1 GLY H  18      38.753  22.465  13.105  1.00  0.00      HYDR H
ATOM     42  HA2 GLY H  18      40.331  22.734  13.964  1.00  0.00      HYDR H
ATOM     43  C   GLY H  18      38.747  24.007  14.556  1.00  1.00      HYDR C
ATOM     44  O   GLY H  18      38.573  24.944  13.781  1.00  1.00      HYDR O

. . .
```

New PDB III

Now, lets only restrain the backbone atoms on conserved secondary structure elements. . . continuing (not starting over) . . . at the console type:

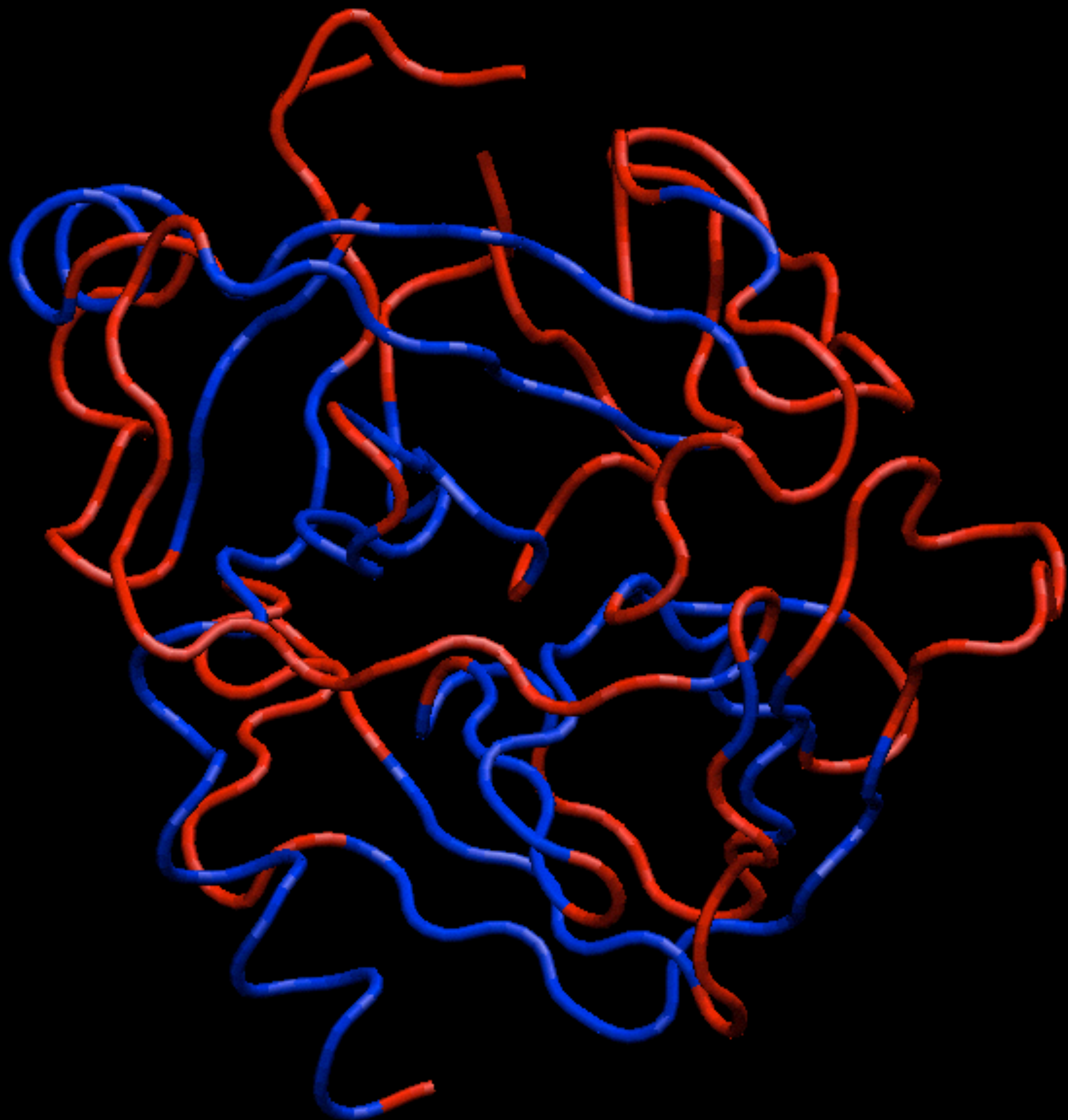
```
vmd > $everyone set beta 0.00

vmd > set sel3 [atomselect top "((protein and helix) or (protein and
betasheet)) and backbone"]
atomselect35

vmd > $sel3 set beta 1.00

vmd > $everyone writepdb fixed_secondary_structure_atoms.pdb

Opened coordinate file fixed_secondary_structure_atoms.pdb for writing.
Info) Finished with coordinate file fixed_secondary_structure_atoms.pdb.
```



MINIMIZATION in steps . . .

1. **Restrain protein atoms (let waters/ions relax)**
2. **Restrain protein backbone (let side-chains and waters/ions relax)**
3. **Restrain secondary structure elements (let loops, etc. relax)**
4. **No restraints**

Let's look at the successive NAMD input files (highlighting changes)

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NAMD INPUT FILE: smin0

```
# sample NAMD configuration file for Minimization w/ fixed atoms, PBC, PME

# molecular system
coordinates             output/ionized_solvated_proteinII.pdb
structure               output/ionized_solvated_proteinII.psf
temperature             300

# restraints

fixedAtoms              on
fixedAtomsForces        on
fixedAtomsFile          output/fixed_protein_atoms.pdb
fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# pbc

cellBasisVector1        71.0 0.0 0.0
cellBasisVector2        0.0 67.0 0.0
cellBasisVector3        0.0 0.0 77.0
```

```
fixedAtomsFile          output/fixed_protein_atoms.pdb
fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# pbc

cellBasisVector1        71.0 0.0 0.0
cellBasisVector2        0.0 67.0 0.0
cellBasisVector3        0.0 0.0 77.0

# electrostatics

PME                     on
PMEGridSpacing          1.0

# output

outputname              output/smin_fixed_protein
binaryoutput            no

# run control

minimize                1000
```

USAGE (unix prompt):

Start a run:

```
>namd2 smin0 >&  smin0.out &
```

Check status:

```
>tail -90f smin0.out
```

Multi-processor run:

```
>charmrun ++local ++p 2  /usr/local/bin/namd/namd2 smin0 >&  smin0.out &
```

NAMD INPUT FILE II: smin1

```
# sample NAMD configuration file for Minimization w/ fixed atoms, PBC, PME

# molecular system
coordinates             output/smin_fixed_protein.coor
structure               output/ionized_solvated_proteinII.psf
temperature             300

# restraints

fixedAtoms              on
fixedAtomsForces        on
fixedAtomsFile          output/fixed_backbone_atoms.pdb
fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# pbc

cellBasisVector1        71.0 0.0 0.0
cellBasisVector2        0.0 67.0 0.0
cellBasisVector3        0.0 0.0 77.0
```

```
fixedAtomsFile          output/fixed_backbone_atoms.pdb
fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# pbc

cellBasisVector1        71.0 0.0 0.0
cellBasisVector2        0.0 67.0 0.0
cellBasisVector3        0.0 0.0 77.0

# electrostatics

PME                     on
PMEGridSpacing          1.0

# output

outputname              output/smin_fixed_backbone
binaryoutput            no

# run control

minimize                1000
```

USAGE (unix prompt):

Start a run:

```
>namd2 smin1 >&  smin1.out &
```

Check status:

```
>tail -90f smin1.out
```

Multi-processor run:

```
>charmrun ++local ++p 2  /usr/local/bin/namd/namd2 smin1 >&  smin1.out &
```

NAMD INPUT FILE III: smin2

```
# sample NAMD configuration file for Minimization w/ fixed atoms, PBC, PME

# molecular system
coordinates              output/smin_fixed_backbone.coor
structure                output/ionized_solvated_proteinII.psf
temperature              300

# restraints

fixedAtoms               on
fixedAtomsForces         on
fixedAtomsFile           output/fixed_secondary_structure_atoms.pdb
fixedAtomsCol            B

# force field
paratypecharmm           on
parameters               /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                  scaled1-4
1-4scaling               1.0
switching                on
switchdist               10
cutoff                   12

# pbc

cellBasisVector1         71.0 0.0 0.0
cellBasisVector2         0.0 67.0 0.0
cellBasisVector3         0.0 0.0 77.0
```

```
fixedAtomsFile          output/fixed_secondary_structure_atoms.pdb
fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# pbc

cellBasisVector1        71.0 0.0 0.0
cellBasisVector2        0.0 67.0 0.0
cellBasisVector3        0.0 0.0 77.0

# electrostatics

PME                     on
PMEGridSpacing          1.0

# output

outputname              output/smin_fixed_secondary
binaryoutput            no

# run control

minimize                1000
```

USAGE (unix prompt):

Start a run:

```
>namd2 smin2 >&  smin2.out &
```

Check status:

```
>tail -90f smin2.out
```

Multi-processor run:

```
>charmrun ++local ++p 2  /usr/local/bin/namd/namd2 smin2 >&  smin2.out &
```

NAMD INPUT FILE IV: smin3

```
# sample NAMD configuration file for Minimization w/ fixed atoms, PBC, PME

# molecular system
coordinates             output/smin_fixed_secondary.coor
structure               output/ionized_solvated_proteinII.psf
temperature             300

# restraints

fixedAtoms              off
#fixedAtomsForces        on
#fixedAtomsFile          output/fixed_secondary_structure_atoms.pdb
#fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# pbc

cellBasisVector1        71.0 0.0 0.0
cellBasisVector2        0.0 67.0 0.0
cellBasisVector3        0.0 0.0 77.0
```

```
#fixedAtomsFile           output/fixed_secondary_structure_atoms.pdb
#fixedAtomsCol            B

# force field
paratypecharmm            on
parameters                /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                   scaled1-4
1-4scaling                1.0
switching                 on
switchdist                10
cutoff                    12

# pbc

cellBasisVector1          71.0 0.0 0.0
cellBasisVector2          0.0 67.0 0.0
cellBasisVector3          0.0 0.0 77.0

# electrostatics

PME                       on
PMEGridSpacing            1.0

# output

outputname                output/smin3
binaryoutput              no

# run control

minimize                  1000
```

USAGE (unix prompt):

Start a run:

```
>namd2 smin3 >&  smin3.out &
```

Check status:

```
>tail -90f smin3.out
```

Multi-processor run:

