

# Computational Techniques in Chemistry

## Session 2: Introduction to molecular dynamics simulations

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Big thanks to Matteo Degiacomi ([matteo.degiacomi@ed.ac.uk](mailto:matteo.degiacomi@ed.ac.uk)) and  
Hannah Pollak ([h.pollak@sms.ed.ac.uk](mailto:h.pollak@sms.ed.ac.uk)) for material development

# Molecular Modeling

## WHY?

- Not every property can be measured experimentally
- Experiments can be expensive, time consuming or dangerous

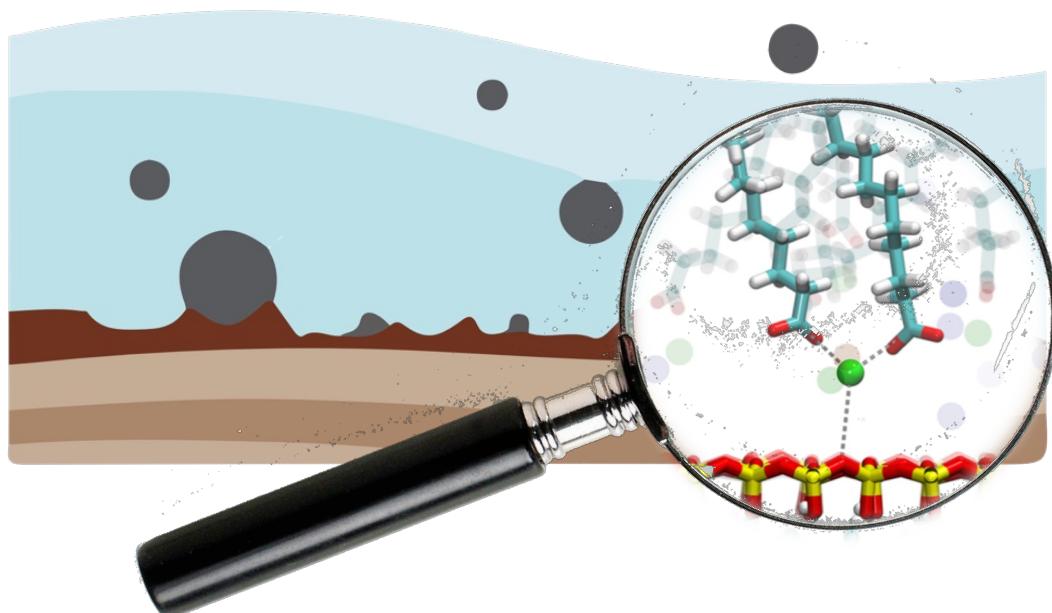


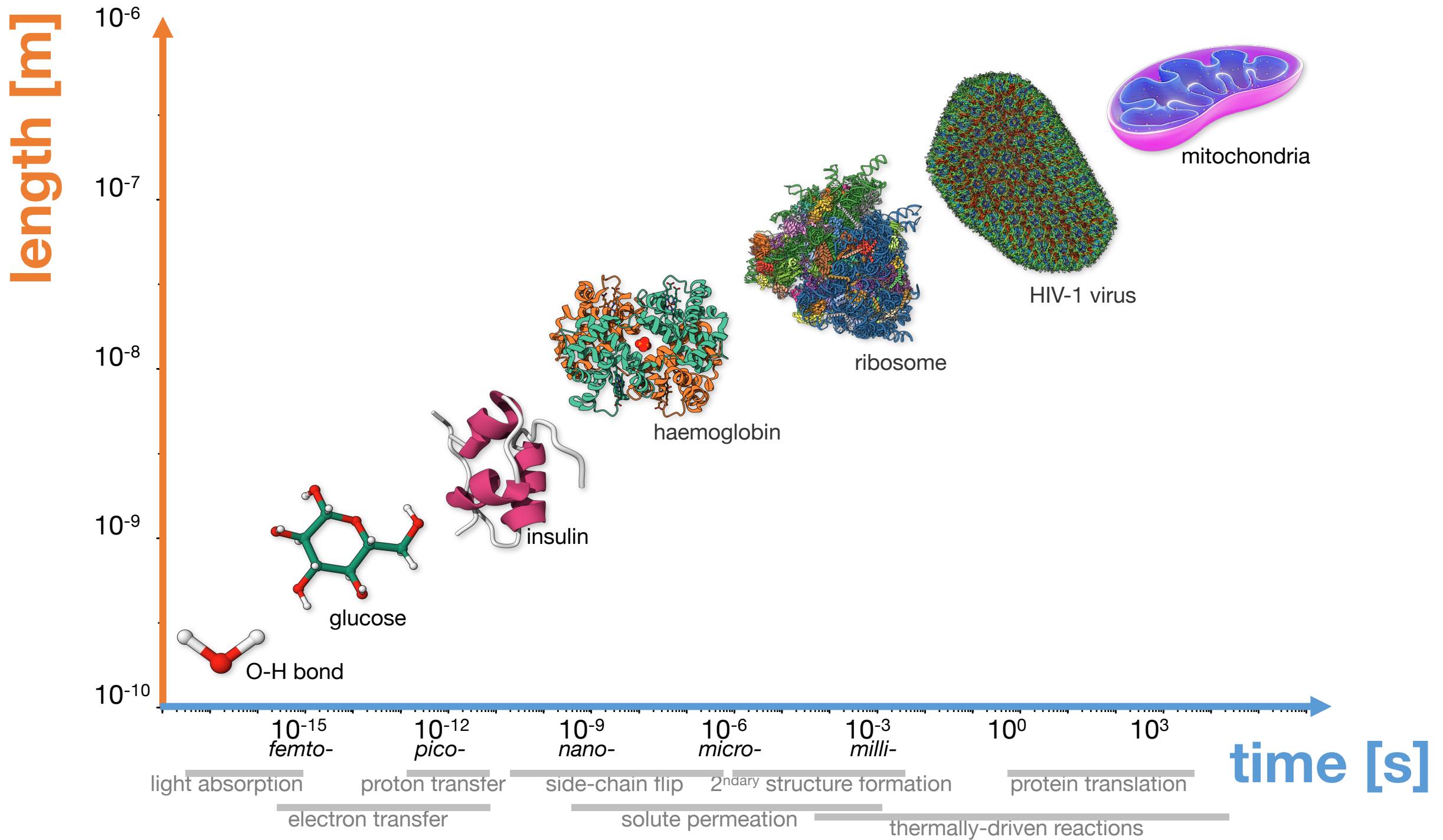
## WHAT?

- Theoretical/computational techniques
- Simulate properties/behavior of molecules

## WHEN?

- Predictive or analytical tool for properties that experiments cannot measure
- Rationalize experimental data and guide further work

