

Molecular Dynamics for biological systems



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What for ?

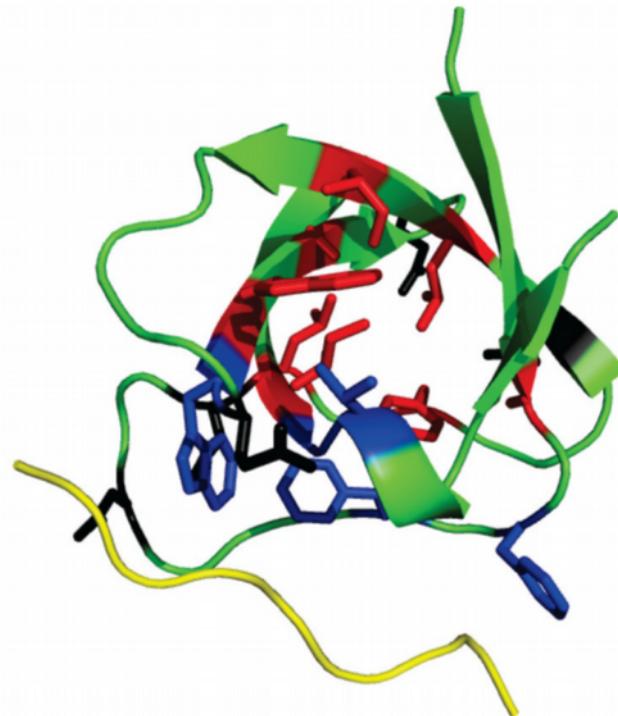
Understanding a biological macromolecule

Karplus, Acc. Chem. Res., 2002, 35 (6), pp 321–323,
doi: 10.1021/ar020082r

Describing living systems in terms of physics and chemistry

Can we predict

- Structural and functional changes
- Solvation free energies
- The microscopic solvation profile



Courtesy of Dominik Domin, ENS

What for ?

Understanding a biological macromolecule

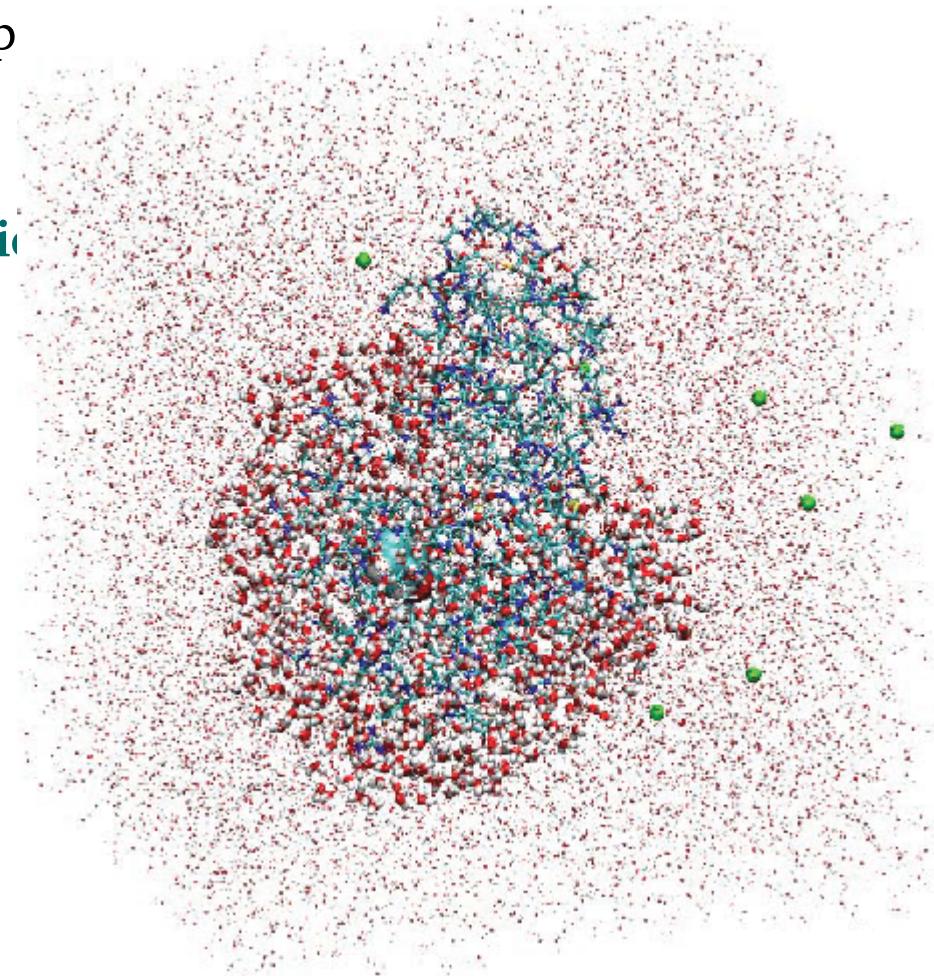
Karplus, Acc. Chem. Res., 2002, 35 (6), p