```
>charmrun ++local ++p 2  /usr/local/bin/namd/namd2 smin3 >&  smin3.out &
```

MINIMIZATION: analysis

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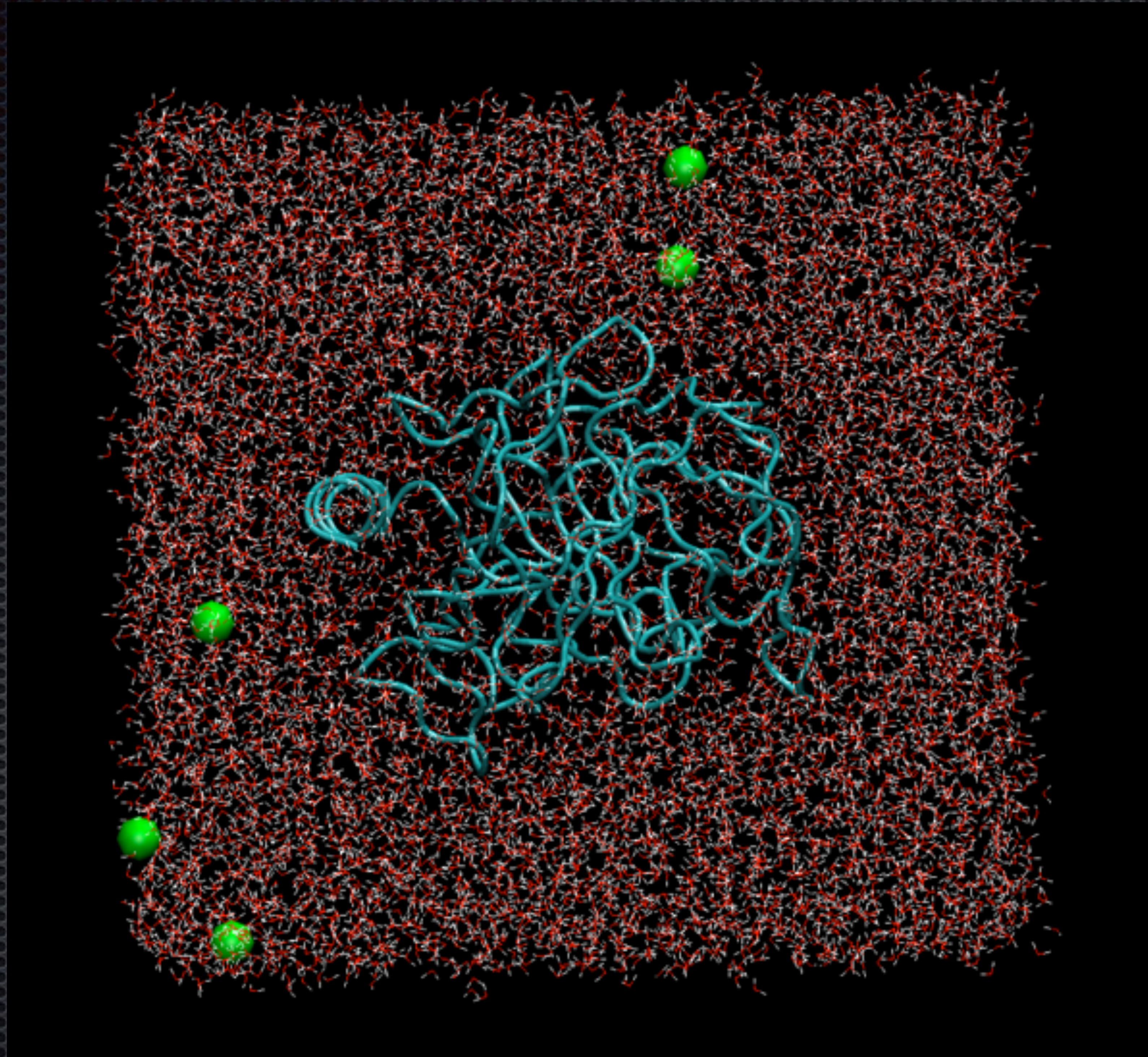
MINIMIZATION: analysis



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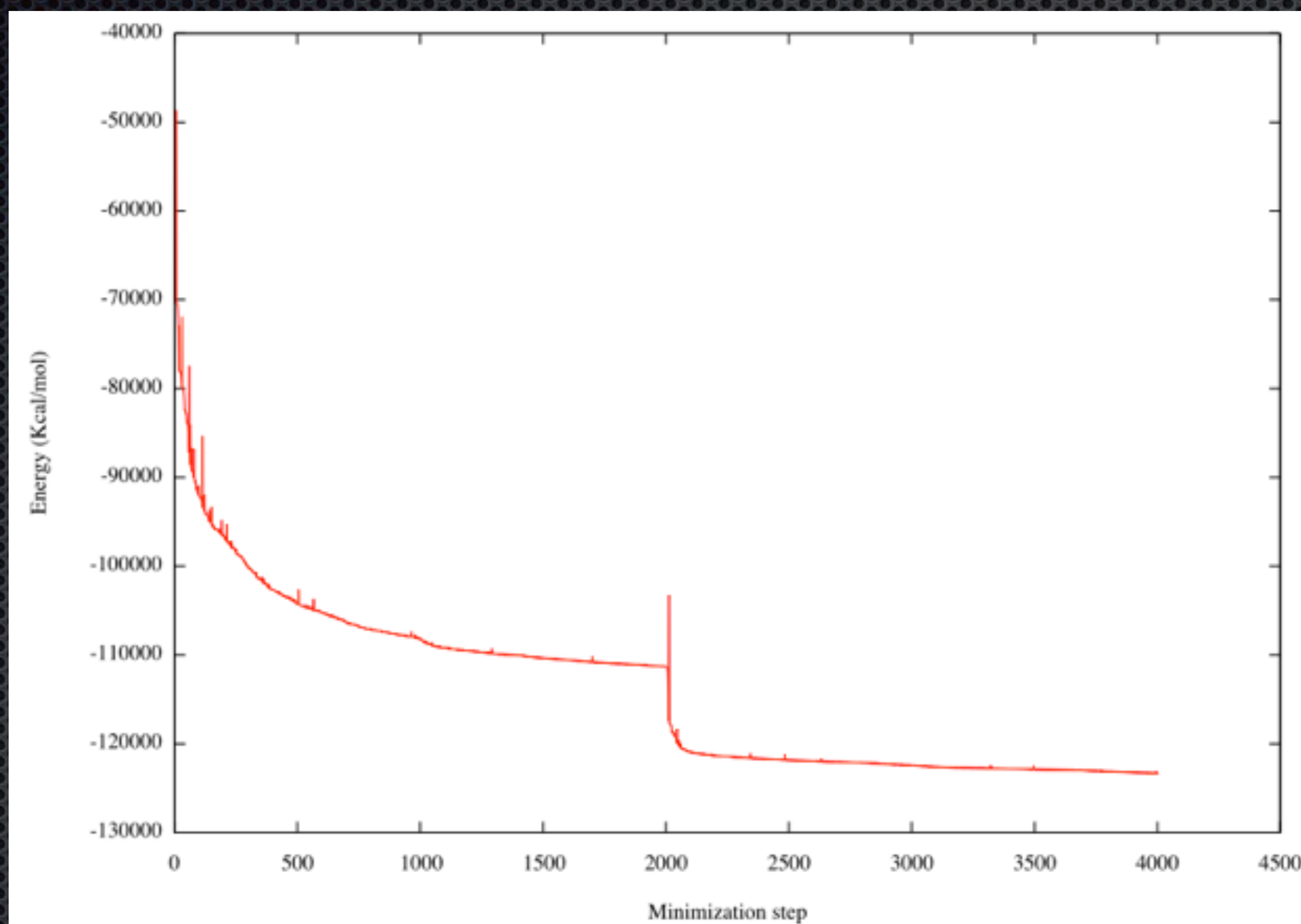
MINIMIZATION: analysis

Plot created from the "output" files : (you will create these in your lab section later today)



Cowboys: they sometimes SKIP the restrained minimizations . . . your mileage will vary.

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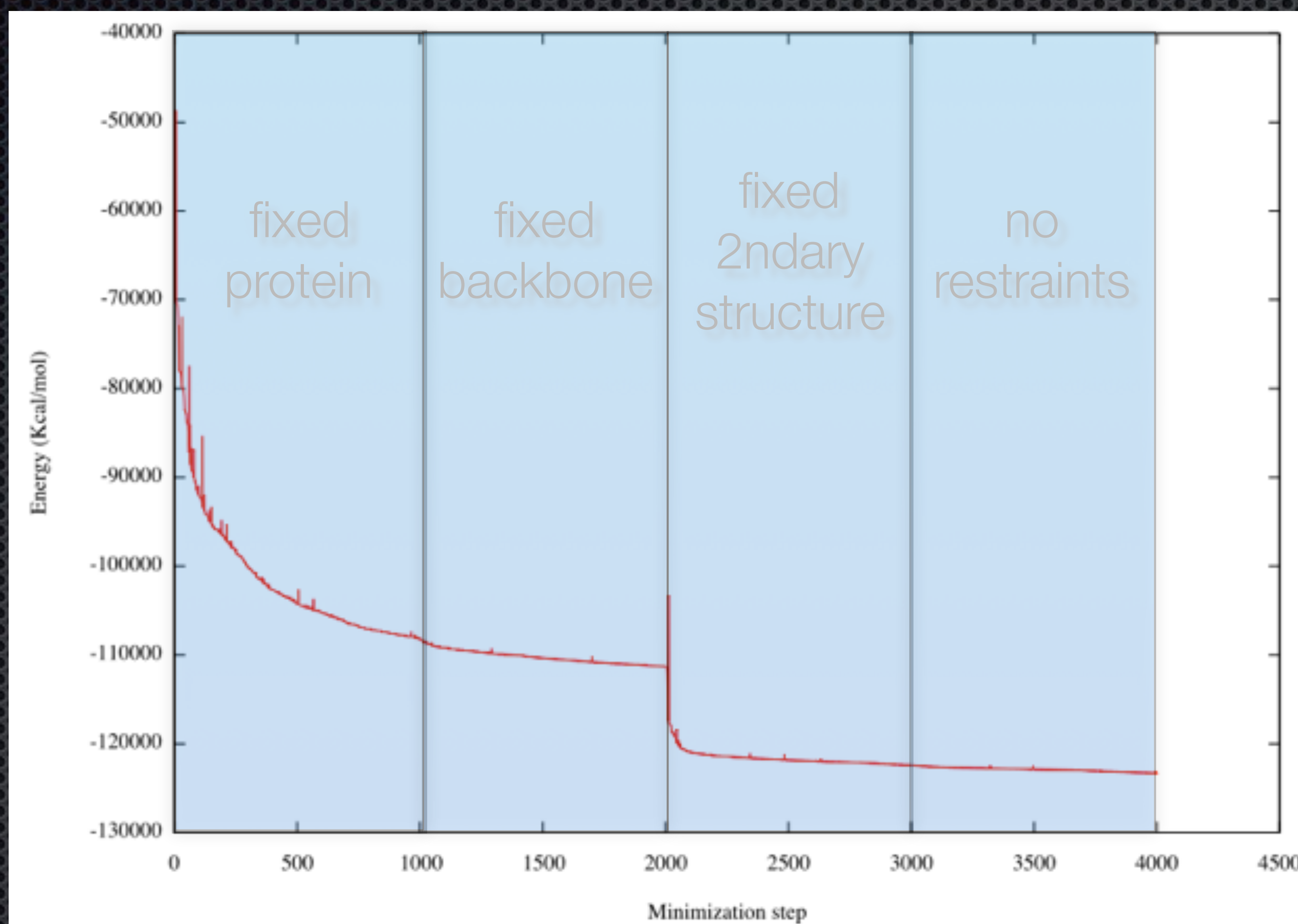
MINIMIZATION: analysis

Plot created from the "output" files : (you will create these in your lab section later today)



Cowboys: they sometimes SKIP the restrained minimizations . . . your mileage will vary.

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DYNAMICS in steps . . .

Now, we have a new coordinate file (that NAMD "names"): `smin3.coor`

which has been minimized and is ready to go.

We are ready to start a molecular dynamics trajectory (time) so have to add some more commands to our input file.

(1) Neighbor lists

(2) Temperature control

(3) Pressure control

(4) Time steps & energy update cycle

(5) Save restart & DCD files (coordinates, velocities, & cell dimensions)

(6) IMD, screen printout stuff, & "run" command

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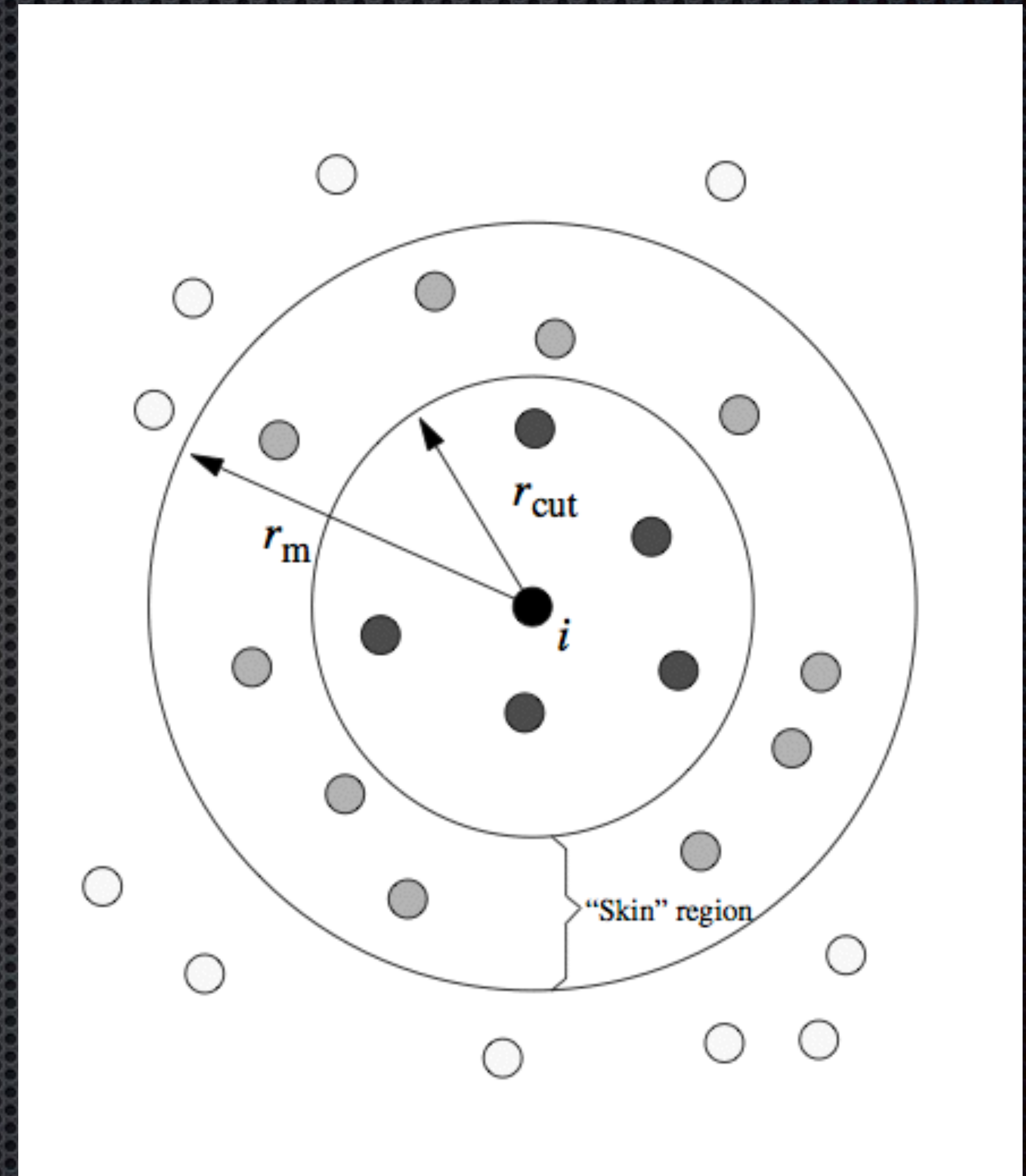
Neighbor Lists

```
. . .

# neighbor lists

pairlistdist                12
margin                      2


. . .

# run control

run                         10000
```



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Temperature Control

```
. . .

# temperature control

langevin                on
langevinDamping         1
langevinTemp            300
langevinHydrogen        no

. . .

# run control

run                     10000
```

← Temperature to maintain

$$m_i \frac{d^2 x_i(t)}{dt^2} = \mathbf{F}_i\{x_i(t)\} - \gamma_i \frac{dx_i(t)}{dt} m_i + \mathbf{R}_i(t)$$

Here, two additional terms on the right hand side accompany the ordinary force the particle experiences. The second term represents a frictional damping that is applied to the particle with frictional coefficient $\gamma_i m_i$. The third term represents random forces which act on the particle (as a result of solvent interaction). These two terms are used to maintain particle kinetic energy to keep system temperature, for instance, at a constant value. Because an unnecessarily high damping constant can significantly slow the system's dynamics, one should always find the minimum `langevinDamping` coefficient sufficient to maintain the temperature. **A value of 1.0 is often a good starting point.**

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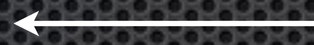
Pressure Control

```
. . .

# pressure control

#useGroupPressure          yes
#useFlexibleCell           no
#LangevinPiston            on
#LangevinPistonTarget      1.01325
#LangevinPistonPeriod      100
#LangevinPistonDecay       50
#LangevinPistonTemp        300
```



Pressure (bar) to maintain

Temperature to maintain

```
. . .

# run control

run                        10000
```

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Time, MTS, & Shake

```
. . .

timestep                1.0
stepspercycle           20

fullElectFrequency      4
nonbondedFreq           2

# shake

rigidBonds              water

. . .

# run control

run                     10000
```

Update frequency of Nearest Neighbor list

Time, MTS, & Shake

```
. . .

timestep                 2.0
stepspercycle            10
fullElectFrequency       2
nonbondedFreq            1

# shake

rigidBonds               all

. . .

# run control

run                      10000
```

Update frequency of Nearest Neighbor list ← (stepspercycle)

Required for 2 fs time step ← (rigidBonds)

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Binary Data & Restart Files

```
. . .

# output

outputname          output/dyn0
binaryoutput        no

DCDfile             output/dyn0.dcd
DCDfreq             1000
DCDUnitCell         yes
#velDCDfile          output/dyn0.vel.dcd
#velDCDfreq          1000
#XstFile             output/dyn0.xst
#XstFreq             1000
wrapAll             on

# restart files

binaryrestart       no
restartsave         no
restartname         output/dyn0.rest.pdb
restartfreq         10000

. . .

# run control

run                 10000
```

ATOM VELOCITIES: C(t)--> Spectra

UNIT CELL SIZE PER STEP (NPT)

USED IF YOU EXPECT A SHUTDOWN OF SOME KIND BEFORE THE END OF A RUN . . . easy restart

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Interactive MD (IMD)

```
. . .

# interactive MD

IMDon                   yes
IMDport                 1085
IMDfreq                 10
IMDwait                 no

# screen output

outputenergies          10
outputtiming            100

. . .

# run control

run                     10000
```

PORT

127.0.0.1

or via internet with real IP

ONE port per MD run you want to attach to . . .

slows computation!!!

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NAMD INPUT FILE V: dyn0

```
# NAMD configuration file for INITIAL Dynamics w/ fixed atoms, PBC, PME

timestep                1.0
stepspercycle           20

fullElectFrequency      4
nonbondedFreq           2

# molecular system
coordinates             output/smin3.coor
structure               output/ionized_solvated_proteinII.psf
temperature             300

# restraints

fixedAtoms              off
fixedAtomsForces        on
fixedAtomsFile          output/fixed_secondary_structure_atoms.pdb
fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12
```

```
# NAMD configuration file for INITIAL Dynamics w/ fixed atoms, PBC, PME

timestep                1.0
stepspercycle           20

fullElectFrequency      4
nonbondedFreq           2

# molecular system
coordinates             output/smin3.coor
structure               output/ionized_solvated_proteinII.psf
temperature             300

# restraints

fixedAtoms              off
fixedAtomsForces        on
fixedAtomsFile          output/fixed_secondary_structure_atoms.pdb
fixedAtomsCol           B

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12
```

```
PME                     on
PMEGridSpacing          1.0

# output

outputname              output/dyn0
binaryoutput            no

DCDfile                 output/dyn0.dcd
DCDfreq                 1000
DCDUnitCell             yes
#velDCDfile              output/dyn0.vel.dcd
#velDCDfreq              1000
#XstFile                 output/dyn0.xst
#XstFreq                 1000
wrapAll                 on

# restart files

binaryrestart           no
restartsave             no
restartname             output/dyn0.rest.pdb
restartfreq             10000

# interactive MD

IMDon                   yes
IMDport                 1085
IMDfreq                 10
IMDwait                 no

# run control

run                     10000
```

USAGE (unix prompt):

Start a run:

>namd2 dyn0 >& dyn0.out &

Check status:

>tail -90f dyn0.out

Multi-processor run:

>charmrun ++local ++p 2 /usr/local/bin/namd/namd2 dyn0 >& dyn0.out &

DYNAMICS "restarting"

Due to file sizes, queuing rules, chance of jobs stopping, . . . one needs a method to continue a simulation without a discontinuity in positions, velocities, boxsizes, etc.

Let's write a new input file to handle this.

(1) Initial time step

(2) Load final coordinates, velocities, box-dimensions from previous run

(3) Comment out "Temperature" & PBC cell definition

(4) Implement pressure control

(5) Save restart & DCD files (coordinates, velocities, & cell dimensions)

(6) IMD OFF, screen printout stuff, & "run" command (1 ns)

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NAMD INPUT FILE V: dyn1

```
# NAMD configuration file for CONTINUING Dynamics w/ fixed atoms, PBC, PME

timestep                 1.0
stepspercycle            20
firsttimestep            10000

fullElectFrequency       4
nonbondedFreq            2

# molecular system
coordinates              output/dyn0.coor
velocities               output/dyn0.vel
extendedSystem           output/dyn0.xsc
structure                output/ionized_solvated_proteinII.psf
#temperature              300

# force field
paratypecharmm           on
parameters               /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                  scaled1-4
1-4scaling               1.0
switching                on
switchdist               10
cutoff                   12

# neighbor lists

pairlistdist             12
```

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```
# NAMD configuration file for CONTINUING Dynamics w/ fixed atoms, PBC, PME

timestep                1.0
stepspercycle           20
firsttimestep           10000

fullElectFrequency      4
nonbondedFreq           2

# molecular system
coordinates             output/dyn0.coor
velocities              output/dyn0.vel
extendedSystem          output/dyn0.xsc
structure               output/ionized_solvated_proteinII.psf
#temperature             300

# force field
paratypecharmm          on
parameters              /home/mdschool/toppar/par_all27_prot_na.inp

# approximations
exclude                 scaled1-4
1-4scaling              1.0
switching               on
switchdist              10
cutoff                  12

# neighbor lists

[illegible]rlistdist    12
```

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```
# restart files

binaryrestart           no
restartsave             no
restartname             output/dyn1.rest.pdb
restartfreq             10000

# interactive MD

IMDon                   no
IMDport                 1085
IMDfreq                 10
IMDwait                 no

# screen output

outputenergies          10
outputtiming            100

# run control

run                     1000000
```

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USAGE (unix prompt):

Start a run:

```
>namd2 dyn1 >&  dyn1.out &
```

Check status:

```
>tail -90f dyn1.out
```

Multi-processor run:

```
>charmrun ++local ++p 2  /usr/local/bin/namd/namd2 dyn1 >&  dyn1.out &
```

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NAMD OUTPUT (DYN.)

```
Charm++: scheduler running in netpoll mode.
Info: NAMD 2.6 for MacOSX-i686
Info:
Info: Please visit http://www.ks.uiuc.edu/Research/namd/
Info: and send feedback or bug reports to namd@ks.uiuc.edu
Info:
Info: Please cite Phillips et al., J. Comp. Chem. 26:1781-1802 (2005)
Info: in all publications reporting results obtained with NAMD.
Info:
Info: Based on Charm++/Converse 50900 for net-darwin-x86-smp
Info: Built Wed Aug 30 12:54:31 CDT 2006 by jim on juneau.ks.uiuc.edu
Info: 1 NAMD  2.6  MacOSX-i686  4    ocho.ncnr.nist.gov  curtisj
Info: Running on 4 processors.
Info: 648656 kB of memory in use.
Info: Memory usage based on ps
Info: Configuration file is dyn0
TCL: Suspending until startup complete.
Warning: The following variables were set in the
Warning: configuation file but were not needed
Warning:    fixedAtomsForces
Warning:    fixedAtomsFile
Warning:    fixedAtomsCol
Info: SIMULATION PARAMETERS:
Info: TIMESTEP               1
Info: NUMBER OF STEPS        0
Info: STEPS PER CYCLE        20
Info: PERIODIC CELL BASIS 1  71 0 0
Info: PERIODIC CELL BASIS 2  0 67 0
Info: PERIODIC CELL BASIS 3  0 0 77
Info: PERIODIC CELL CENTER   0 0 0
```

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```
Info:           MAX ITERATIONS : 500
Info: RIGID WATER USING SETTLE ALGORITHM
Info: NONBONDED FORCES EVALUATED EVERY 2 STEPS
Info: RANDOM NUMBER SEED     1308949783
Info: USE HYDROGEN BONDS?    NO
Info: COORDINATE PDB         output/smin3.coor
Info: STRUCTURE FILE         output/ionized_solvated_proteinII.psf
Info: PARAMETER file: CHARMM format! Info: PARAMETERS             /Users/
curtisj/research/toppar/par_all27_prot_na.inp
Info: USING ARITHMETIC MEAN TO COMBINE L-J SIGMA PARAMETERS
Info: SUMMARY OF PARAMETERS:
Info: 253 BONDS
Info: 628 ANGLES
Info: 1057 DIHEDRAL
Info: 73 IMPROPER
Info: 0 CROSSTERM
Info: 130 VDW
Info: 0 VDW_PAIRS
Info: ****************************
Info: STRUCTURE SUMMARY:
Info: 32067 ATOMS
Info: 22464 BONDS
Info: 15401 ANGLES
Info: 8444 DIHEDRALS
Info: 569 IMPROPERS
Info: 0 CROSSTERMS
Info: 0 EXCLUSIONS
Info: 30463 RIGID BONDS
Info: 65738 DEGREES OF FREEDOM
Info: 11238 HYDROGEN GROUPS
Info: TOTAL MASS = 196616 amu
Info: TOTAL CHARGE = 1.78814e-06 e

. . .
```

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NAMD OUTPUT (DYN.) II

```
. . .

TIMING: 10000  CPU: 1666.31, 0.166343/step  Wall: 1607.39, 0.163882/step, 0
hours remaining, 711036 kB of memory in use.
ETITLE:      TS           BOND           ANGLE           DIHED           IMPRP
ELECT             VDW       BOUNDARY           MISC         KINETIC
TOTAL            TEMP         TOTAL2         TOTAL3         TEMPAVG
PRESSURE      GPRESSURE         VOLUME       PRESSAVG       GPRESSAVG

ENERGY:    10000        650.0702      1728.6069      1094.7965        104.4904
-105158.6301      8258.5326         0.0000         0.0000      19724.1503
-73597.9832       301.9758    -73561.6372    -73556.0246        302.8336
-17532.4835     -1227.9700    366289.0000     -1103.7734      -1101.8505

WRITING EXTENDED SYSTEM TO RESTART FILE AT STEP 10000
WRITING COORDINATES TO DCD FILE AT STEP 10000
WRITING COORDINATES TO RESTART FILE AT STEP 10000
FINISHED WRITING RESTART COORDINATES
WRITING VELOCITIES TO RESTART FILE AT STEP 10000
FINISHED WRITING RESTART VELOCITIES
WRITING EXTENDED SYSTEM TO OUTPUT FILE AT STEP 10000
WRITING COORDINATES TO OUTPUT FILE AT STEP 10000
CLOSING COORDINATE DCD FILE
WRITING VELOCITIES TO OUTPUT FILE AT STEP 10000
==========================================
WallClock: 1619.131104  CPUTime: 1678.077148  Memory: 707260 kB
```

SUMMARY

WHEW!!! So many details, AGAIN!!!