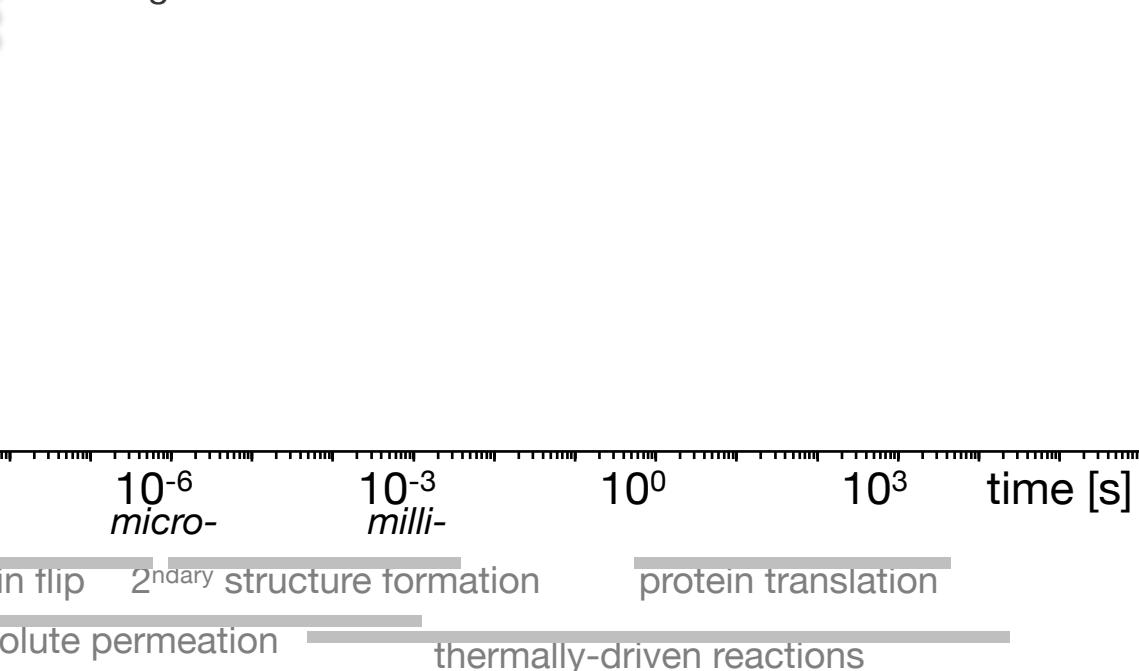


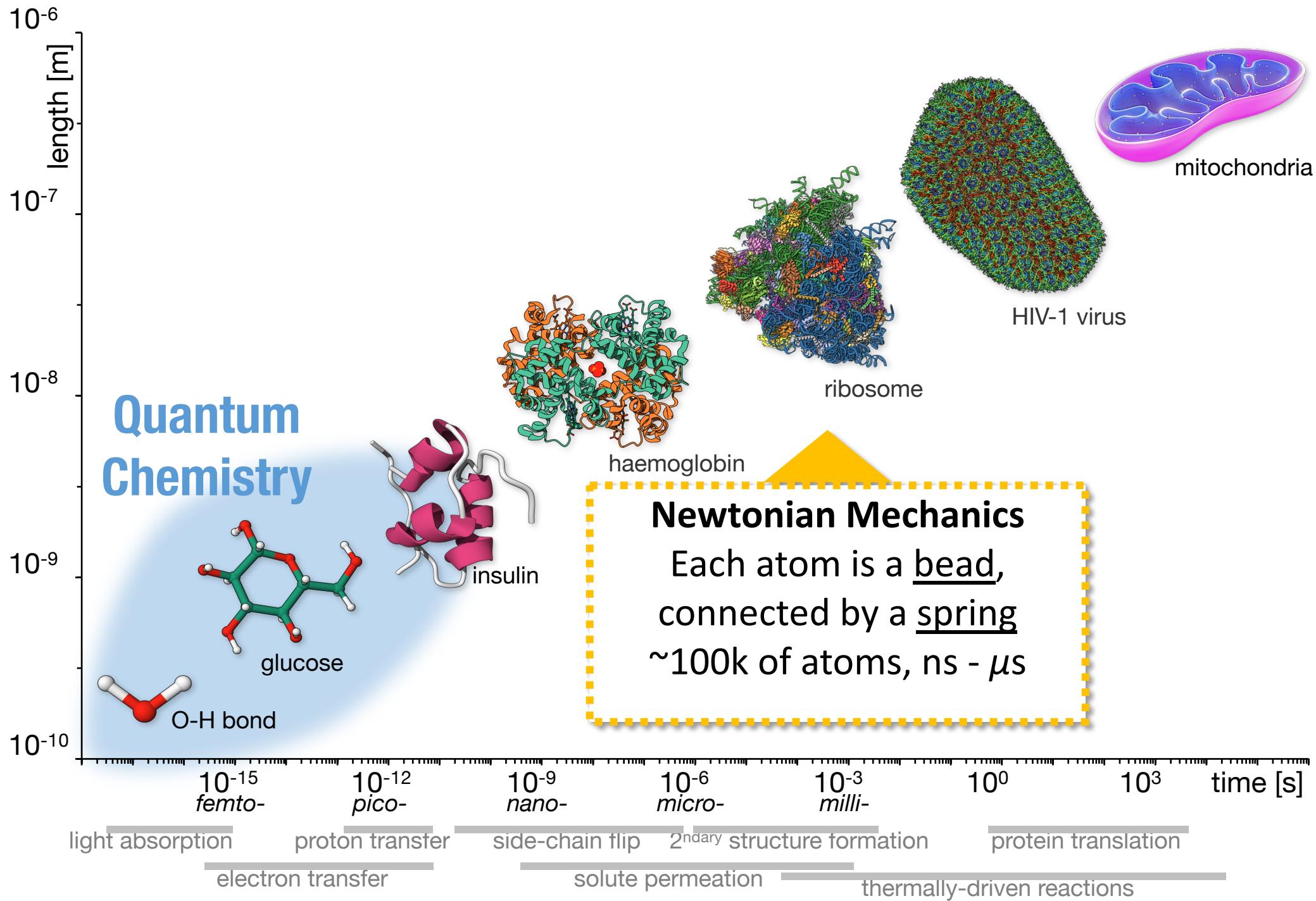


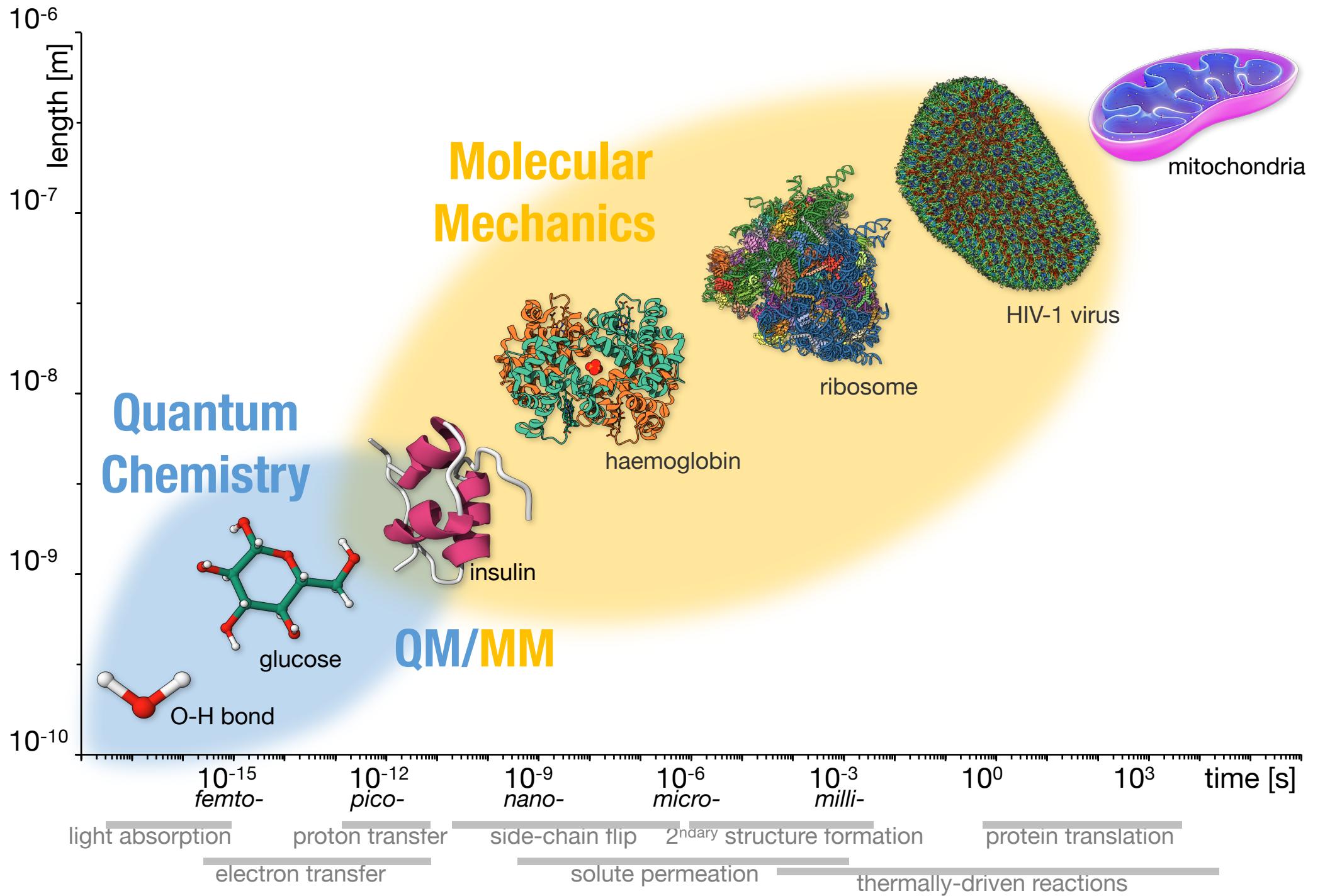