doi: 10.1021/ar020082r

Describing living systems in terms of physics

Can we predict

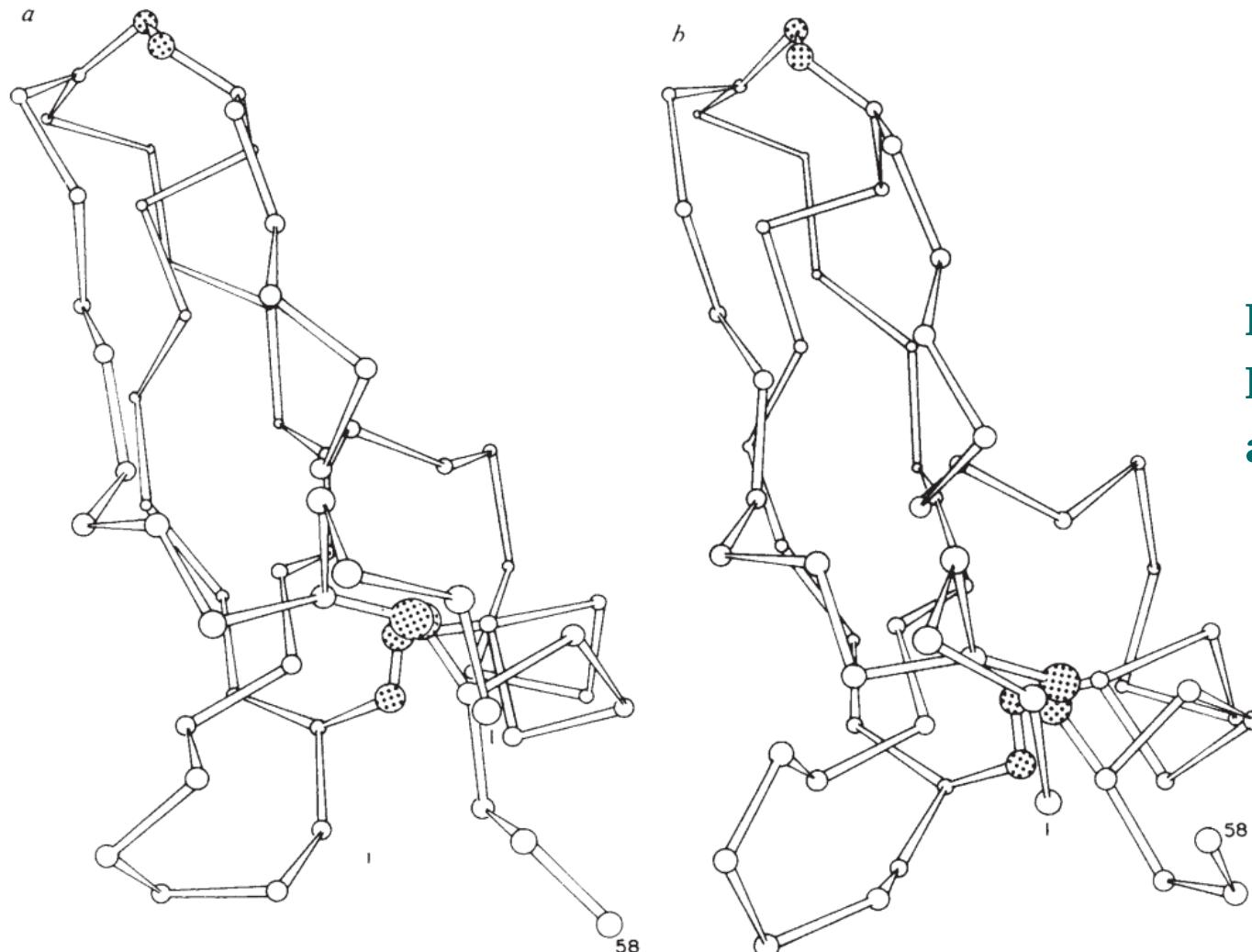
- Structural and functional changes
- Solvation free energies
- The microscopic solvation profile



Courtesy of J. Dziedzic, S. J. Fox, T. Fox,
C. S. Tautermann and C.-K. Skylaris

Since when ?

In the 70' : McCammon, Gelin and Karplus, Dynamics of folded proteins
Nature 1977, 267, 585-590



MD 50's
MD for liquid Ar 60's
accurate X-rays ~ 70's

8.8 ps by steps of 1 fs

Fig. 1 The peptide backbone (α carbons) and disulphide bonds of PTI. *a*, X-ray structure²¹. *b*, Time evolved structure after 3.2 ps of dynamical simulation.

So late !?

In the 70' : McCammon, Gelin and Karplus, Dynamics of folded proteins
Nature 1977, 267, 585-590