You observed how to build up a system from “minimized” vacuum coordinates to a solvated box running NPT MD.

Energy Minimization

run name	run_0		
reference pdb	Browse... No file selected.	or Browse server	*Server*: no_project_specified/dyn0.pdb
input filename (dcd or pdb)	Browse... No file selected.	or Browse server	*Server*: no_project_specified/dyn0.pdb
PSF file name	Browse... No file selected.	or Browse server	*Server*: no_project_specified/ionized_solvated_proteinII.psf
output file name (dcd)	min_run_0.dcd		
number of processors	8		
keep run output files	yes		
run type	supply input file		

namd input file — Browse... dyn1 — or Browse server *Local*: dyn1

check box to enter restart files — ☑

velocity restart file — Browse... dyn0.vel dyn0.vel — or Browse server *Local*:

extended system restart file — Browse... dyn0.xsc dyn0.xsc — or Browse server *Local*:

FEEDBACK

DOCS

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MD Analysis and NS

Atomistic Modeling of Small-Angle Scattering Data Using SASSIE-web

September 21-23, 2016

Advanced Photon Source

Argonne National Laboratory, Argonne, IL

EPSRC Engineering and Physical Sciences Research Council

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Barriers: BUILD; EQUILIBRATE; PROPAGATE; ANALYZE

What software package(s) and force-fields do I use?

Starting structure?

How do I clean up the structure?

How do I set up a trajectory (time or space)?

How do I calculate scattering observables correctly?

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Overview

Analyze NAMD trajectory

Checking validity of equilibration run
Standard analysis

Neutron Scattering (dynamics)

What is measured

I(q,t) & S(q,w) from MD

Connecting MD trajectory (time) to S(q,w)
Multiple Time Origins (MTO)
Examples

FURTHER READING

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OUTPUT FILES I

Picking up from where we left off yesterday using our ionized_solvated_proteinII system (hydrolase)

1. NVT 10 ps
2. NPT 1 ns

Focussing on the 1ns equilibration run, several files were written "output/":

dyn1.dcd ← `Coordinates sampled over run (BINARY)`

dyn1.coor ← `Final coordinates (PDB) [[ VMD: namdbin ]]`

dyn1.vel ← `Final velocities (PDB)`

dyn1.xst ← `Final PBC box dimensions`

dyn1.xsc ← `All PBC box dimensions sampled over run`

dyn1.rest.pdb.coor
dyn1.rest.pdb.vel
dyn1.rest.pdb.xsc ← `Restart coords., velocities, and cell dimensions`

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namdstats.tcl

Run log files (e. g. dyn1.out) exist for nearly all MD/MMC packages. PYTHON

NAMD has a useful TCL script for parsing their output files: namdstats.tcl

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namdstats.tcl

Run log files (e. g. dyn1.out) exist for nearly all MD/MMC packages. PYTHON

NAMD has a useful TCL script for parsing their output files: namdstats.tcl

USAGE (VMD prompt):

Source the script:

vmd > source namdstats.tcl

run:

vmd > data_avg dyn1.out

chose a subset of the trajectory (say step 1000 to the end of the run):

vmd > data_avg dyn1.out 1000 last

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namdstats.tcl

```
vmd > source namdstats.tcl
vmd > data_avg dyn1.out
Calculating averages...
CALCULATING DATA FROM TIMESTEP 10000 TO 68830:
BOND: 1104.51939235
ANGLE: 1706.60535144
DIHED: 1090.54615195
IMPRP: 106.136829793
ELECT: -358288.083821
VDW: 8887.13411618
BOUNDARY: 0.0
MISC: 0.0
KINETIC: 20020.0703061
TOTAL: -325373.071694
TEMP: 299.396949898
TOTAL2: -325319.666106
TOTAL3: -325319.288662
TEMPAVG: 300.127975612
PRESSURE: -19167.892317
GPRESSURE: -0.444661811693
VOLUME: 317515.797541
PRESSAVG: -2.03941170972
GPRESSAVG: 0.706860605031
```

THERMO. DISTRIBUTIONS

Select subset of output file to analyze thermodynamic variables

USAGE (VMD prompt):

Source the script:

```
vmd > source namdstats.tcl
```

run:

```
vmd > data_time TEMP dyn1.out
```

chose a subset of the trajectory (say step 1000 to the end of the run):

```
vmd > data_time TEMP dyn1.out  1000 last
```

Saves data to a file called TEMP.dat (VDW.dat, DIHED.dat, etc.)

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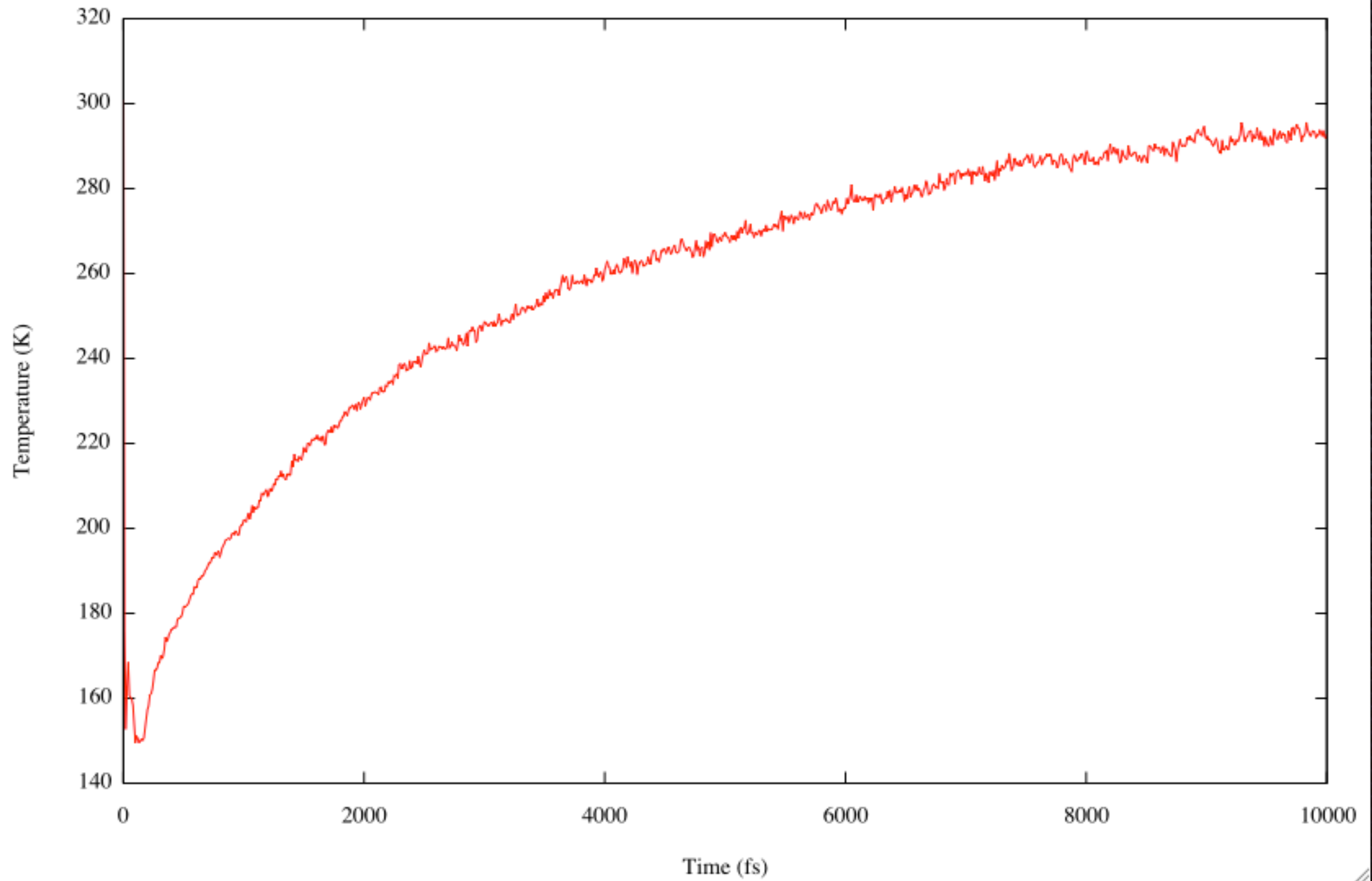

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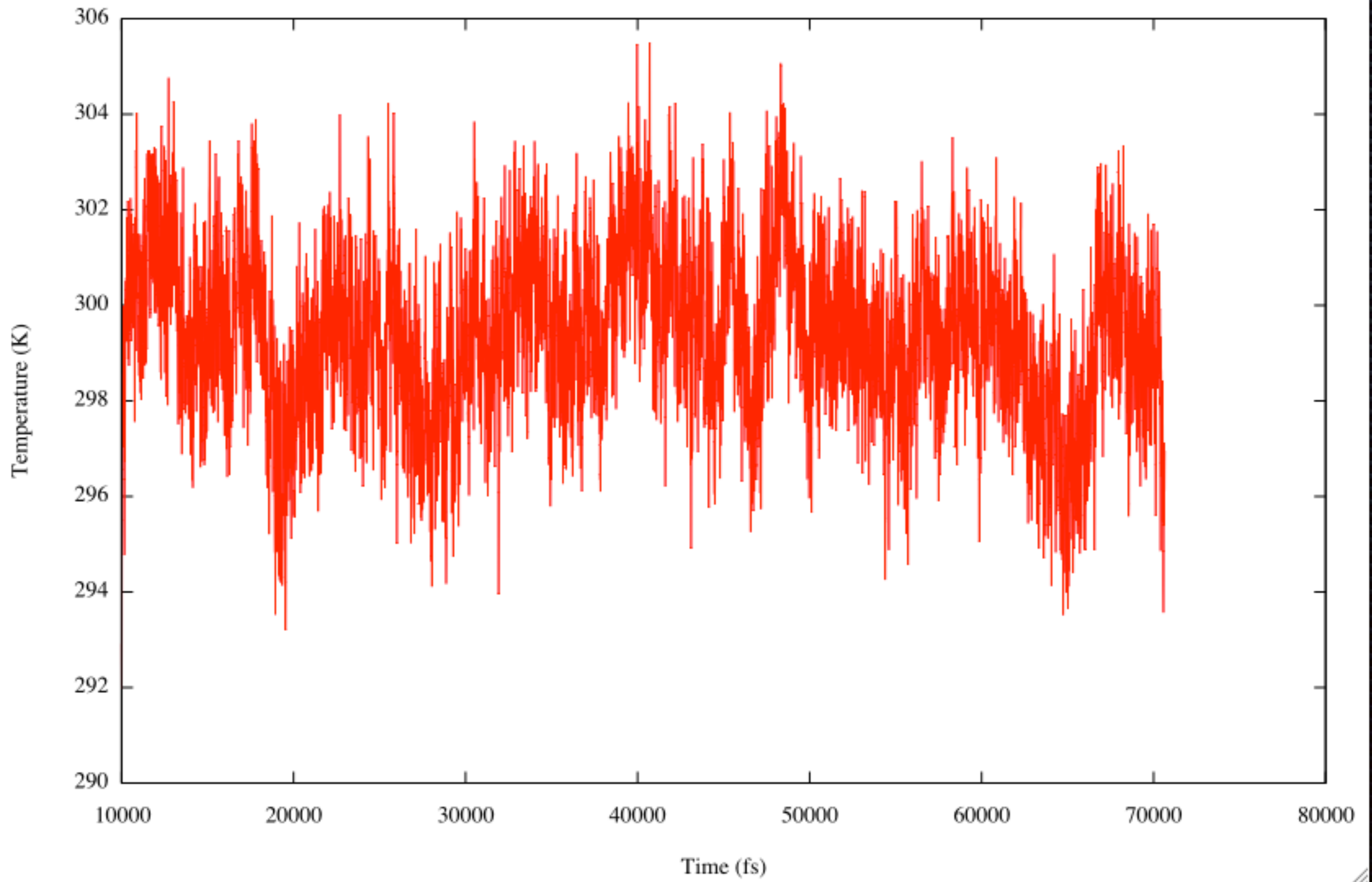

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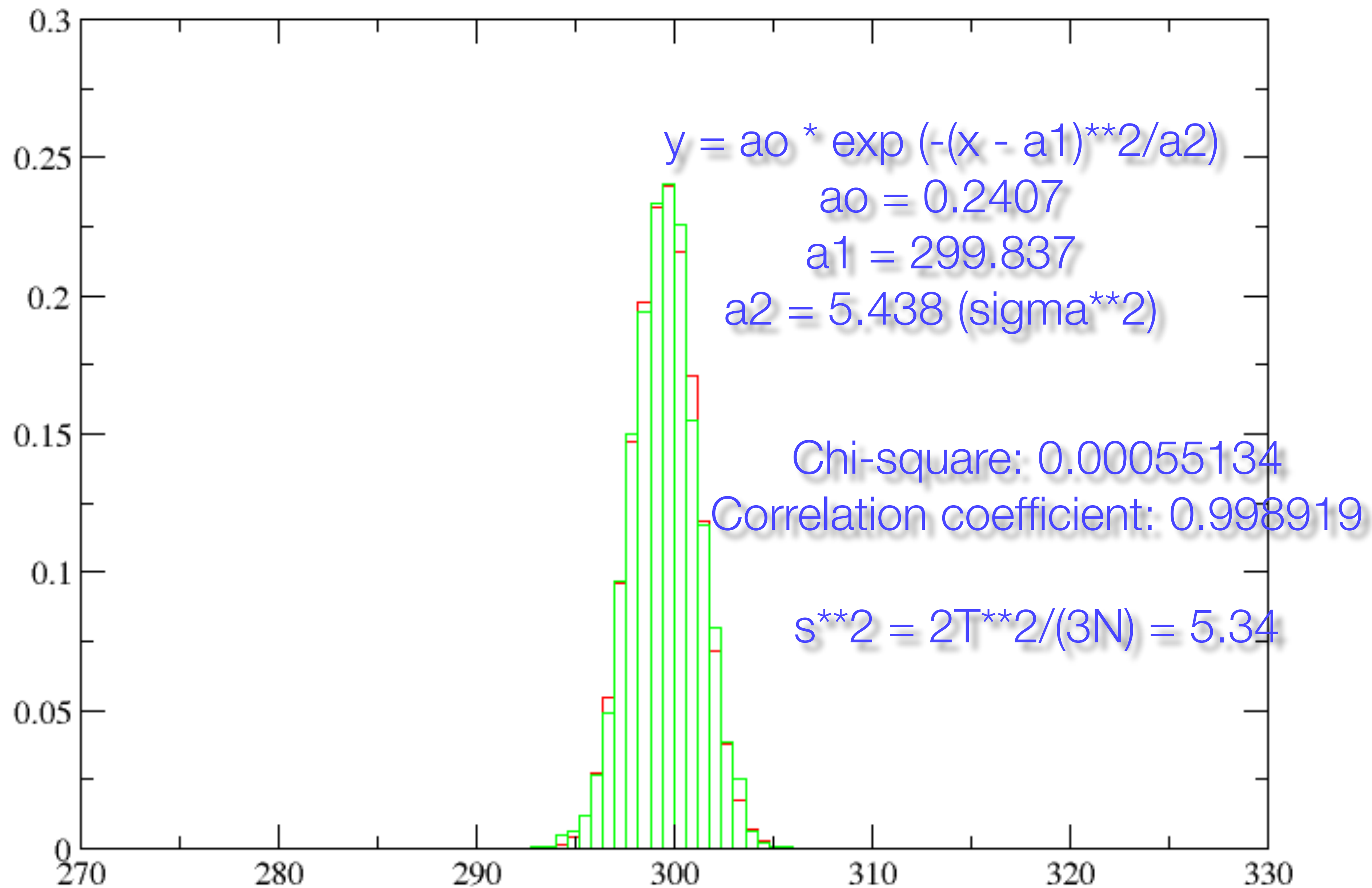
NSF



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Protein conformational Eq.

Load ionized_solvated_proteinII.psf into VMD

Load dyn1.dcd into the same molecule

run the rmsd.tcl script within the vmd console

```
vmd > source rmsd.tcl
```

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Protein conformational Eq.