$10^{-6}$

## Schrödinger equation

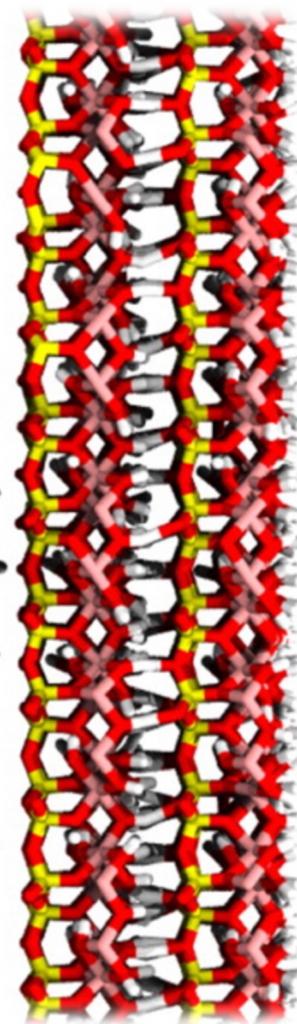
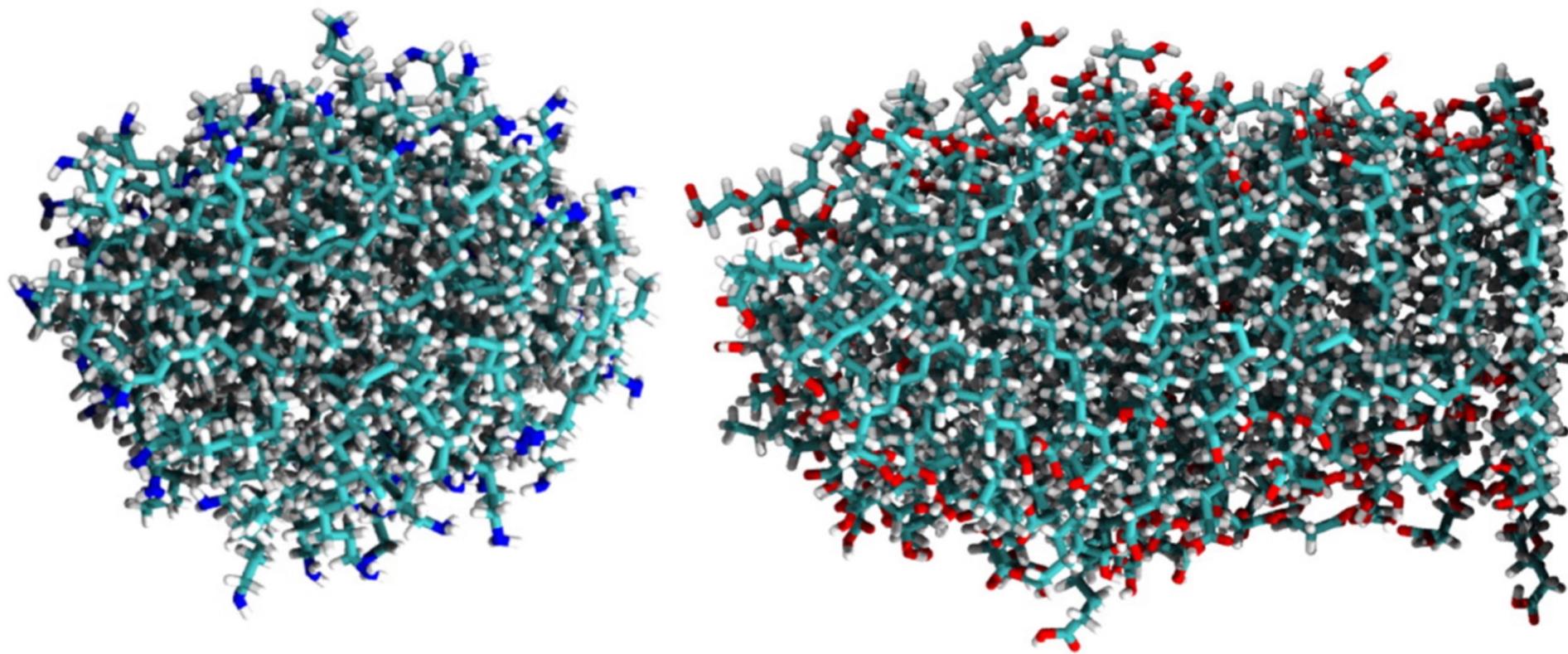
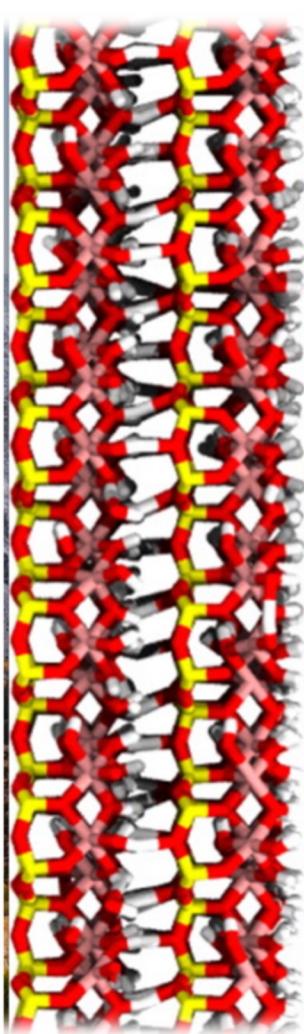
- Exact only for H and He
- Approximations:
  - ab-initio: directly derived
  - semi-empirical and empirical: fitted to experiments
- Properties that cannot be isolated: transition & excited states
- ~100 of atoms, ps motions