- Time-averaged structure and fluctuations

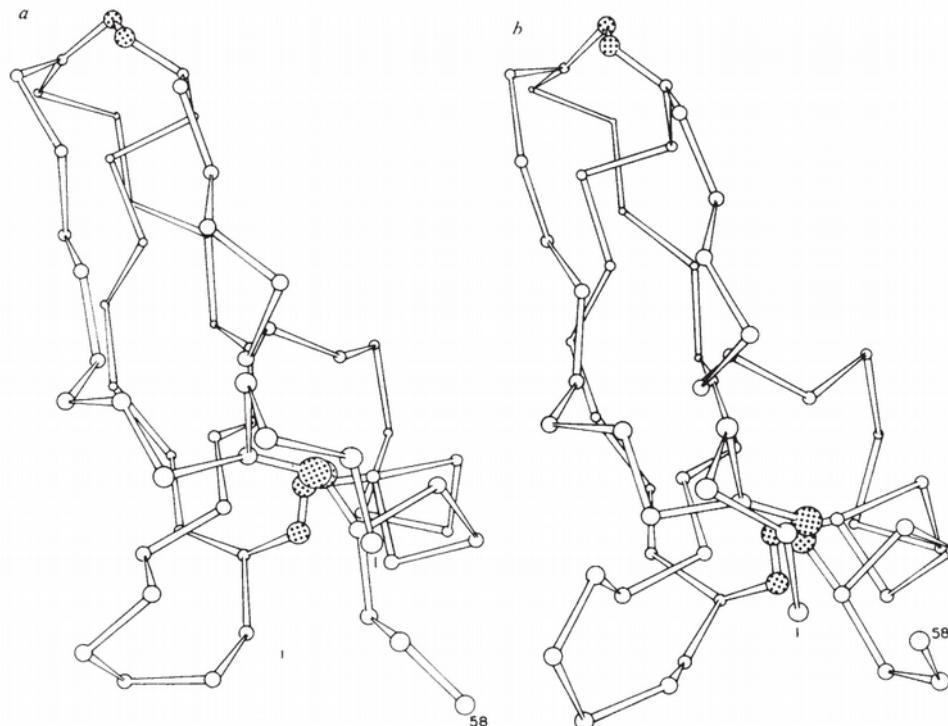
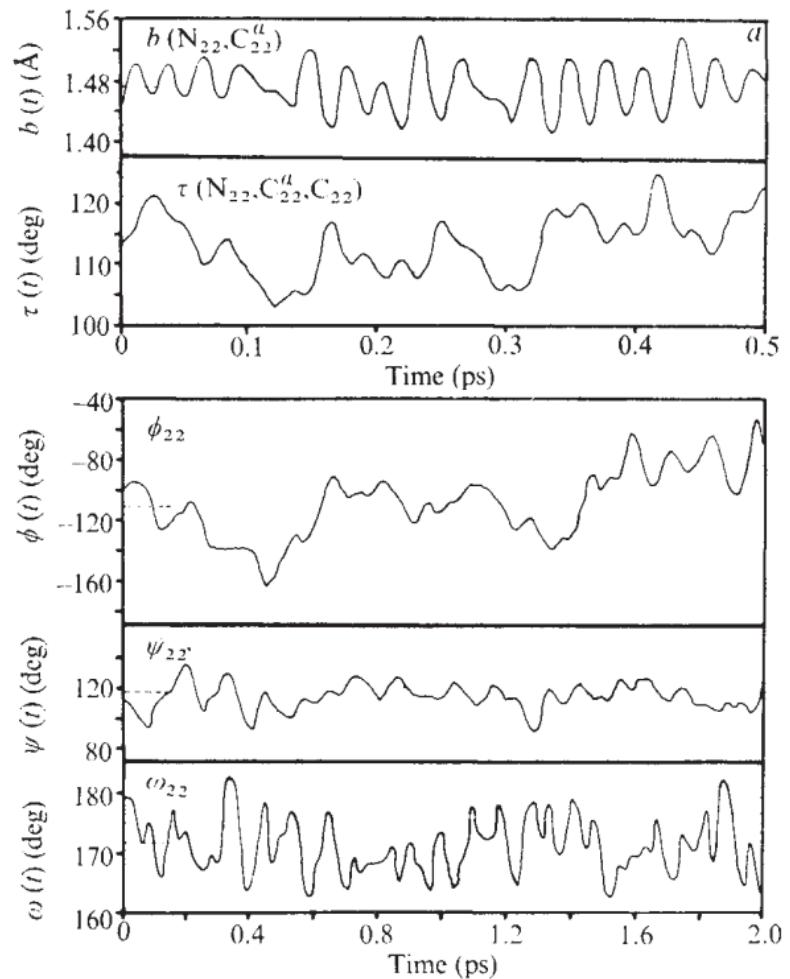


Fig. 1 The peptide backbone (α carbons) and disulphide bonds of PTI. *a*, X-ray structure²¹. *b*, Time evolved structure after 3.2 ps of dynamical simulation.

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- Time-averaged structure and fluctuations
- **Time-dependence of motions**

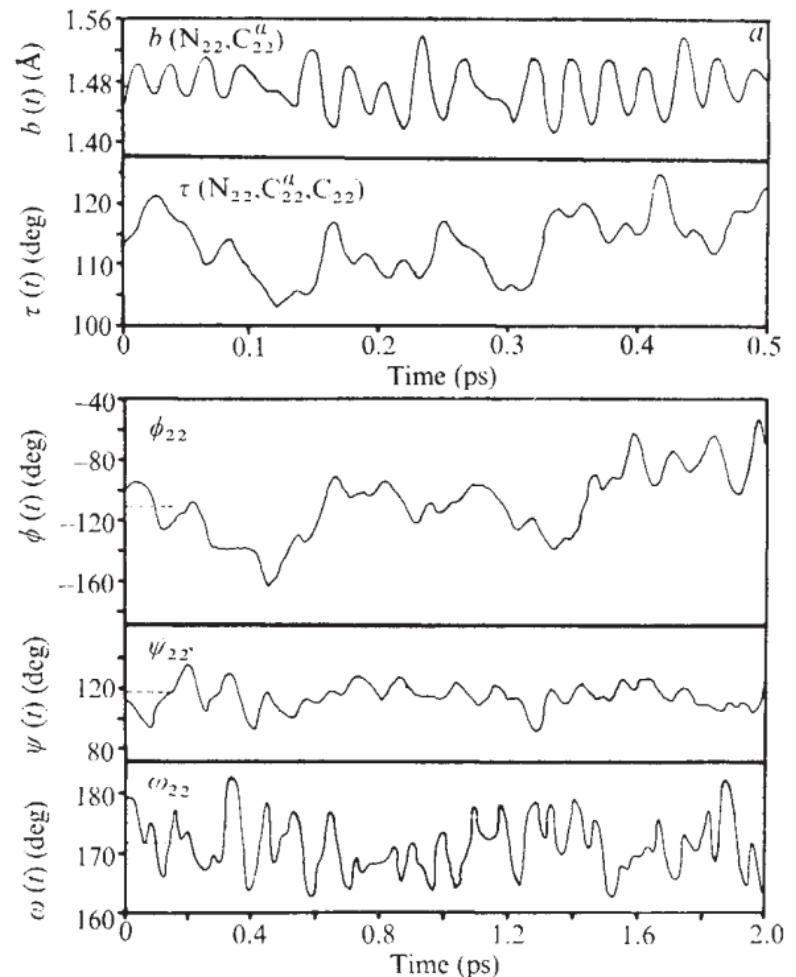


So late !?