Load ionized_solvated_proteinII.psf into VMD

Load dyn1.dcd into the same molecule

run the rmsd.tcl script within the vmd console

```
set outfile [open rmsd.dat w]
set nf [molinfo top get numframes]
set frame0 [atomselect top "protein and backbone and noh" frame 0]
set sel [atomselect top "protein and backbone and noh"]

for { set i 1 } { $i <= $nf } { incr i } {
 $sel frame $i
 $sel move [measure fit $sel $frame0]
 puts $outfile "[measure rmsd $sel $frame0]"
}
close $outfile
```

```
vmd > source rmsd.tcl
```

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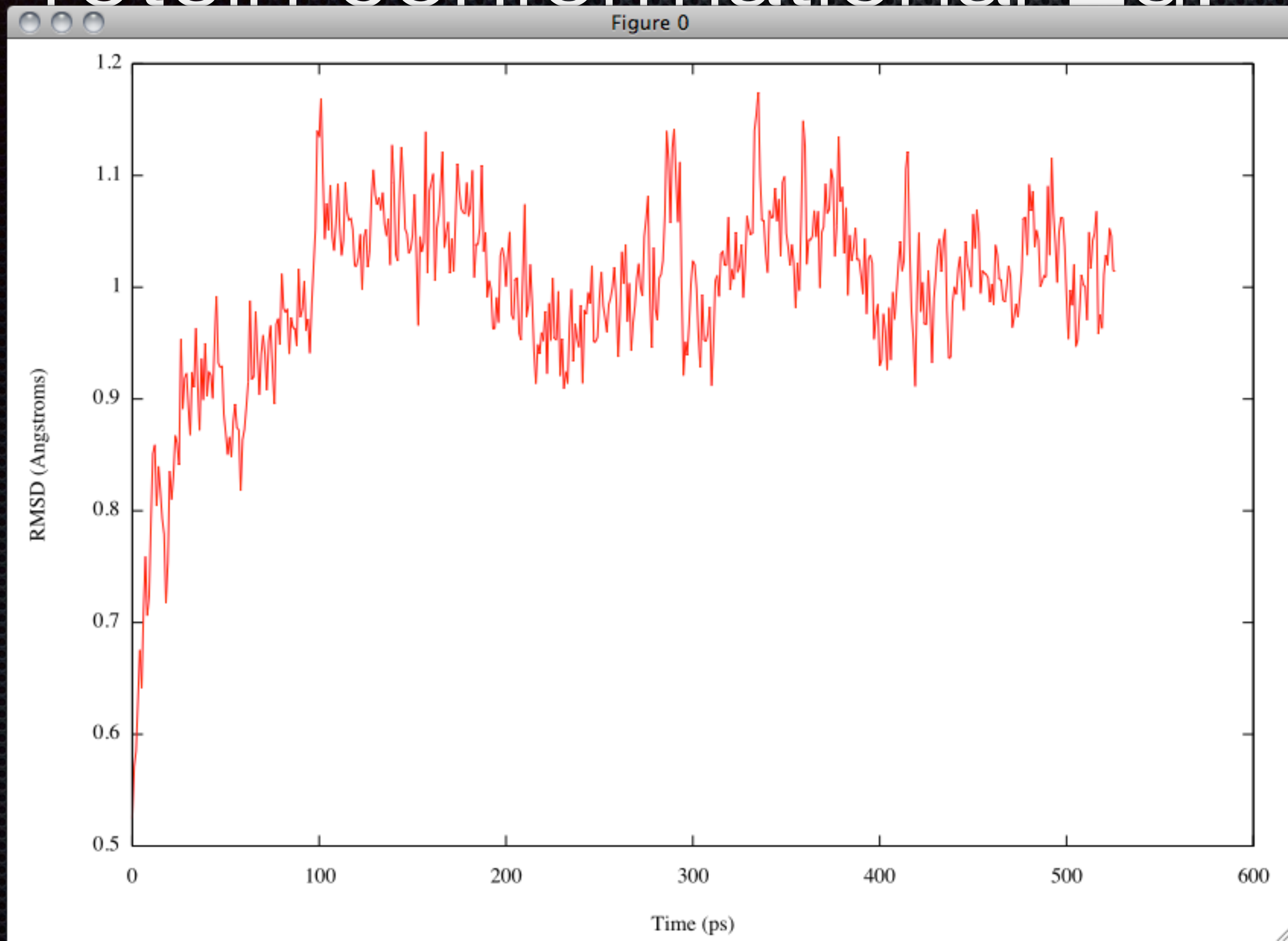
Protein conformational Eq.



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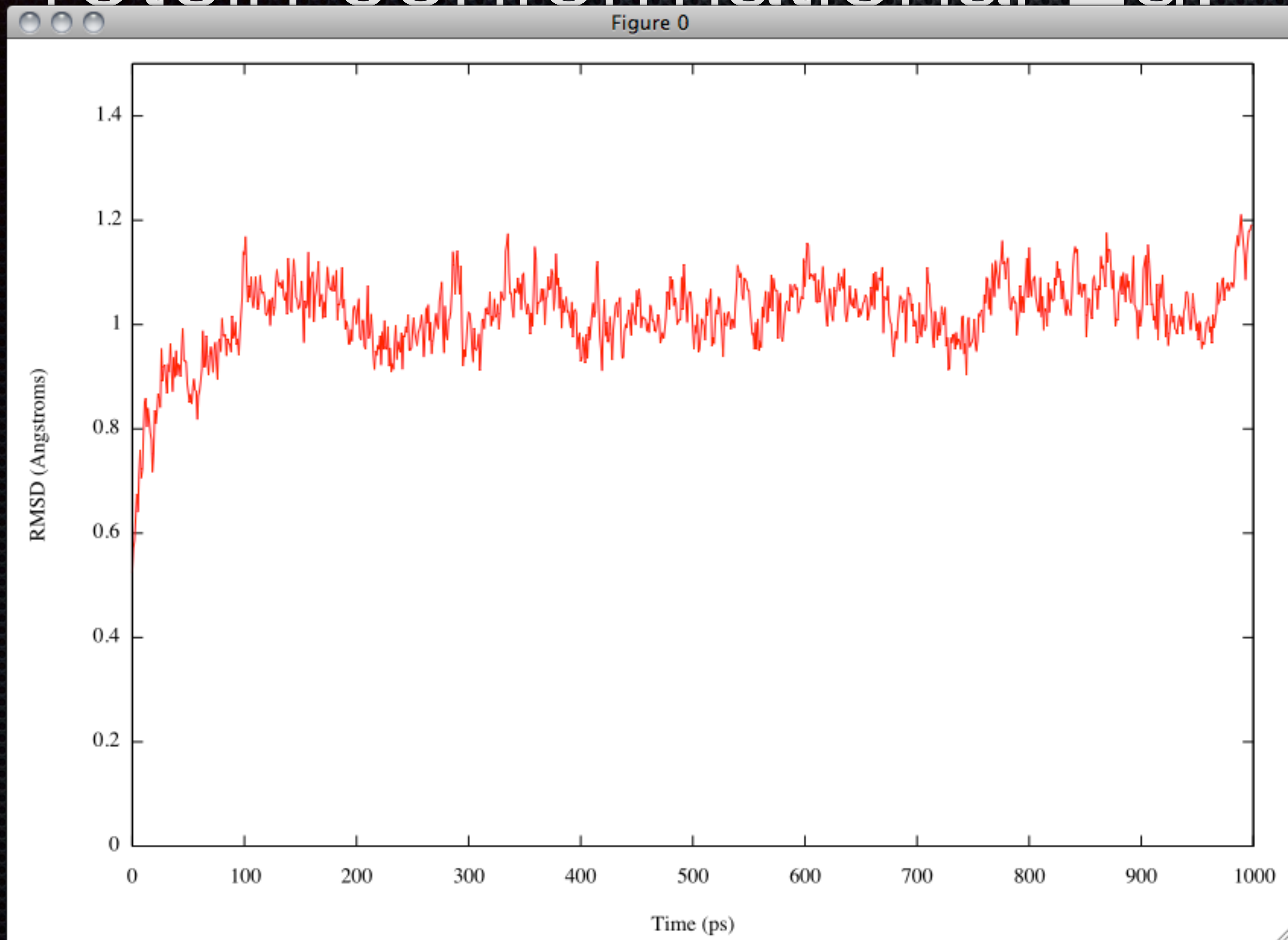
Protein conformational Eq.



Protein Conformational Eq.

Load ionized_solvated_proteinII.psf into VMD

Load dyn1.dcd into the same molecule

Run the residue_rmsd.tcl script within the vmd console

```
vmd > source residue_rmsd.tcl
vmd > set sel_resid [[atomselect top “protein and alpha”] get resid]
vmd > rmsd_residue_over_time top $sel_resid
```

which will write a file “residue_rmsd.dat” to your directory AND add the residue rmsd values to a “User” field so you can view on the molecule

Hot loops, colder core . . .

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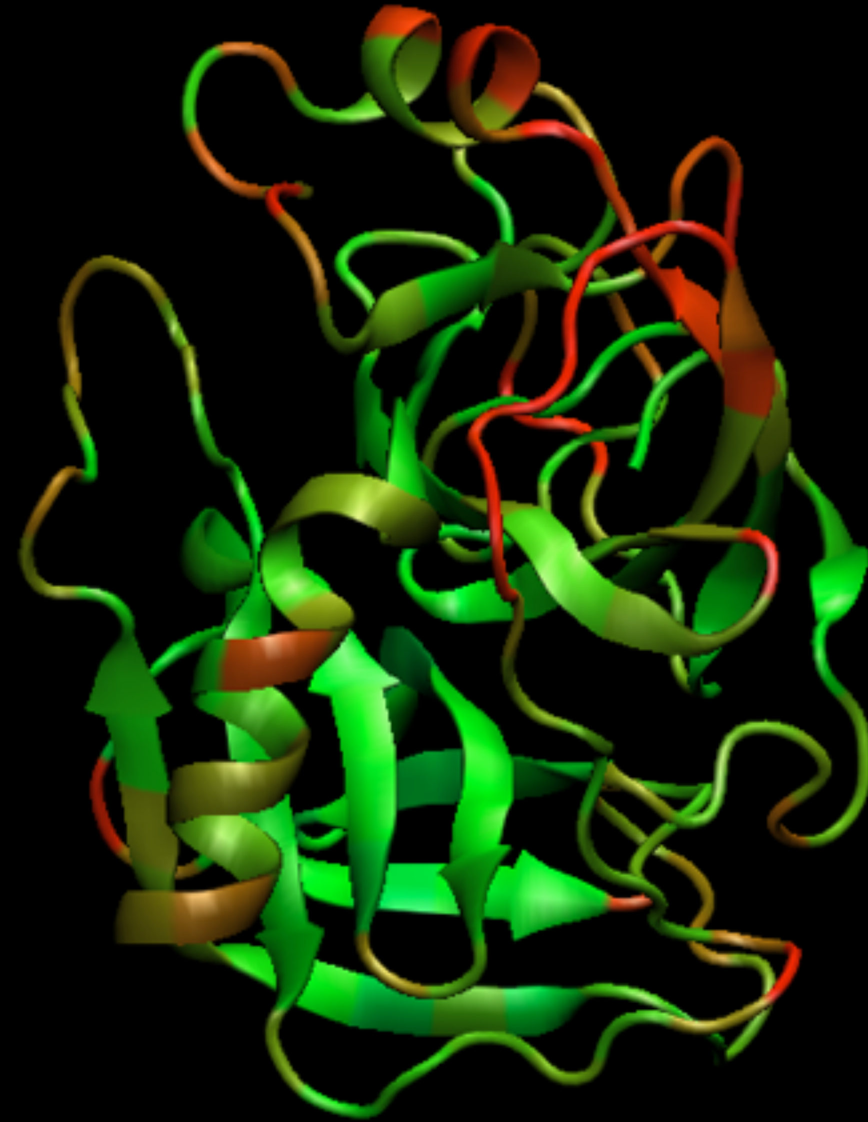

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Equilibration notes

Thermodynamic variables will fluctuate about a mean value.

Biological molecules will fluctuate about a mean structure (1-3 A)

Once the thermodynamic variables and structure are fluctuating normally, you are ready to continue the trajectory to collect a "production run".

These production runs vary in time (1 ns to 1 us) depending on what observable you wish to predict.

One should do a similar analysis of the complete trajectory to validate the system prior to further analysis.

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Points to Remember

Wrapping -->

If you are **never** going to be interested in motions of the solvent then it is okay to wrap coordinates prior to saving to file (*.coor, *.dcd).

You can “wrap” the coordinates afterwards via boxsize information from DCD header or *.xsc files.

Energy loss -->

MD integrators / numerical precision / etc. do not conserve linear or angular momentum: need to “center” entire system and “overlap” bio-molecule prior to calculating dynamical quantities.

Velocities -->

One should save these if you are interested in calculating time-autocorrelation functions: “classical spectra” = FT (< v(t) . v(0)>)

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Points to Remember

Wrap or not to wrap:

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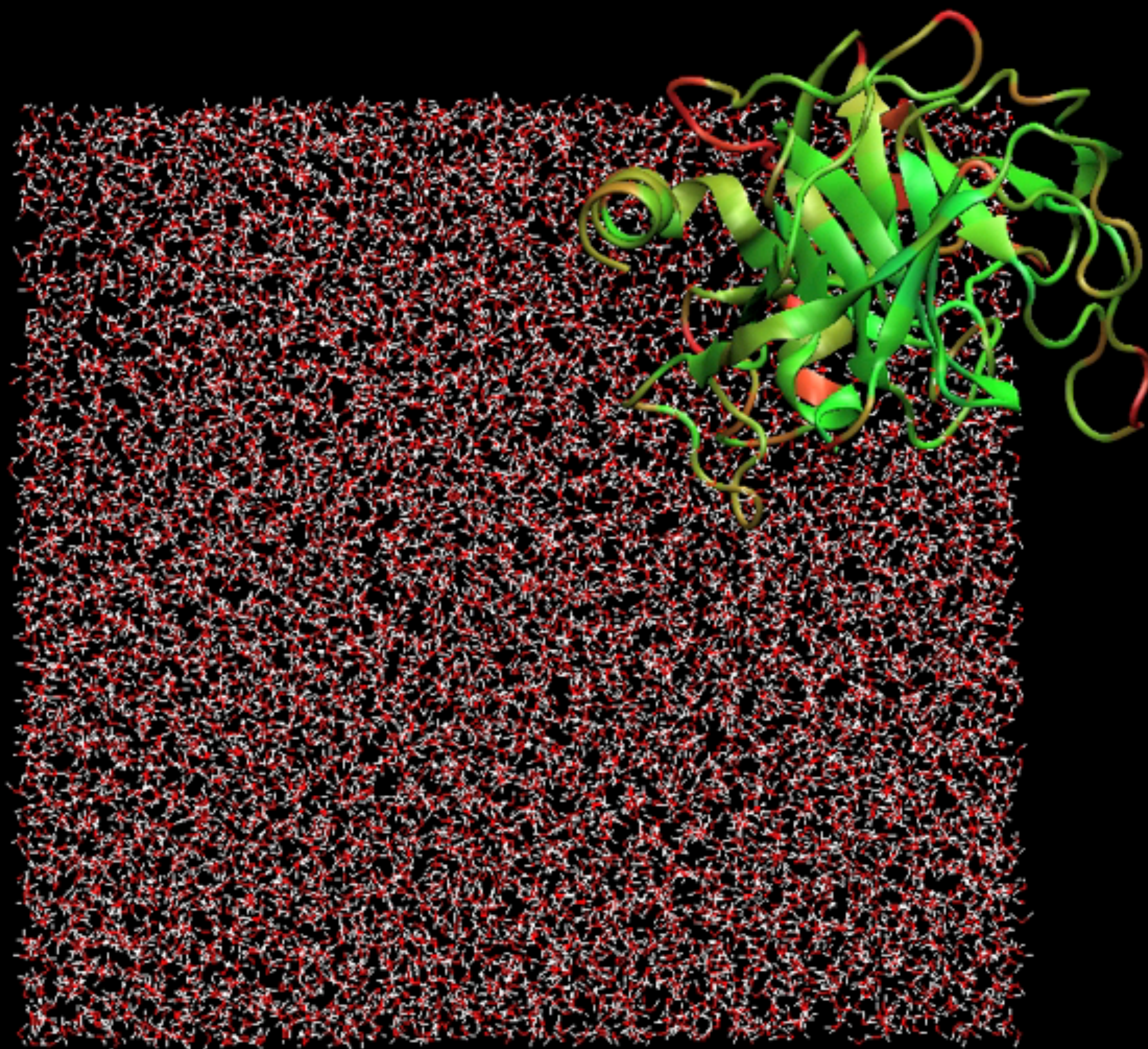

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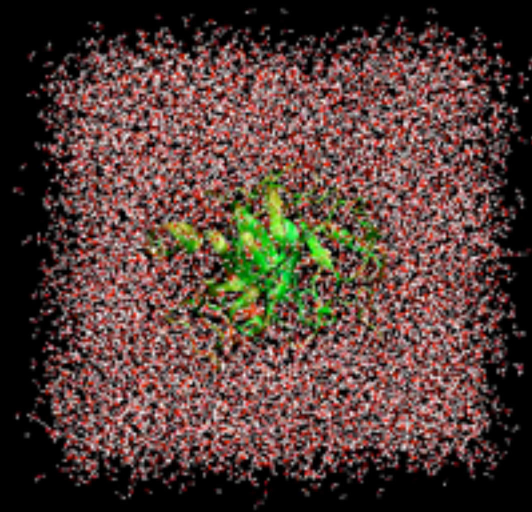