In the 70' : McCammon, Gelin and Karplus, Dynamics of folded proteins

Nature 1977, 267, 585-590

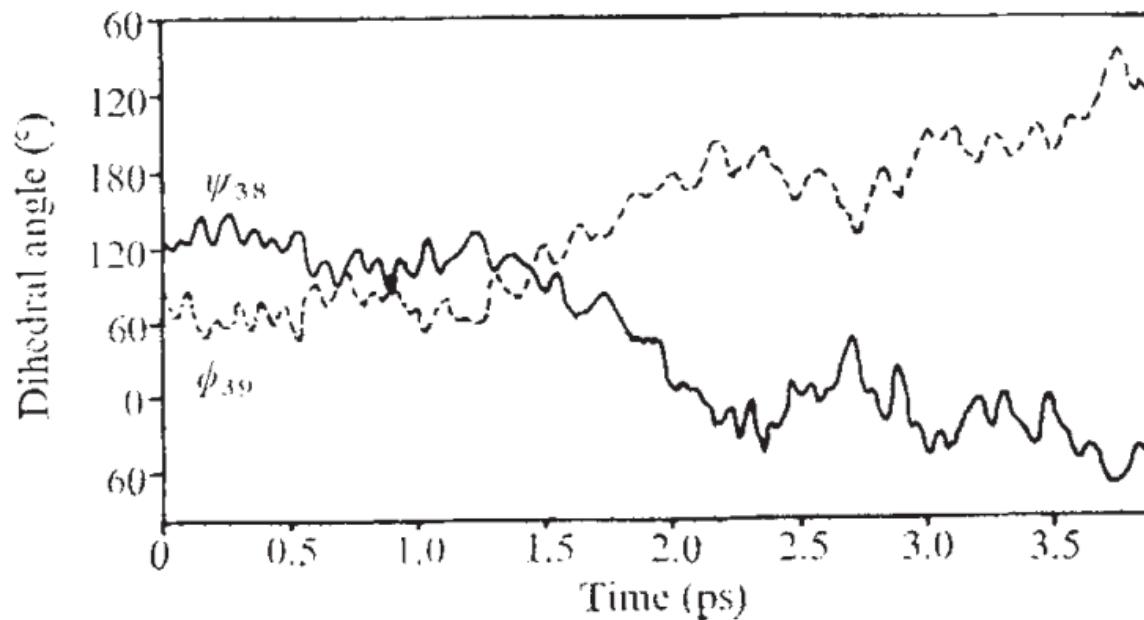
- Time-averaged structure and fluctuations
- Time-dependence of motions
- Concerted fluctuations
- Concerted motions



So late !?

In the 70' : McCammon, Gelin and Karplus, Dynamics of folded proteins
Nature 1977, 267, 585-590

Fig. 5 Amide group transition; the time development of ψ_{38} and ϕ_{39} during the transition is shown.



« It is clear [...] the protein [...] samples highly anharmonic regions of the potential surface [...] confined multidimensional space [...] »

So late !?

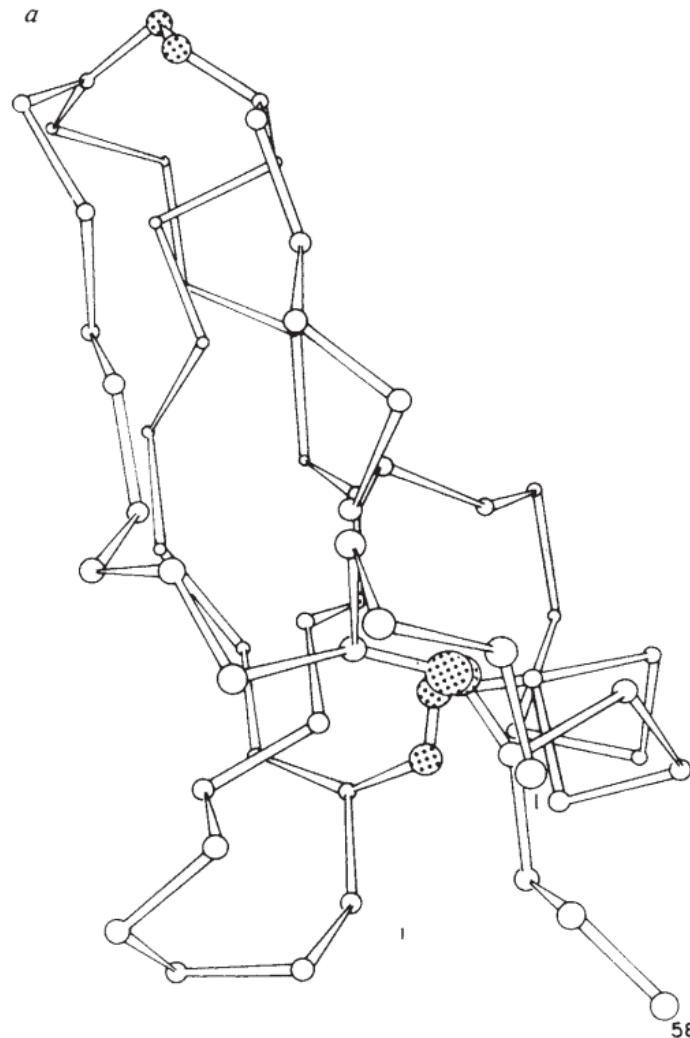
In the 70' : McCammon, Gelin and Karplus, Dynamics of folded proteins
Nature 1977, 267, 585-590

« It is clear [...] the protein [...] samples highly anharmonic regions of the potential surface [...] confined multidimensional space [...] »