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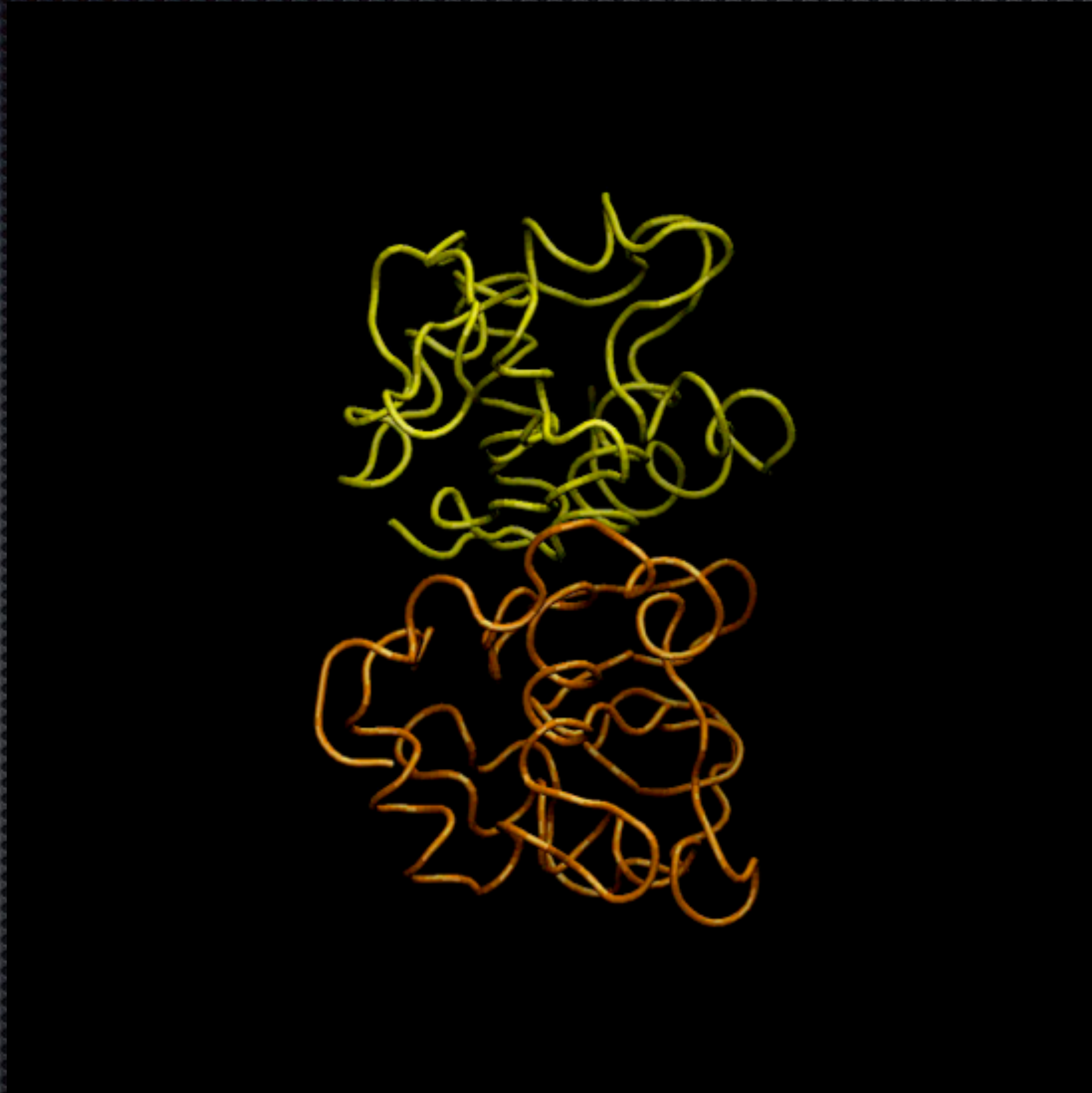
Points to Remember

Energy loss: Lysozyme (2) 6 ns trajectory : dt for movie = 100 ps (1 fs in sim.)



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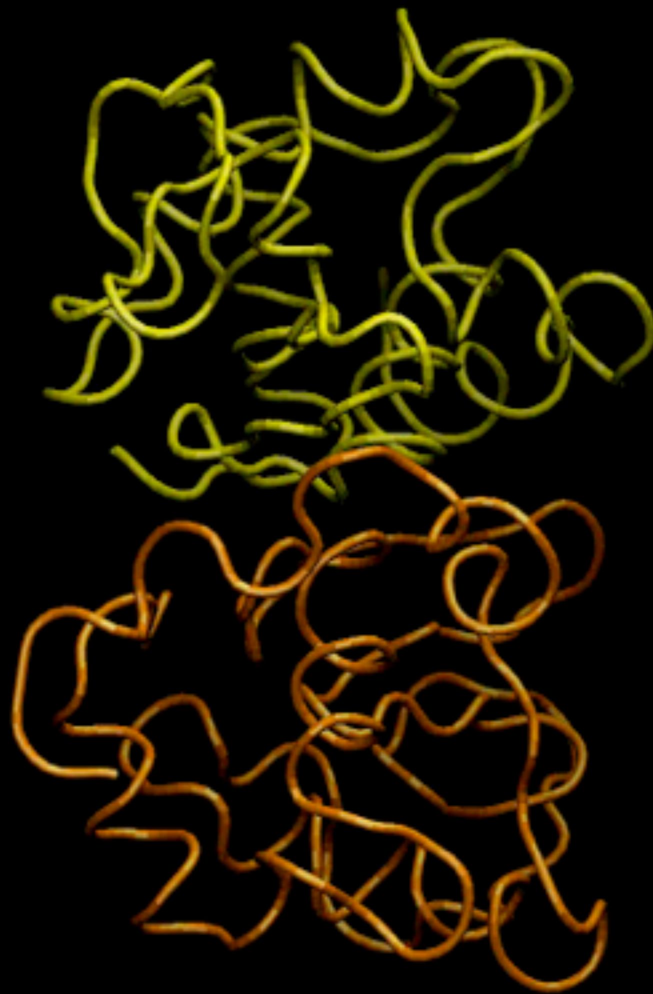
Points to Remember

Energy loss: Lysozyme (2) 6 ns trajectory : dt for movie = 100 ps (1 fs in sim.)



Kabsch W (1976). "A solution for the best rotation to relate two sets of vectors". *Acta Crystallographica* **32** (5): 922–923

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So many options . . .

Bio-simulation (All-atom MD packages):

Amber*
CHARMM*
NAMD*
GROMACS*
GROMOS
LAMPPS*
PINYMD*
HIPPO
GPIUTMD
DL_POLY*
ESPResSo
MacroModel*
MACSIMUS
MOLDY
MOSCITO
ProtoMol
TINKER*
MDGrape
Materials Studio (InsightII)*
. . .

Classical force fields:

Amber*
CHARMM*
CVFF
COSMOS-NMR
GROMACS*
GROMOS
OPLS*
ENZMIX
ECEPP/2
QCFF/PI
[illegible]
CFF*
MMFF
MM2, MM3, MM4*
XPOL
SIBFA
AMOEBA
VALBOND
DRF90
CG MD*
. . .

Methods & details*:

Thermostats
Barostats
Electrostatics (PBC)
Polarizability
Implicit Solvent
Langevin Dynamics
Replica Exchange
Parallel Tempering
Steered MD
Free-Energy Calculations
Umbrella Sampling
Normal Mode Analysis
VMD
Pymol
Chimera, O
APBS
Gaussian, Gamess, CPMD
Beowulf, GPU Clusters
Rosetta
PHYRE
Folding @ Home
TIP3, TIP3P, TIP4P, SPC, ST2
. . .

"HOW TO" . . .
Start you on the path

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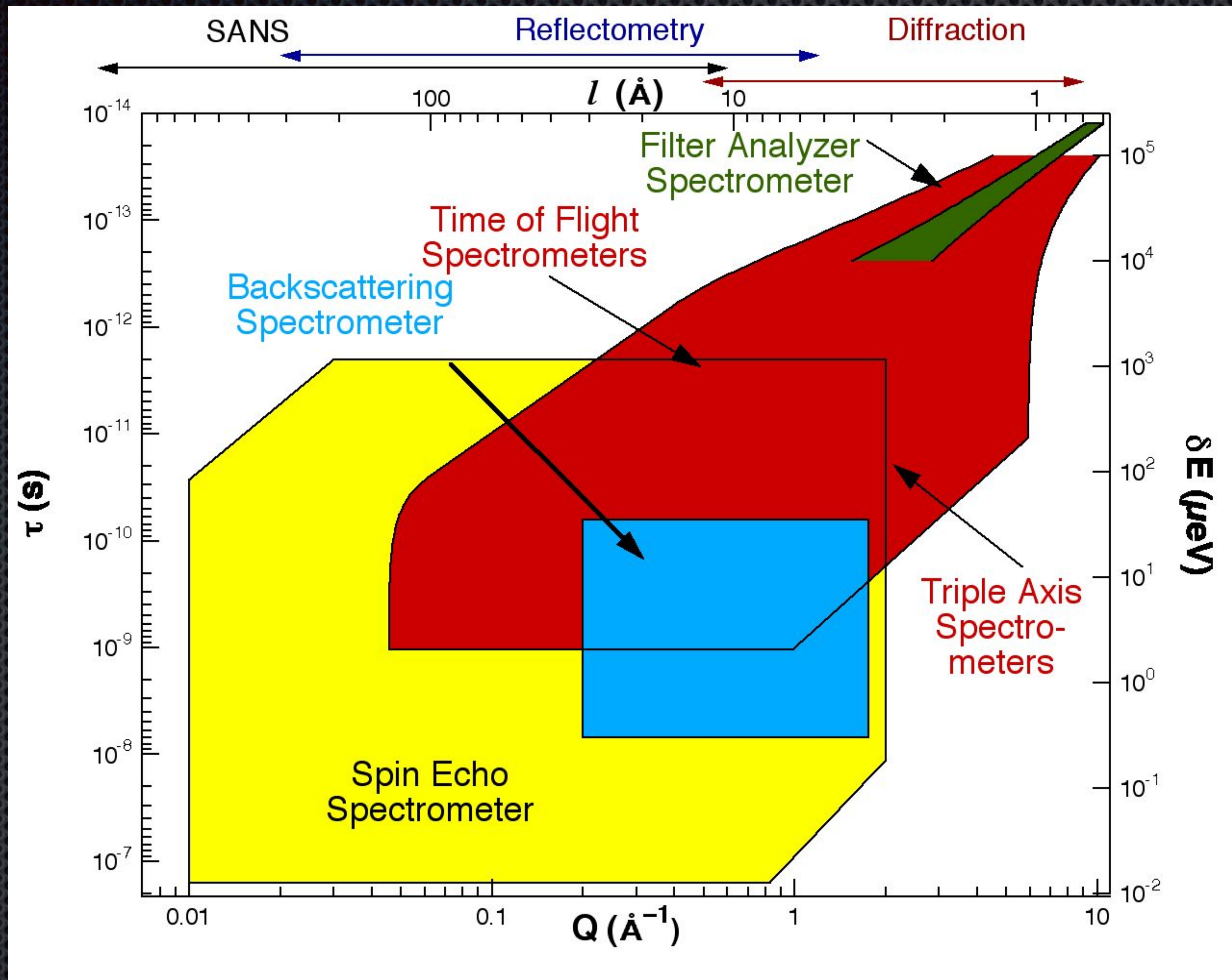
NCNR Dynamics Instruments



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NS Instruments (dynamics)

Disk Chopper Spectrometer at the NCNR

The DCS is an extremely versatile instrument. Useful incident wavelengths range from < 2Å to at least 9Å; correspondingly the elastic energy resolution (FWHM) varies from ~1500 to ~15 μeV: picosecond dynamics

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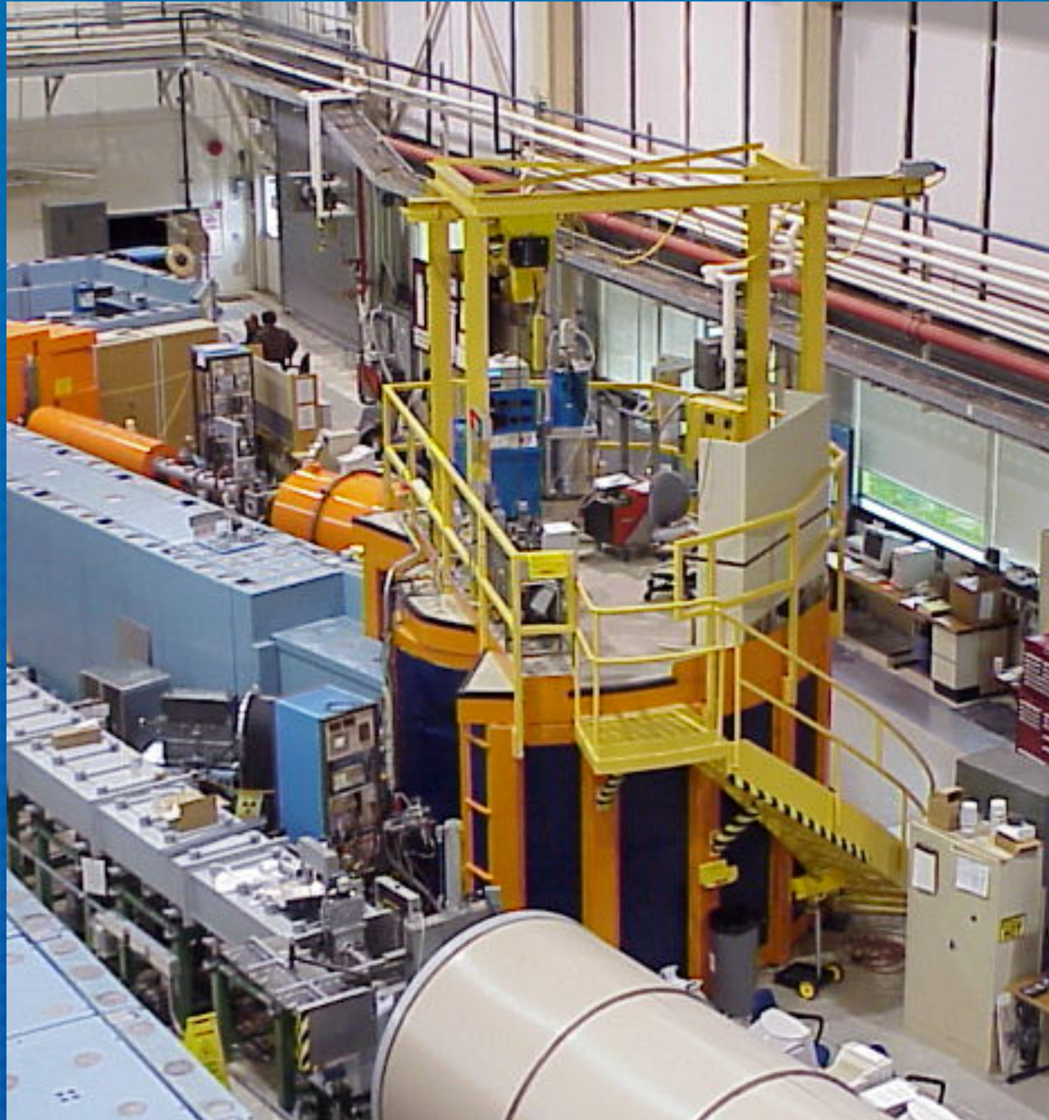
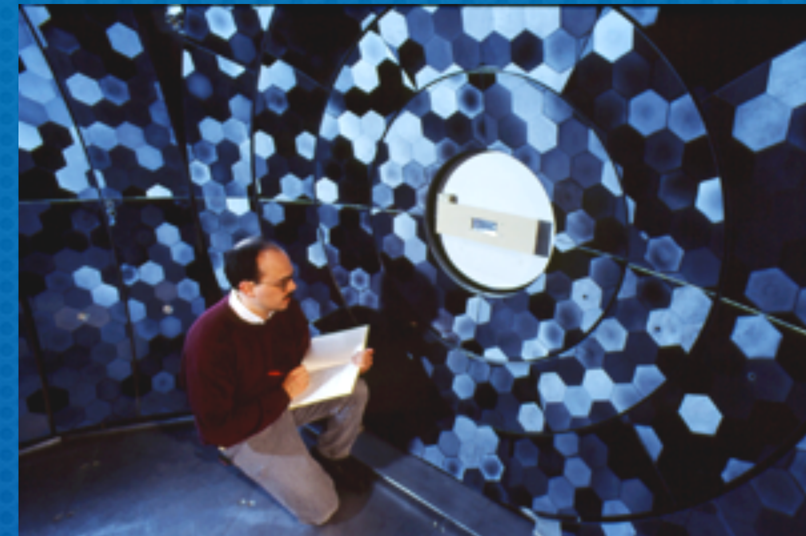
NS Instruments (dynamics) II





~ ns : MSD (S(q,0))

The instrumental energy resolution is a Gaussian-like lineshape, with a full-width-half-maximum (FWHM) about **1 μeV:** **picosecond to ~5 nanoseconds**

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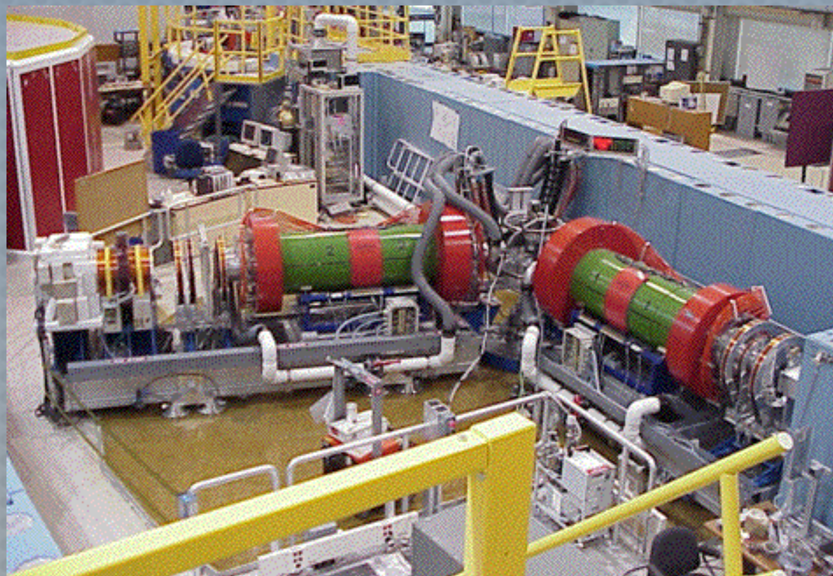
NS Instruments (dynamics) III

Directly measure the energy transfer => Spin Echo

Advantage - high "energy" resolution using a broad energy band

***Actually measures* I(Q,t)/I(Q,0)**

Easier to measure Coherent Scattering, Particularly good for small Q



Cold neutron instruments

=> "Energy" Resolution 0.00001 to 0.001 meV

Examples – IN11, IN15, MESS, G1bis, SPAN, FRJ2, NSE

Dynamic range:

from 5 ps to 15 ns at λ = 6

from 10 ps to 40 ns at λ = 8

from 35 ps to 100 ns at λ = 12

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Example "Bio" Publications

DCS:

J.M. Borreguero, J. He, F. Meilleur, K. Weiss, C.M. Brown, D.A. Myles, K.W. Herwig, and P.K. Agarwal, "Redox-Promoting Protein Motions in Rubredoxin", J. Phys. Chem. B, Article ASAP.

D. Russo, J. Teixeira, L. Kneller, J.R.D. Copley, J. Ollivier, S. Perticaroli, E. Pellegrini, and M.A. Gonzalez, "Vibrational density of states of hydration water at biomolecular sites: hydrophobicity promotes low density amorphous ice behaviour", J. Am. Chem. Soc. **133**, 4882 (2011).

M.E. Johnson, C. Malardier-Jugroot, and T. Head-Gordon, "Effects of co-solvents on peptide hydration water structure and dynamics", Phys. Chem. Chem. Phys. **12**, 393 (2010).

C. Malardier-Jugroot, D.T. Bowron, A.K. Soper, M.E. Johnson and T. Head-Gordon, "Structure and water dynamics of aqueous peptide solutions in the presence of co-solvents", Phys. Chem. Chem. Phys. **12**, 382 (2010).

HFBS:

B. Wang, M. Cicerone, Y. Aso, and M.J. Pikal, The impact of thermal treatment on the stability of freeze-dried amorphous pharmaceuticals: II. aggregation in an IgG1 fusion protein, Journal of Pharmaceutical Sciences, **99**, 683, (2010).

X.-q. Chu, M. Lagi, E. Mamontov, E. Fratini, P. Baglioni, and S.-H. Chen, Experimental evidence of logarithmic relaxation in single-particle dynamics of hydrated protein molecules, Soft Matter, **6**, 2623-2627, (2010).

S. Khodadadi, J. H. Roh, A. Kisliuk, E. Mamontov, M. Tyagi, S. A. Woodson, R. M. Briber, A. P. Sokolov, Dynamics of Biological Macromolecules: Not a Simple "Slaving" by Hydration Water, Biophys. J., **98**, 1321-1326, (2010).

M.E. Johnson, C. Malardier-Jugroot, R.K. Murarka, and T. Head-Gordon, Hydration Water Dynamics near Biological Interfaces, J. Phys. Chem. B, **113**, 4082, (2009).

NSE:

J.-H. Lee, S.-M. Choi, C. Doe, A. Faraone, P.A. Pincus, and S.R. Kline, "Thermal Fluctuation and Elasticity of Lipid Vesicles Interacting with Pore-Forming Peptides" Phys. Rev. Lett., **105**, 038101 (2010).

M.B. Boggara, A. Faraone, and R. Krishnamoorti, "Effect of pH and Ibuprofen on the Phospholipid Bilayer Bending Modulus" J. Phys. Chem. B, **114**, 8061 (2010).

L. Porcar, P. Falus, W.-R. Chen, A. Faraone, E. Fratini, K. Hong, P. Baglioni, and Y. Liu, "Formation of the Dynamic Clusters in Concentrated Lysozyme Protein Solutions" J. Phys. Chem. Lett., **1**, 126 (2010).

Observables from MD

Experiment Dynamical quantity	Corresponding time correlation function
Neutron scattering r position of atom	$\left\langle \sum e^{-iQ\cdot r_m(0)} e^{iQ\cdot r_n(t)} \right\rangle$
Raman scattering u transition dipole	$\langle P_2[u(0)\cdot u(t)] \rangle$
Infrared absorption u transition dipole	$\langle u(0)\cdot u(t) \rangle$
Dielectric relaxation u permanent dipole	$\sum \langle u_i(0)\cdot u_j(t) \rangle$
NMR lineshape M_x magnetization	$\langle M_x(0)\cdot M_x(t) \rangle$
Self-diffusion v velocity	$\langle v(0)\cdot v(t) \rangle$

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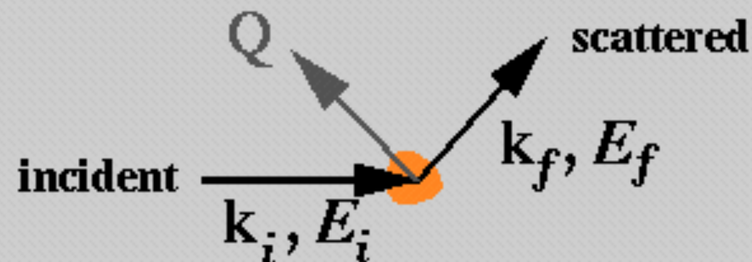
Neutron Scattering

Neutrons scatter from the nuclei in a sample:



$Q = k_f - k_i$ = momentum transfer

$\Delta E = E_f - E_i = \hbar\omega$ = energy transfer

Measure double differential cross–section:

$\frac{\partial^2\sigma}{\partial\Omega\partial\omega}$ = probability that neutron scatters within solid angle $d\Omega$ of direction Ω and ω within $d\omega$ of $E_i/\hbar$

$$\propto \frac{k_f}{k_i}\left[\sigma^{coh}S^{coh}(Q,\omega) + \sigma^{inc}S^{inc}(Q,\omega)\right]$$

where $S(Q,\omega)$, the dynamical structure factors, contain information on the structure and dynamics of the sample

coherent ⇒ structure (diffraction), collective motions

incoherent ⇒ single–particle motions (e.g. vibrations, diffusion)

Each nucleus has unique cross–sections, σ^{coh} and σ^{inc}

Neutron Scattering II

The composition of the system determines whether the scattering is primarily coherent, incoherent, or both

Because σ_H^{inc} >> all other σ, in organic molecules the scattering is primarily incoherent

$\Rightarrow$ probe <u>single particle</u> motions of H atoms

Connection to the time–domain through the Van Hove Theory for the structure factor (1954):

$$S(Q,\omega) = (1/2\pi)\int_{-\infty}^{\infty} I(Q,t)\, e^{-i\omega t}\, dt$$

$$I(Q,t) = (1/N)\sum_j \langle e^{iQ\cdot r_j(t)}\, e^{-iQ\cdot r_j(0)} \rangle$$

is the <u>incoherent intermediate scattering function</u> which we can calculate from simulation and FT to obtain the structure factor

Typical instrumental and MD time and length scales overlap very well

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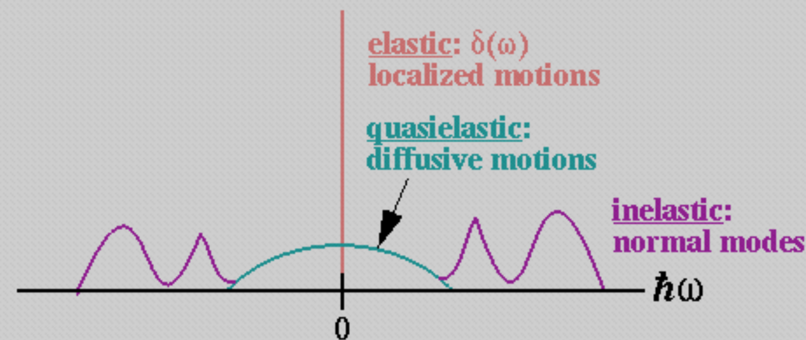
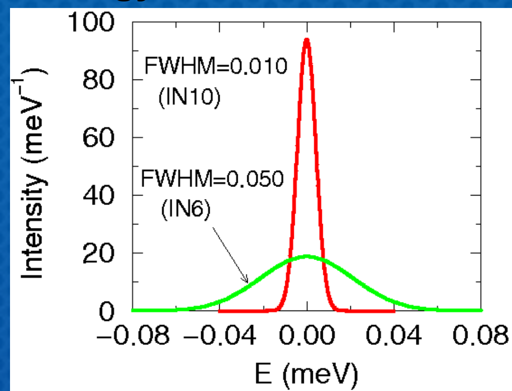
Neutron Scattering III



$$S_{measured}(Q,\omega) = S(Q,\omega) \otimes R(\omega)$$

R(ω) determines time scale probed by measurement:

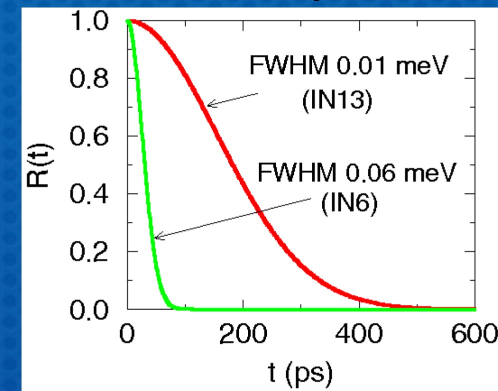
Energy resolution functions



Fourier transform

Convolution with energy resolution function = multiplication by its FT in time domain

Time domain equivalents



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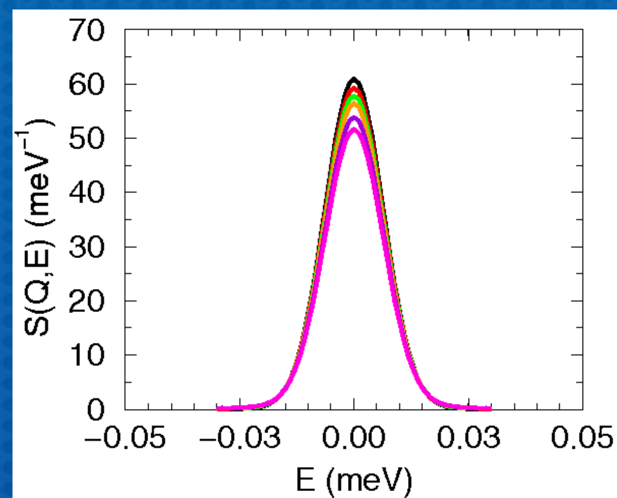
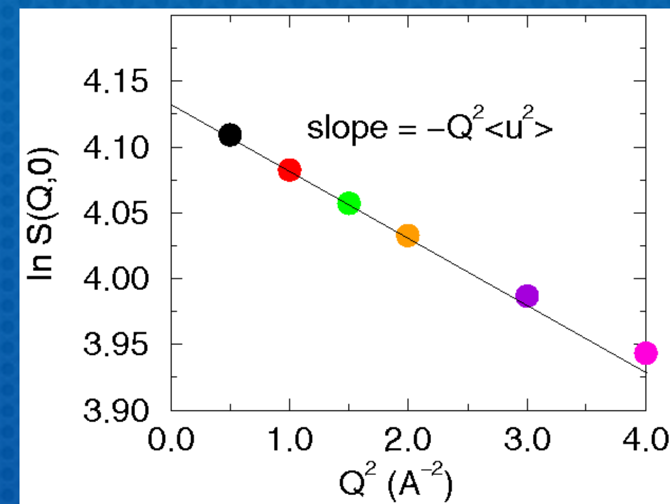
Neutron Scattering IV

Most neutron scattering studies of protein dynamics to date have been based on measuring the temperature dependence of mean-squared displacements of H atoms ($\langle u^2 \rangle$) via elastic scattering

Estimate mean-squared displacement from elastic intensity via Debye-Waller factor: $S(Q, E=0) = \exp(-Q^2\langle u^2 \rangle)$

In practice, the number of counts within the instrumental resolution (ΔE) of the elastic line is used, i.e. $S(Q,0) \sim S(Q,\pm\Delta E)$





$\langle u^2 \rangle = -\text{slope}/Q^2$

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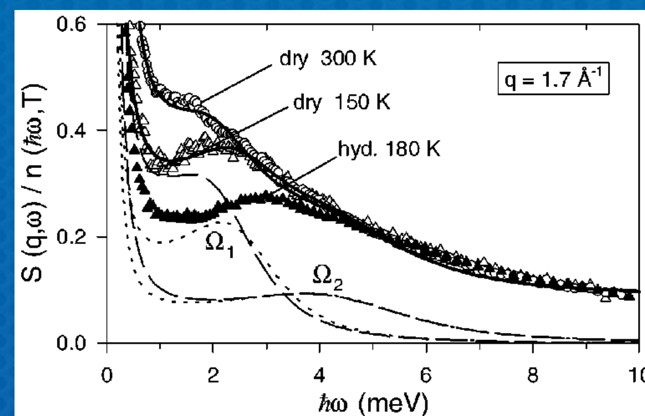
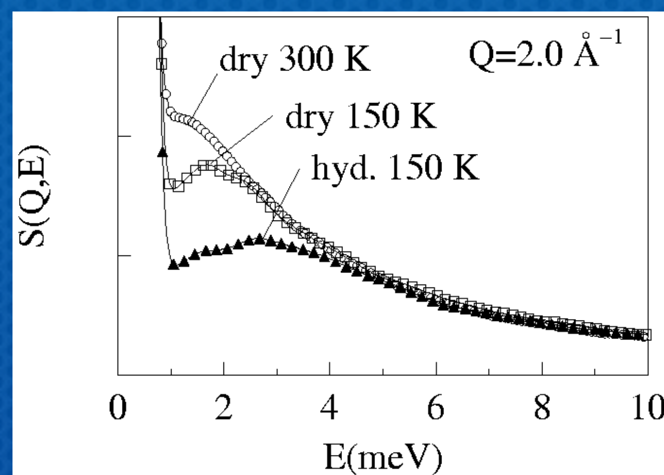
Neutron Scattering V

"Boson peak" in low frequency inelastic spectrum

Incoherent neutron scattering on Mb powders
[Leyser et al., Phys. Rev. Lett. (1999)]

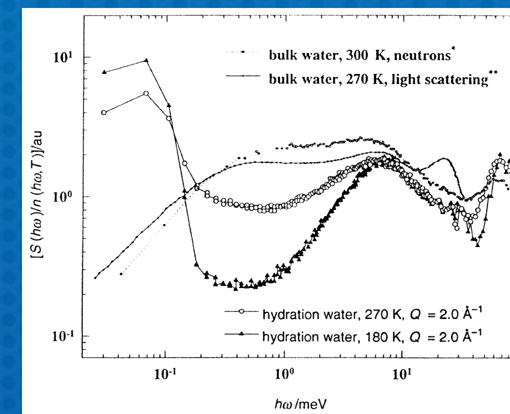


MD simulations of RNase powders
[Tarek & Tobias, J. Chem. Phys. (2000)]

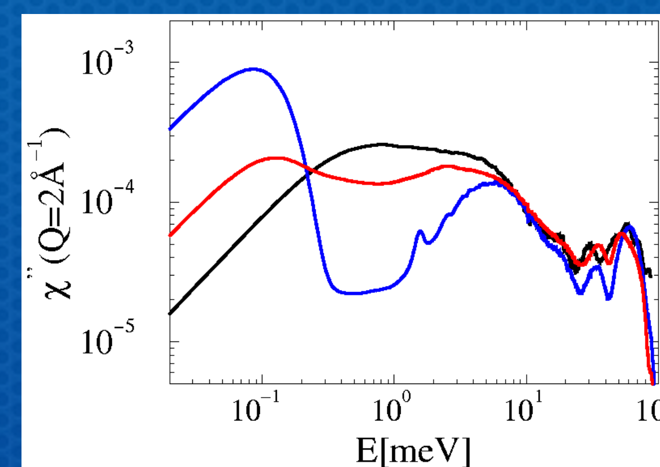


Dynamical susceptibility

Dynamical structure factors:
bulk vs. protein hydration water
[Settles & Doster, Faraday Disc. 103, 269 (1996)]



MD simulations of RNase powders
(protein signal subtracted)
[Tarek & Tobias, Biophys. J. 79, 3244 (2000)]



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Steps to Calculate I(q,t)

$$I(Q,t) = \frac{1}{N}\sum_j \left\langle e^{-iQ\cdot r_j(0)} e^{iQ\cdot r_j(t)} \right\rangle$$

Correct of COM & rotation of system

Create subset trajectory with only non-exchangeable hydrogens

Need a method to sample over “Q”

Write code (Python & C) to extract positions and calculate I(q,t) using MTO

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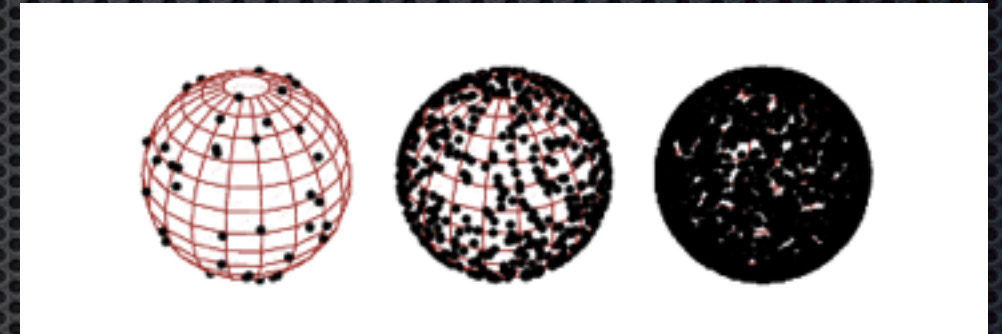
Steps to Calculate I(q,t) II

$$I(Q,t) = \frac{1}{N}\sum_j \left\langle e^{-iQ\cdot r_j(0)} e^{iQ\cdot r_j(t)} \right\rangle$$



```
def random_vector_sphere():
    '''
    von Neumann method
    '''
    looking=True
    while(looking):
        r1=random.random()
        r2=random.random()
        r3=random.random()
        z1=1-2*r1 ; z2=1-2*r2 ; z3=1-2*r3
        sumz2=z1*z1+z2*z2+z3*z3
        if(sumz2 < 1):
            z=math.sqrt(sumz2)
            vector=[z1/z,z2/z,z3/z]
            looking=False
    return vector
```

Need a method to sample over “Q”

Code to generate a random vector on a unit sphere

Call this snippet to create an array of q-vectors to loop over (8 - 32 for convergence)

The magnitude of q, q = |q|*unit vector

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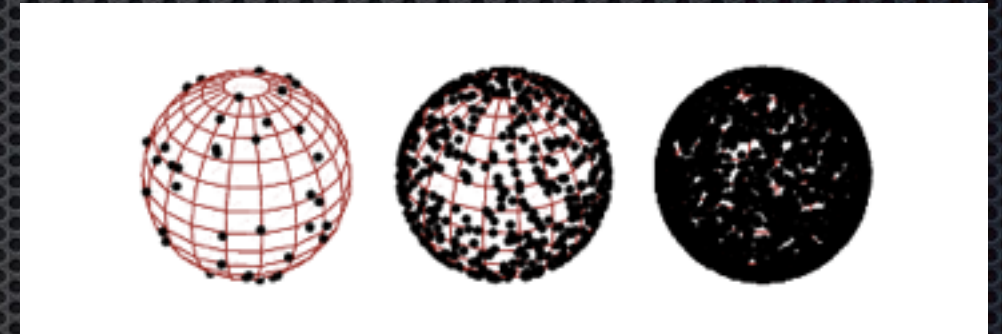
Steps to Calculate I(q,t) II

$$I(Q,t) = \frac{1}{N}\sum_j \left\langle e^{-iQ\cdot r_j(0)} e^{iQ\cdot r_j(t)} \right\rangle$$



```
argo=tqx*xo+tqy*yo+tqz*zo ;
argt=tqx*xt+tqy*yt+tqz*zt ;
re=cos(argo)*cos(argt)+sin(argo)*sin(argt) ;
im=sin(argo)*cos(argt)-cos(argo)*sin(argt) ;
```

Create array of q vectors
Read in coordinates
Loop over atoms
    Loop over q-vectors
        Calculate q . r
        I(q,t) = I(q,t) + cos(old)*cos(new) . . .
Normalize
Print results

Poor convergence with a finite trajectory. Need a method to get more out of the data ---> Multiple Time Origins (MTO)

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MTO

A correlation function of some function, A(t), can be written as:

$$C(\tau) = \langle A(\tau)A(0)\rangle = \frac{1}{\tau_{max}} \sum_{\tau_o=1}^{\tau_{max}} A(\tau_o)A(\tau_o + \tau)$$

Thus, we average over tmax time origins the product of A(to) and A(to+dt) later.