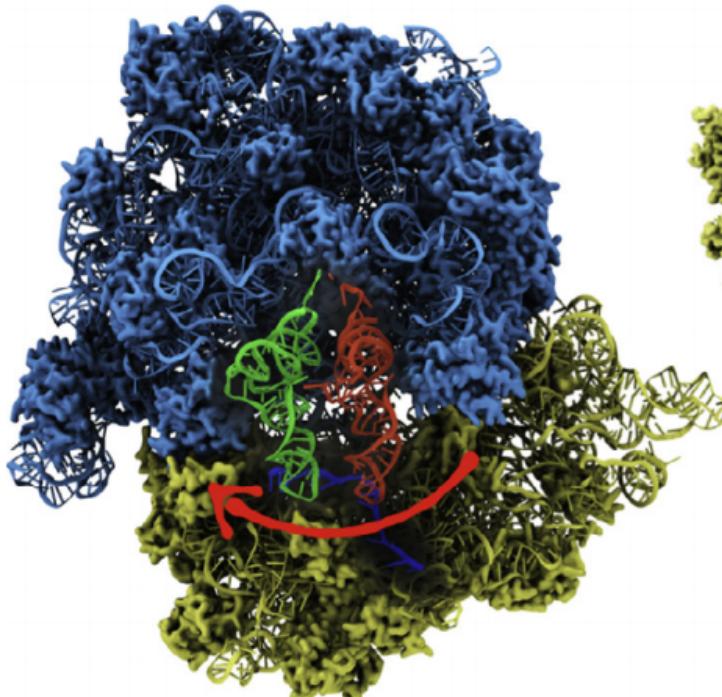
Still, we understood proteins are not rigid.

So late !?

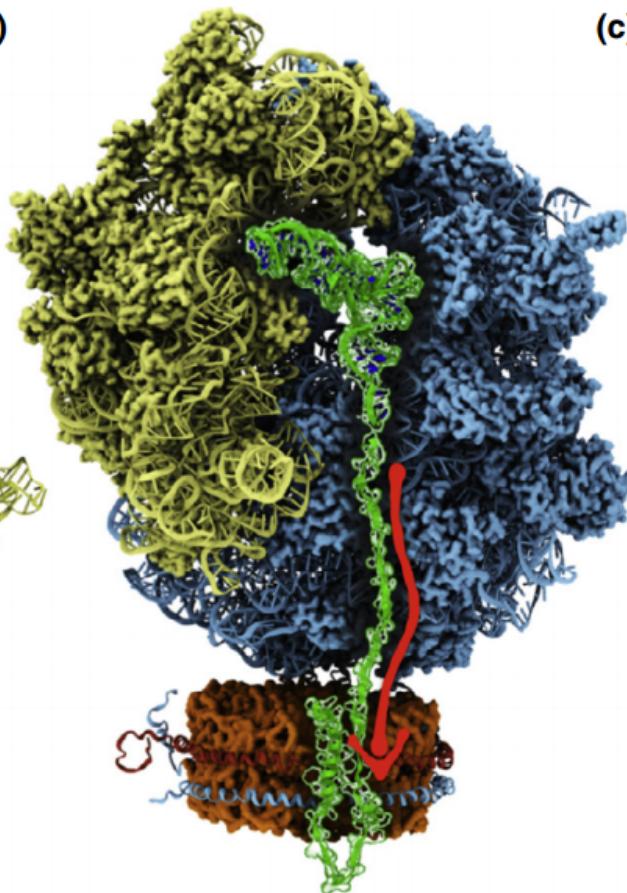


Biological systems studied today

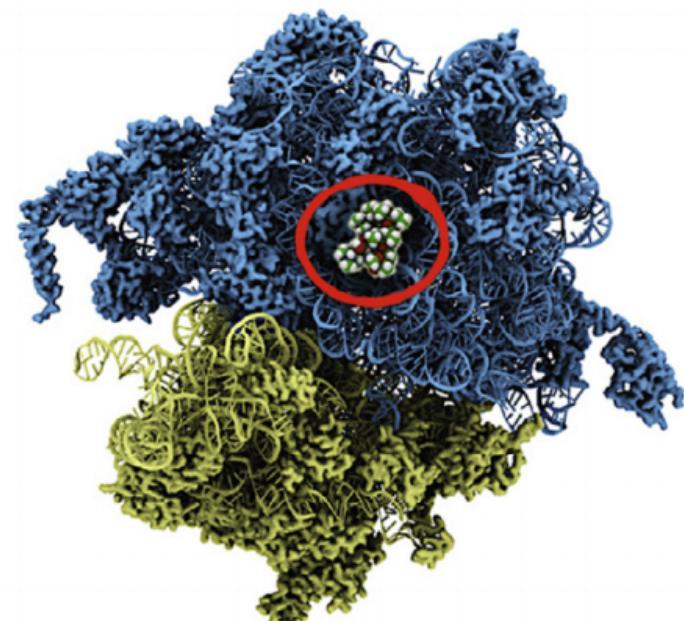
(a)



(b)



(c)