Thus, each successive data point is used as an origin (to).

In practice, use every 5 or 10th point to avoid correlations.

Must not exceed data length, so each “window” uses a different number of points. --> need to normalize correctly.

```
def corfun(trun, tcor, a, acf, norm):

  for t in xrange(tcor):

    acf(t) = 0.0
    norm(t) = 0.0

  for t0 in range(1,trun):

    a0 = a(t0)
    tt0max = min(trun, t0 + tcor)

    for tt0 in xrange(t0, tt0max):

      t = tt0 - t0
      acf(t) = acf(t) + a0 * a(tt0)
      norm(t) = norm(t) + 1.0

  for t in xrange(tcor):

    acf(t) = acf(t) / norm(t)

  return acf
```

See: Allen & Tildesley “Computer Simulation of Liquids”, Oxford Univ. Press, NY, 1997, page 185-188.
PLUS FFT methods ...

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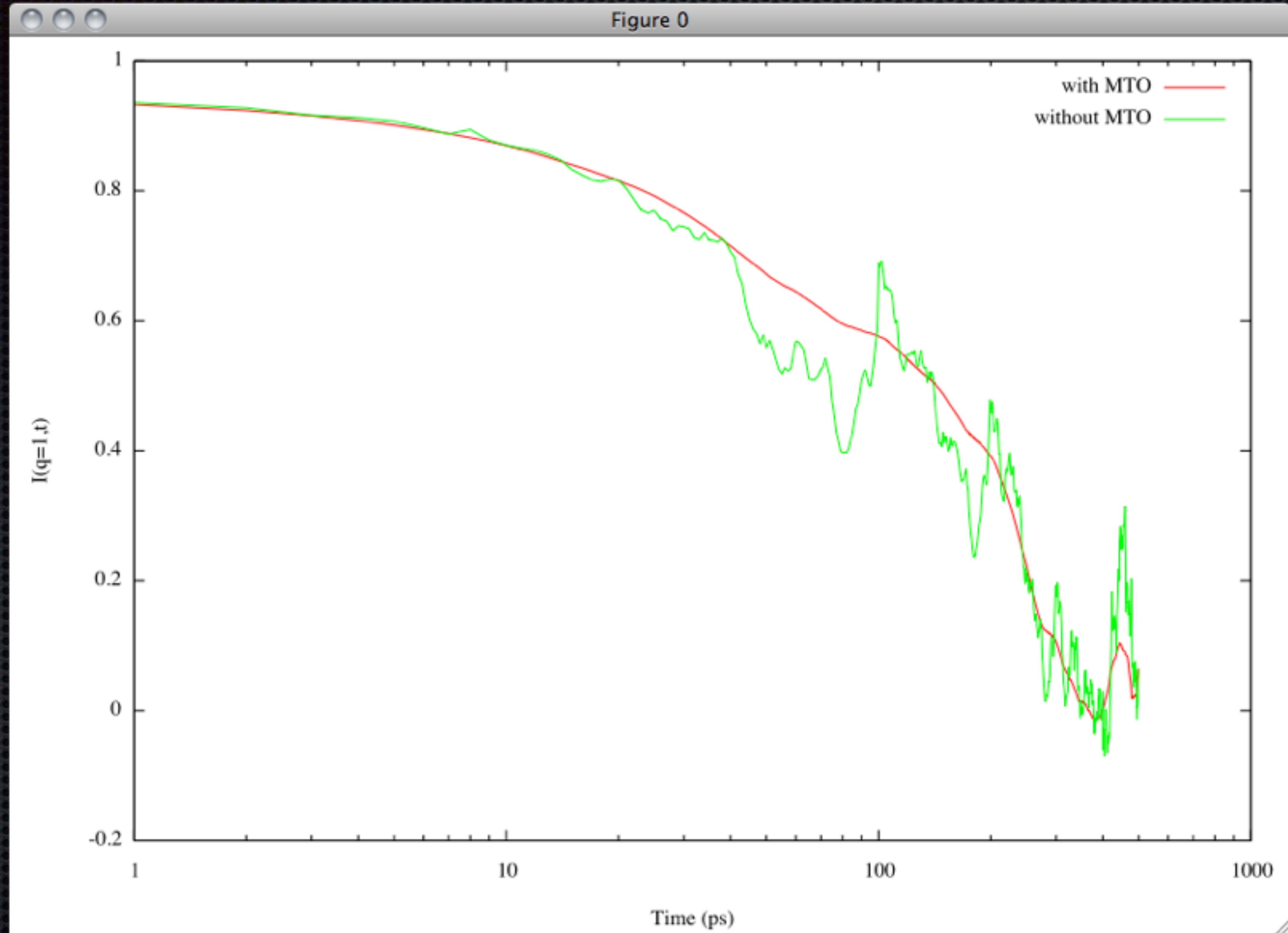
MTO Example



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Steps to Calculate S(q,w), X”(q,w) & $< u^2 >$

$$S(Q,\omega) = (1/2\pi)\int_{-\infty}^{\infty} I(Q,t)\, e^{-i\omega t}\, dt$$

$$S_{measured}(Q,\omega) = S(Q,\omega) \otimes R(\omega)$$

GOAL: to compare MD S(q,w) to measured S(q,w)

Multiply I(q,t) by R(t) to incorporate instrumental resolution function

Take the discrete Fourier Transform of I(q,t) x R(t) = S(q,w)

BONUS: X”(q,w) ~ w*S(q,w)

Estimate $< u^2 >$ by plotting ln(S(q,0)) -vs- q^2

$< u^2 > = -slope/q^2$

$< u^2 >$ is usually studied as a function of temperature $< u^2(T) >$

DWF

$S(q,w=0) = \exp(-q^2 < u^2 >)$

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Examples

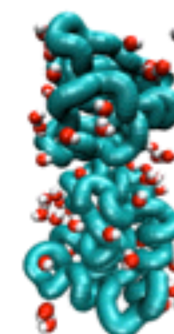
Lysozyme Powder Under Pressure

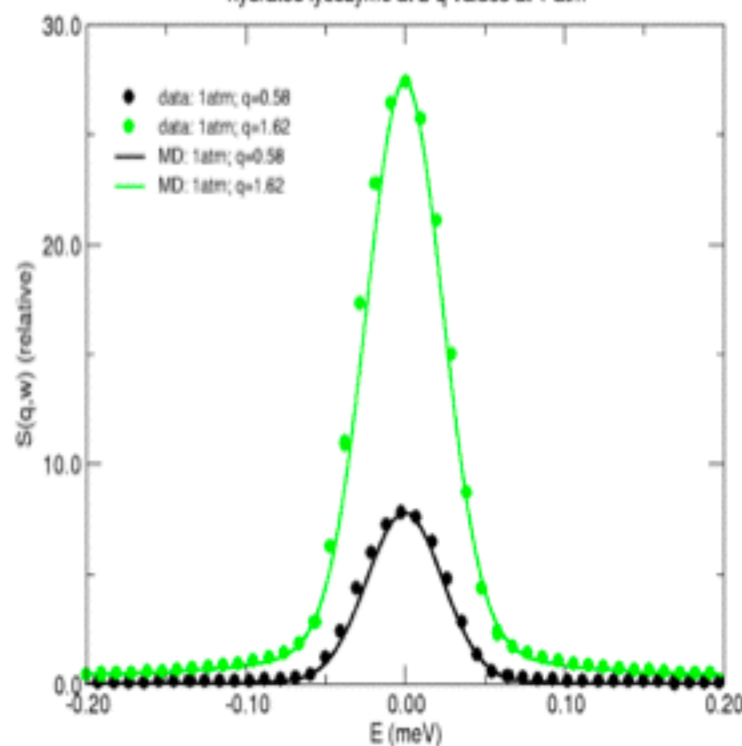
INS of hydrated lysozyme (h=0.3) at two pressures and two length scales

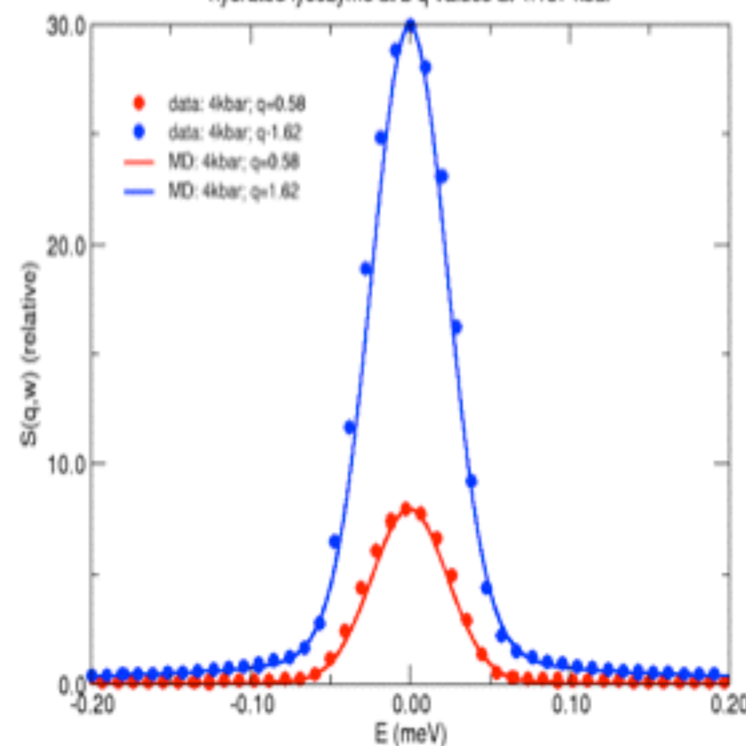
Agreement with simulation is robust and allows for further atomic scale analysis

RMSD (A^2)

Ref.	1 atm	4kbar
xtal	2.01	2.22
Self	0.62	0.53
1 atm	-	2.36







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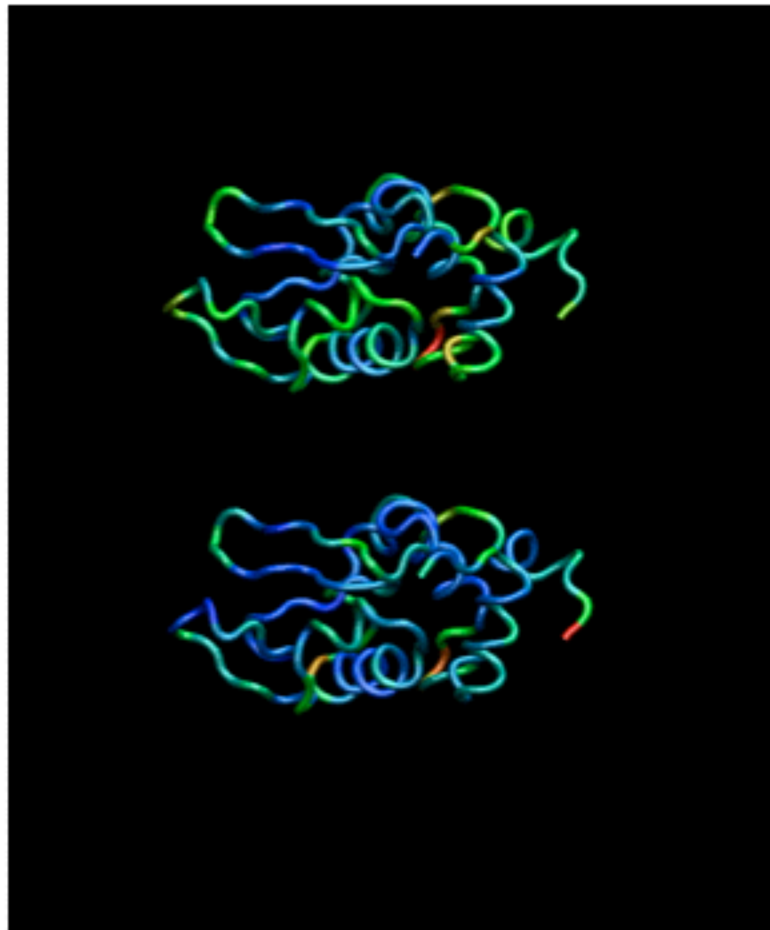
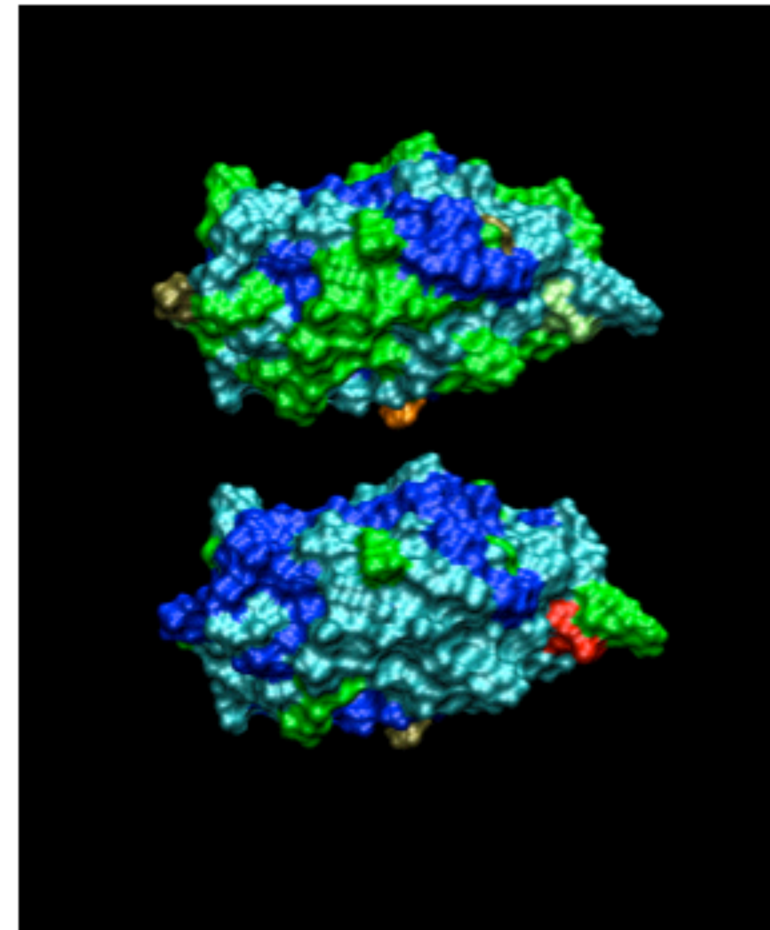
Examples