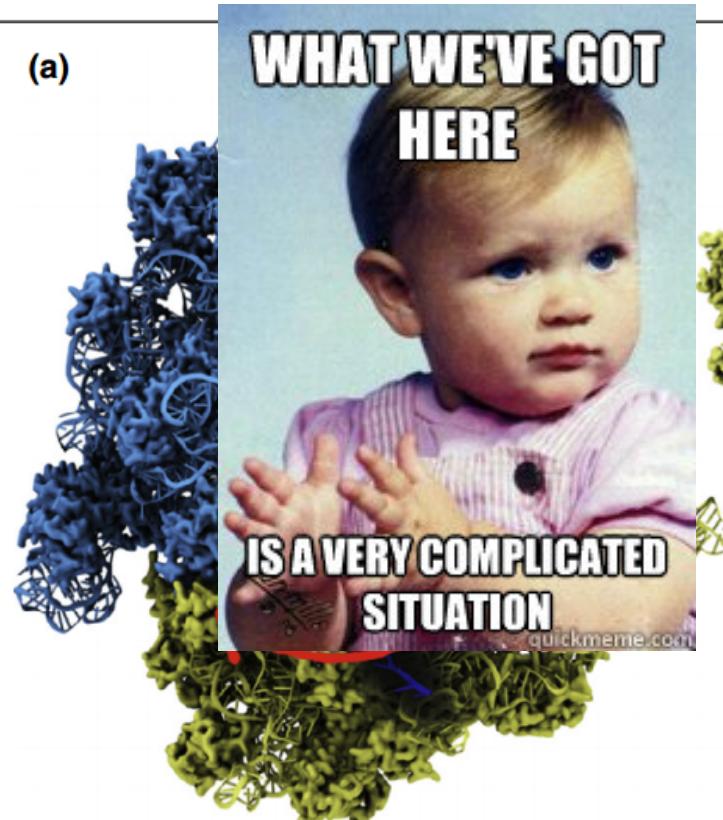
5 nm

Current Opinion in Structural Biology

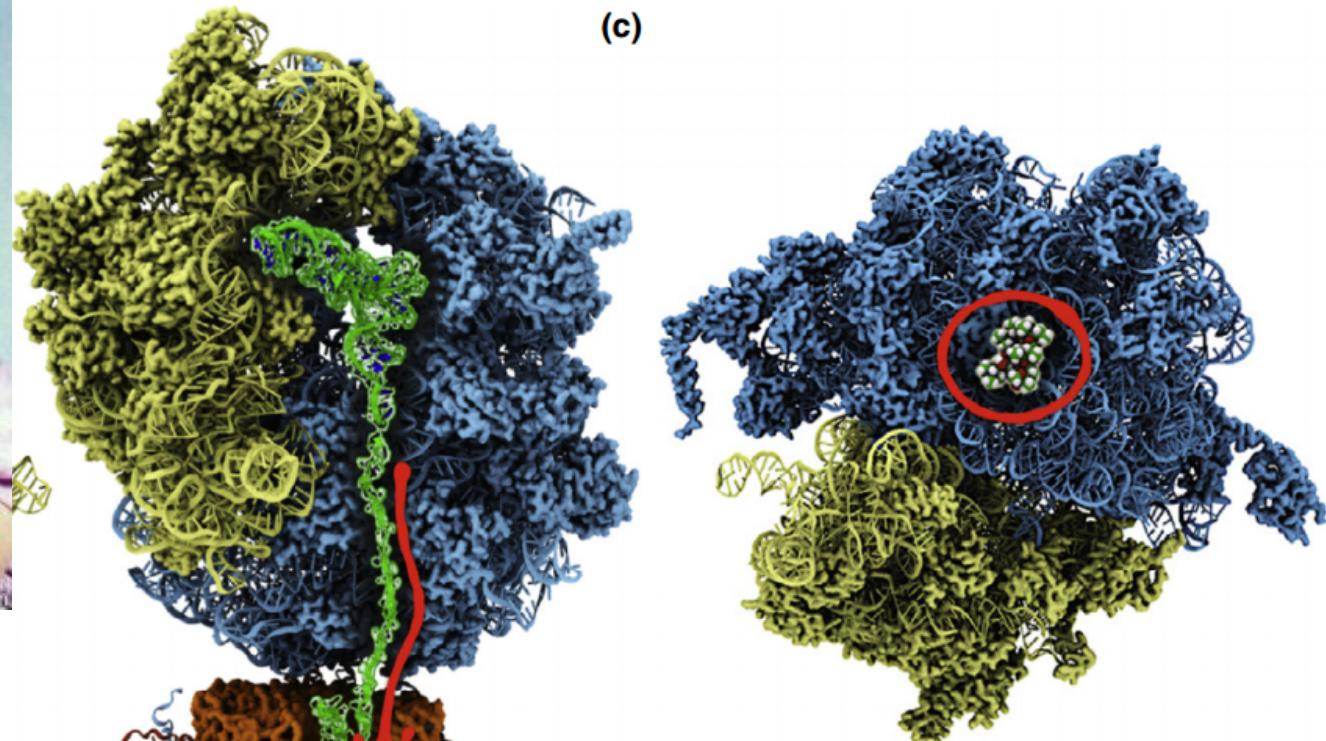
(a) Translocating ribosome at the pretranslocation state with an A-site tRNA (red) and a P-site tRNA (green) [49^{**}]. A red arrow shows the direction of tRNA's traversal motion. **(b)** Insertion of a nascent protein by the ribosome into a nanodisc [50] membrane working with the SecYE translocon [51]. The nascent protein and P-site tRNA are shown in green. A red arrow shows the direction of the nascent protein's insertion motion. C. Bacterial ribosome with the antibiotic drug *erythromycin* (in red circle) shown at its binding site inside the ribosome [16^{*}].

Biological systems studied today

(a)



(c)



(a) Translocating ribosome at the pretranslocation state with an A-site tRNA's traversal motion. (b) Insertion of a nascent protein by the ribosome [51]. The nascent protein and P-site tRNA are shown in green. A Bacterial ribosome with the antibiotic drug erythromycin (in red c

m
I Biology

direction
nslocon
C.

Code names to keep in mind

CHARMM

Chemistry at HARvard Macromolecular Mechanics

AMBER



NAMD

Scalable Molecular Dynamics

GROMACS<sup>FAST.
FLEXIBLE.
FREE.</sup>

Petascale, exascale, Xtreme-scale, Xxtreme, XXX...