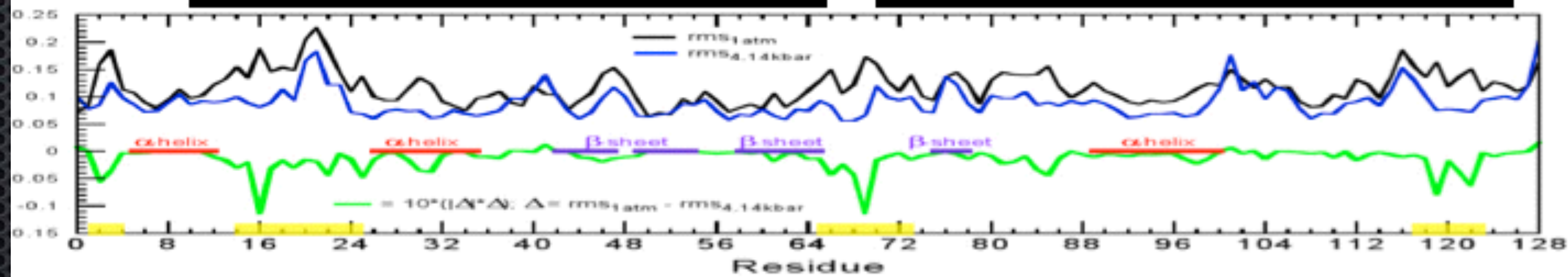
Atomic details … pressure

1 Atm

4137 MPa







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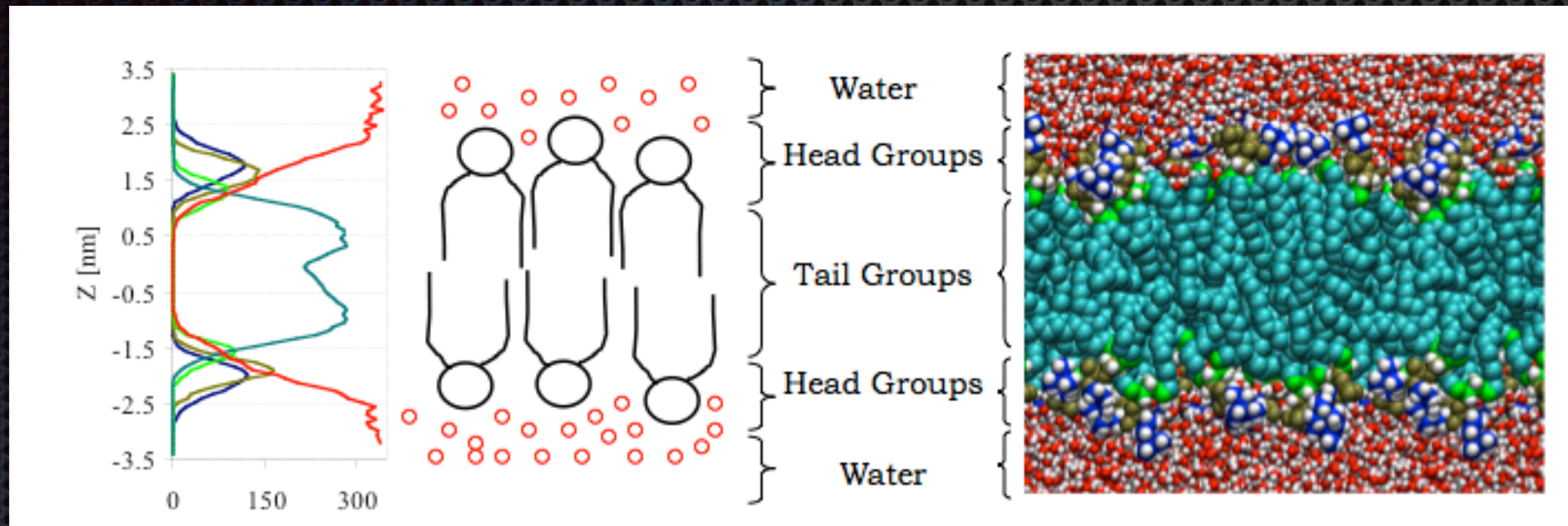
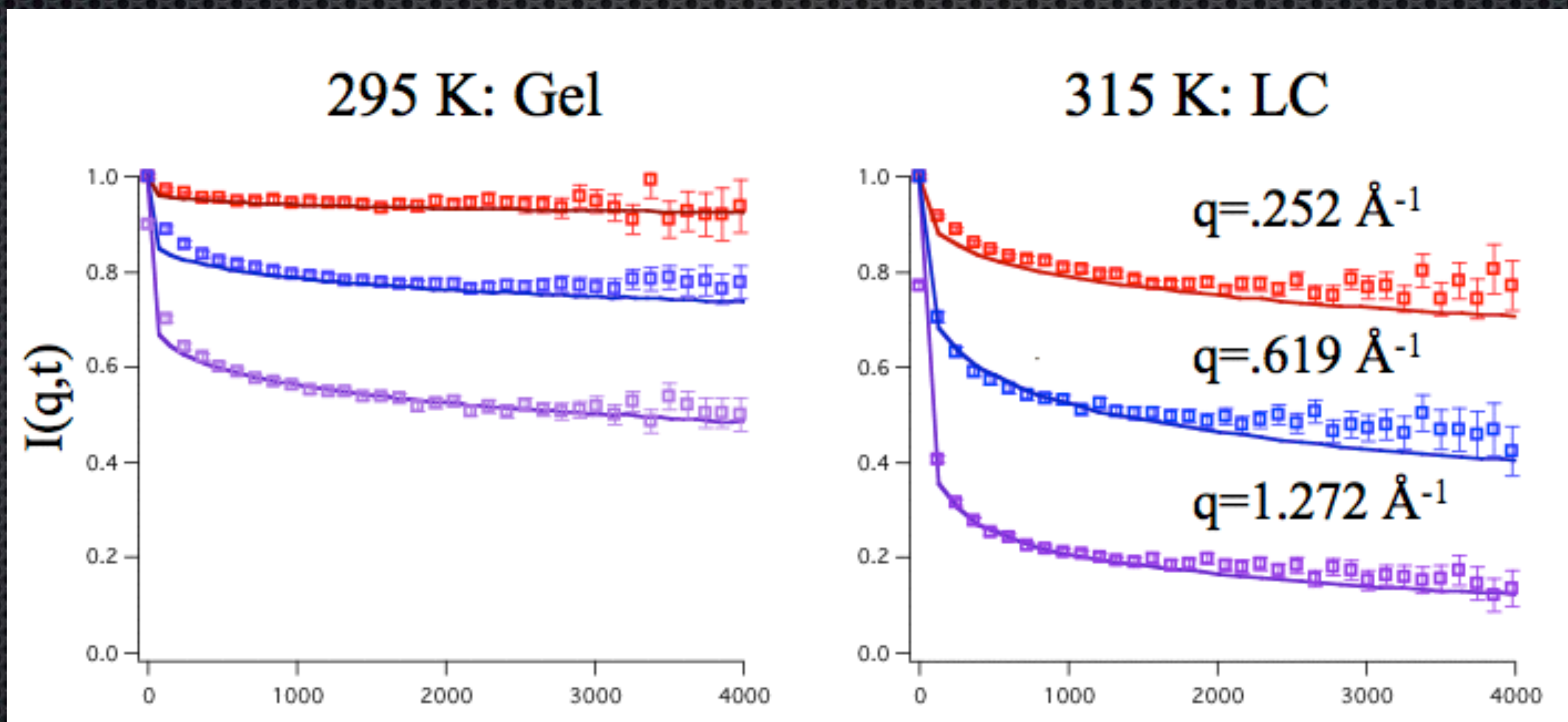
Examples





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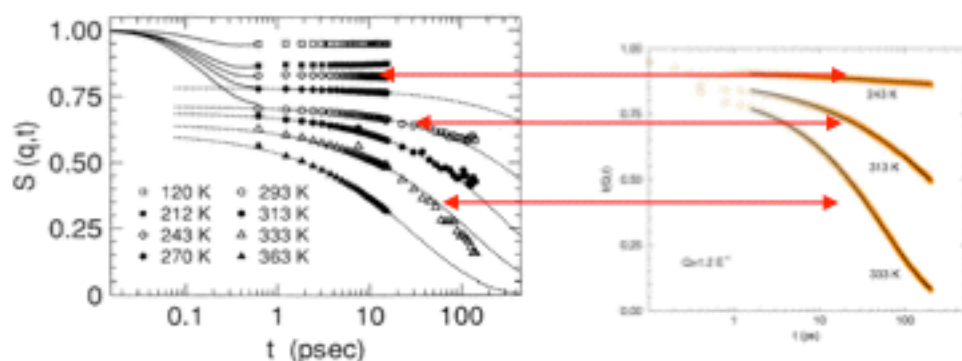
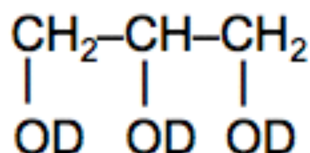
Examples

Validation of FF and Pure Glass Systems

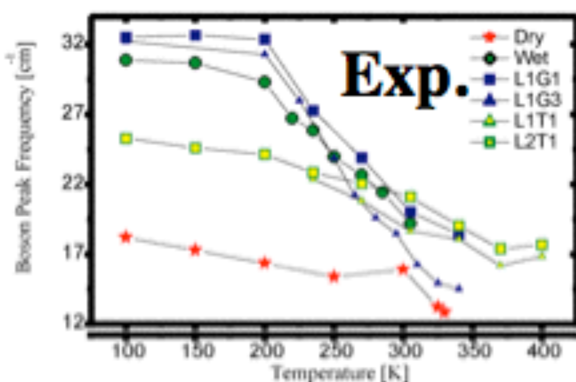
Glycerol

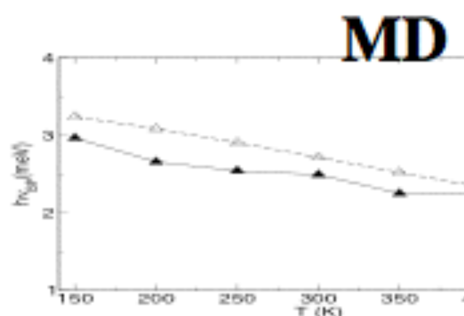
Fourier inversion of neutron scattering spectra
[Wuttke et al., PRE 52, 4026 (1995)]





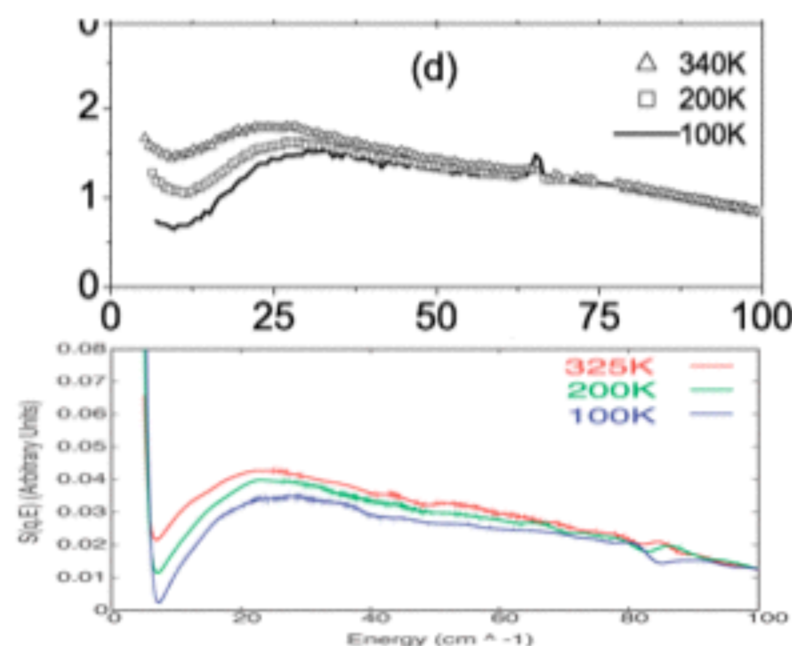
100s of ps





Trehalose

Raman spectra of lysozyme in dehydrated trehalose
[Caliskan et al., J. Non-Cryst. Solids (2002)]



ps

$$S(q,\nu)=\frac{A\nu_o}{\nu_0^2+\nu^2}+B\exp\left\{-\frac{[\ln(\nu/\nu_{BP})]^2}{2[\ln(W/\nu_{BP})]^2}\right\}$$

JCP **122**, 244910 (2005), JCP **124**, 1-8 (2006)

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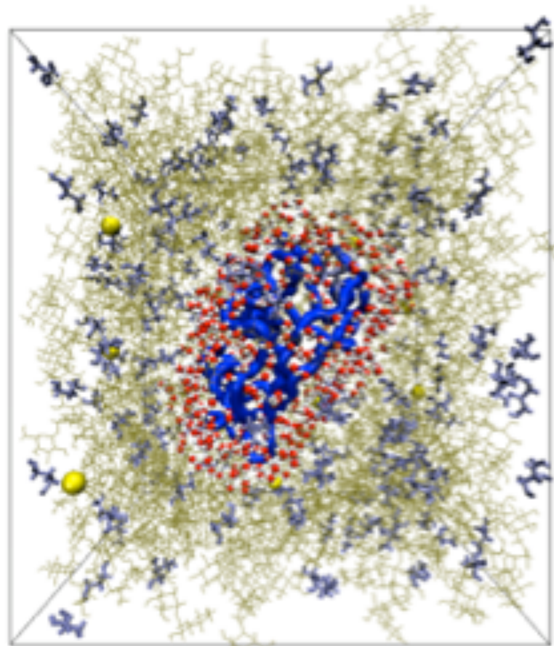
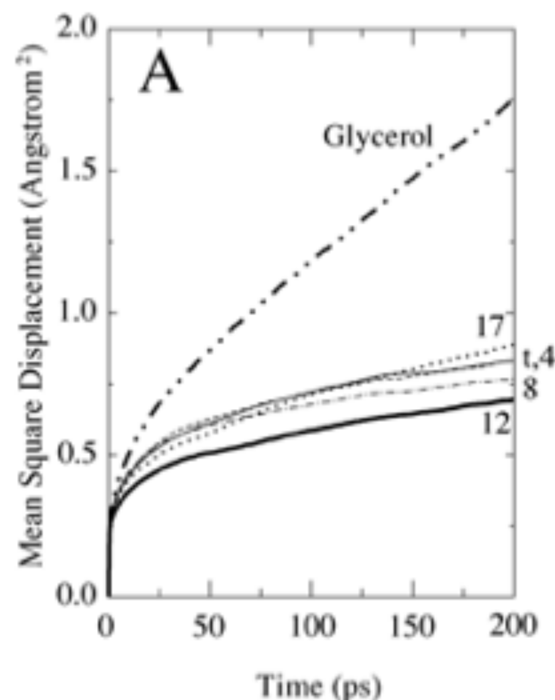
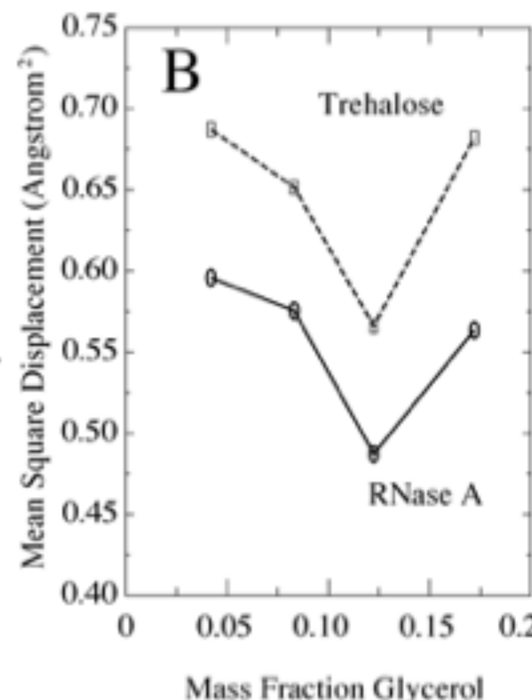
Examples

Binary glasses and protein dynamics: glycerol in trehalose

Moderate Protein Density (7 mM)







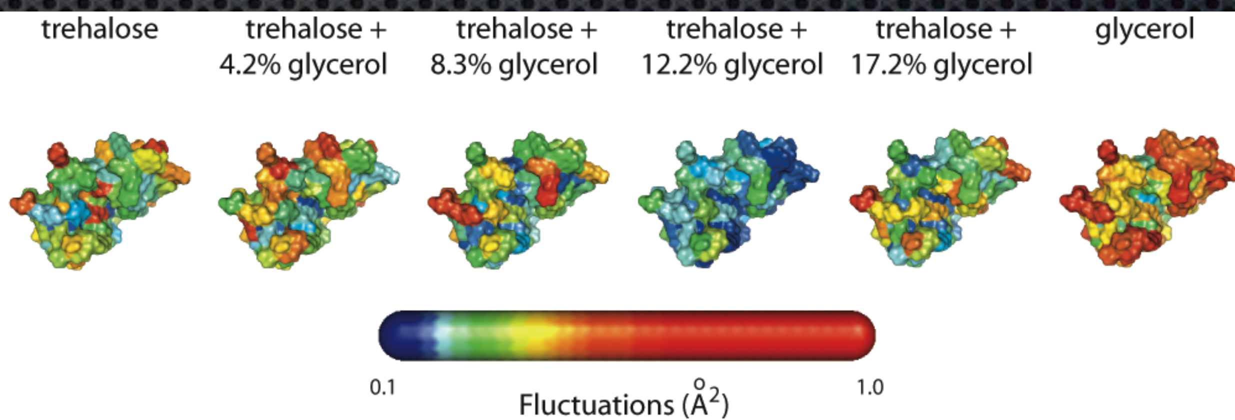
RMSD (Ca) < 2Å
MSD (H2O) --> 8Å

~30,000 atoms, 10 ns

6 protein/glass combinations

"What distinguishes one glass formulation from another?"

Dehydrated binary glass is rigidified by glycerol-trehalose hydrogen bonds (JCP **122**, 114505 (2005), JCP **122**, 244910 (2005 JCP **124**, 1-8 (2006)).



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Further Reading

NAMD

http://www.ks.uiuc.edu/Training/Tutorials/

CHARMM & AMBER

http://www.charmm.org/

http://ambermd.org/

MD

Frenkel & Smit : Understanding Molecular Simulation, ISBN: 0122673514

Allen & Tildesley : Computer Simulation of Liquids, ISBN: 9780198556459

Leach : Molecular Modelling: Principles and Applications, ISBN: 0582382106

Schlick : Molecular Modeling and Simulation, ISBN: 038795404X

Key Papers

Electrostatics calculations: latest methodological advances. P. Koehl. *Current Opinion in Structural Biology*, 16:142-151, 2006.

Empirical force fields for biological macromolecules: Overview and issues. A. D. MacKerell. *Journal of Computational Chemistry*, 25:1584-1604, 2004.

Molecular dynamics simulation of nucleic acids: successes, limitations, and promise. T. E. Cheatham and M. A. Young. *Biopolymers*, 56:232-256, 2000.

Molecular dynamics simulations of lipid bilayers. S. E. Feller. *Current Opinion in Colloid & Interface Science*, 5:217–223, 2000.

The MARTINI forcefield: coarse grained model for biomolecular simulations. S. J. Marrink, H. J. Risselada, S. Yefimov, D. P. Tieleman, and A. H.de Vries. *Journal of Physical Chemistry B.*, 111:7812-7824, 2007.

So many options . . .

Bio-simulation (All-atom MD packages):

Amber*
CHARMM*
NAMD*
GROMACS*
GROMOS
LAMPPS*
PINYMD*
HIPPO
GPIUTMD
DL_POLY*
ESPResSo
MacroModel*
MACSIMUS
MOLDY
MOSCITO
ProtoMol
TINKER*
MDGrape
Materials Studio (InsightII)*
. . .

Classical force fields:

Amber*
CHARMM*
CVFF
COSMOS-NMR
GROMACS*
GROMOS
OPLS*
ENZMIX
ECEPP/2
QCFF/PI
UFF
CFF*
MMFF
MM2, MM3, MM4*
XPOL
SIBFA
AMOEBA
VALBOND
DRF90
CG MD*
. . .

Methods & details*:

Thermostats
Barostats
Electrostatics (PBC)
Polarizability
Implicit Solvent
Langevin Dynamics
Replica Exchange
Parallel Tempering
Steered MD
Free-Energy Calculations
Umbrella Sampling
Normal Mode Analysis
VMD
Pymol
Chimera, O
APBS
Gaussian, Gamess, CPMD
Beowulf, GPU Clusters
Rosetta
PHYRE
Folding @ Home
TIP3, TIP3P, TIP4P, SPC, ST2
. . .

“HOW TO” . . .
Start you on the path

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