From laptops to **Tianhe-2** (heterogeneous architecture, 3 120 000 cores)
55 PFLOP/S

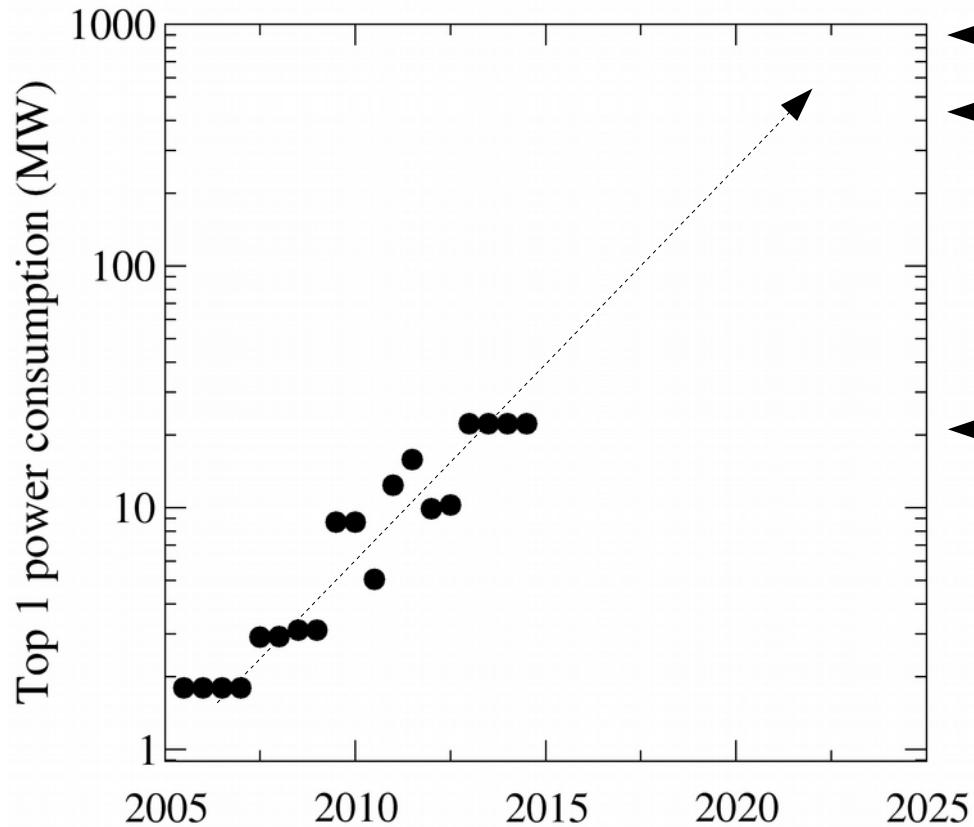
... to propagate sum of forces = mass × acceleration

Petascale, exascale, Xtreme-scale, Xxtreme, XXX...

From laptops to **Tianhe-2** (heterogeneous architecture, 3 120 000 cores)

55 PFLOP/S 18 MW

... to propagate sum of forces = mass \times acceleration



← Fessenheim (reactor 1)
← Fukushima Daiichi (reactor 1)
← Tianhe-2, nov. 2014



Petascale, exascale, Xtreme-scale, ..., ASICS

A short story for the coffee time !

David E. Shaw Research

\$\$\$\$script

hedge fund < parallel computing > billions | bioMDresearch > milliseconds
\$\$\$

Application Specific Integrated Circuits (ASICs) designed for MD of proteins

ANTON



Protein Data Bank

Centralised repository for experimental structures :

<http://www.wwpdb.org/>

Three portals :

- Europe : <http://www.ebi.ac.uk/pdbe>
- Japan : <http://pdjb.org>
- United-States : <http://www.rcsb.org>



May 2016 : 119137 Biological Macromolecular Structures

Berman, Nucl. Acids Res. (2000) 28 (1): 235-242,
doi: 10.1093/nar/28.1.235

A short tutorial

This tutorial is a shortened and discussed version of GROMACS tutorial
« **Lysozyme in water** » by Justin A. Lemkul, University of Maryland

We recommend you do the whole tuto online once back home
Plus you could drop Justin Lemkul an email to thank him !
(jalemkul@outerbanks.umaryland.edu)

<http://www.bevanlab.biochem.vt.edu/Pages/Personal/justin/gmx-tutorials/lysozyme/>

Our target protein (egg lysozyme) in a target solvent (water)

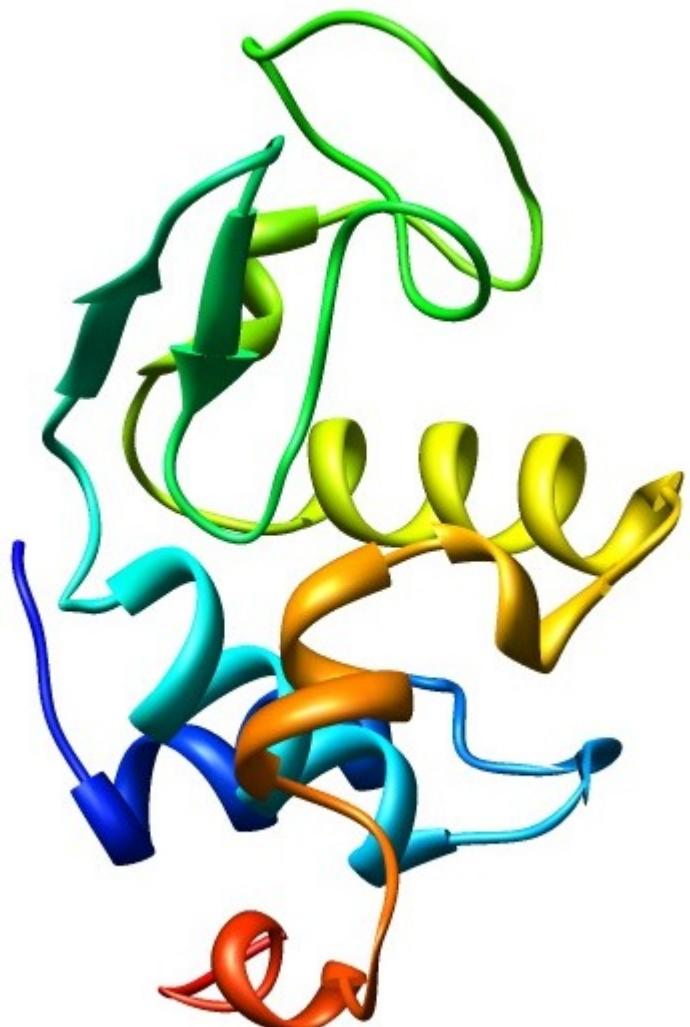
- 1/ Chose a model and generate input files
- 2/ Define a simulation box
- 3/ Solvate
- 4/ Add ions
- 5/ Energy minimization
- 6/ Equilibration NVT / NPT
- 7/ Production
- 8/ Analysis

1/ Choose a model and generate input files

Our target protein (egg lysozyme) in a target solvent (water)

1/ get the structure from the Protein Data Bank

```
 wget http://files.rcsb.org/download/1AKI.pdb
```



Follow the online tutorial ! This is just a summary

2/ remove water molecules

```
grep ^ATOM 1AKI.pdb > 1AKI_noWater.pdb
```

3/ put the protein in the simulation box

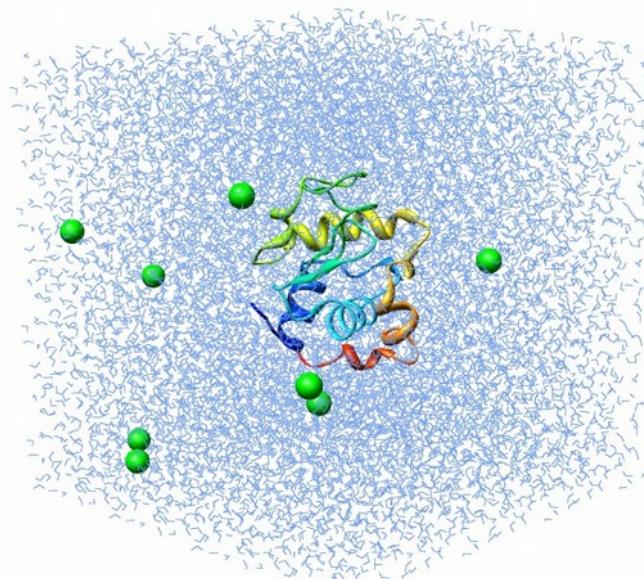
```
gmx pdb2gmx -f 1AKI_noWater.pdb -o 1AKI_processed.gro -water spce  
gmx editconf -f 1AKI_processed.gro -o 1AKI_newbox.gro -c -d 1.0 -bt cubic
```

4/ solvate the protein (put water molecules inside the box)

```
gmx solvate -cp 1AKI_newbox.gro -cs spc216.gro -o 1AKI_solv.gro -p topol.top
```

5/ make the system neutral by adding ions

```
gmx grompp -f ionsmdp -c 1AKI_solv.gro -p topol.top -o ions.tpr  
gmx genion -s ions.tpr -o 1AKI_solv_ions.gro -p topol.top -pname NA -nname CL -nn 8
```



Follow the online tutorial ! This is just a summary

6/ stabilize the generated system

```
gmx grompp -f minim.mdp -c 1AKI_solv_ions.gro -p topol.top -o em.tpr  
gmx mdrun -v -deffnm em -ntmpi 8 -ntomp 1 -pin on
```

Plot the evolution of the energy to convince yourself it diminished

```
gmx energy -f em.edr -o potential.xvg
```

7/ stabilize the temperature to 300 K (takes few minutes)

```
gmx grompp -f nvt.mdp -c em.gro -p topol.top -o nvt.tpr  
gmx mdrun -v -deffnm nvt -ntmpi 8 -ntomp 1 -pin on
```

Plot the evolution of the temperature to convince yourself it is fluctuating around 300K

```
gmx energy -f nvt.edr -o temperature.xvg
```

8/ Stabilize also the pressure to 1 atmosphere (takes few minutes)

```
gmx grompp -f npt.mdp -c nvt.gro -t nvt.cpt -p topol.top -o npt.tpr  
gmx mdrun -v -deffnm npt -ntmpi 8 -ntomp 1 -pin on
```

Plot both pressure and density to convince yourself

```
gmx energy -f npt.edr -o pressure.xvg
```

```
gmx energy -f npt.edr -o density.xvg
```

Follow the online tutorial ! This is just a summary

9/ Production run ! The one you will extract something about your protein (takes few hours)

```
gmx grompp -f mdmdp -c npt.gro -t npt.cpt -p topol.top -o md_0_1.tpr  
gmx mdrun -v -deffnm md_0_1 -ntmpi 8 -ntomp 1 -pin on
```

10/ Some examples of analysis

```
gmx trjconv -s md_0_1.tpr -f md_0_1.xtc -o md_0_1_noPBC.xtc -pbc mol -ur compact  
gmx rms -s md_0_1.tpr -f md_0_1_noPBC.xtc -o rmsd.xvg -tu ns  
gmx rms -s em.tpr -f md_0_1_noPBC.xtc -o rmsd_xtal.xvg -tu ns  
gmx gyrate -s md_0_1.tpr -f md_0_1_noPBC.xtc -o gyrate.xvg
```