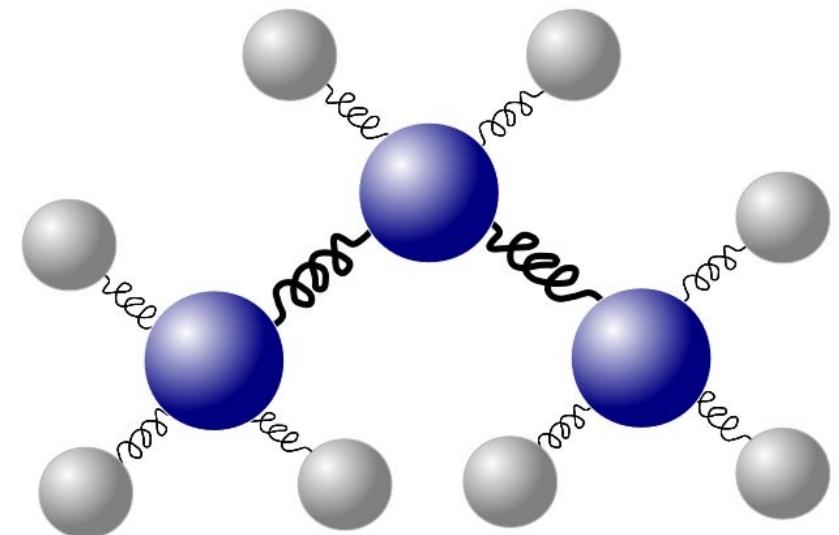


# Molecular Mechanics or Force Field Methods



# Force Field Methods

- A molecule is represented by a set of *balls* connected with *springs*
- System's energy depends on *classical* interactions between balls and springs
- Interactions are described by pre-assigned parameters = *force fields*

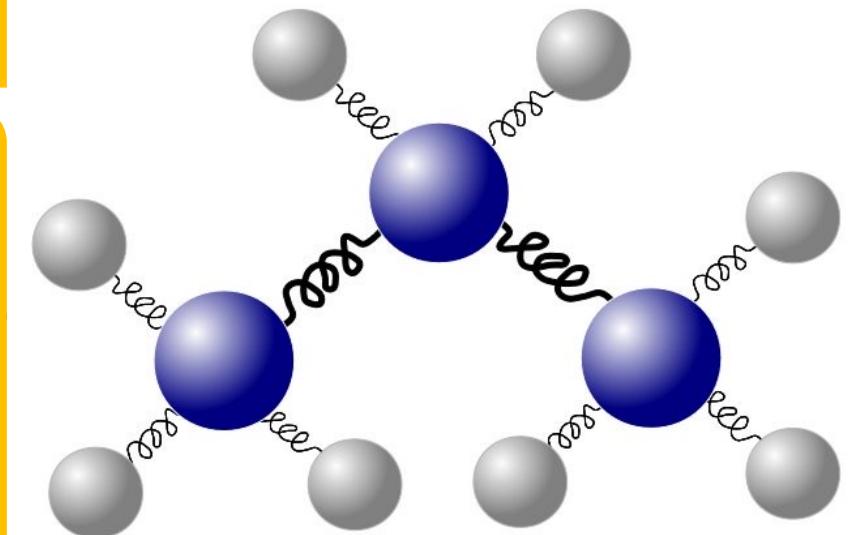


# Force Field Methods

- A molecule is represented by a set of *balls* connected with *springs*

## ASSUMPTIONS:

- Nuclei and electrons are combined in an atom, represented by a *ball*
- Balls have radius, constant charge and a given softness
- Covalent bonds are represented by *springs*
- Springs have an equilibrium length and can vary in stiffness



# Force Field Energy

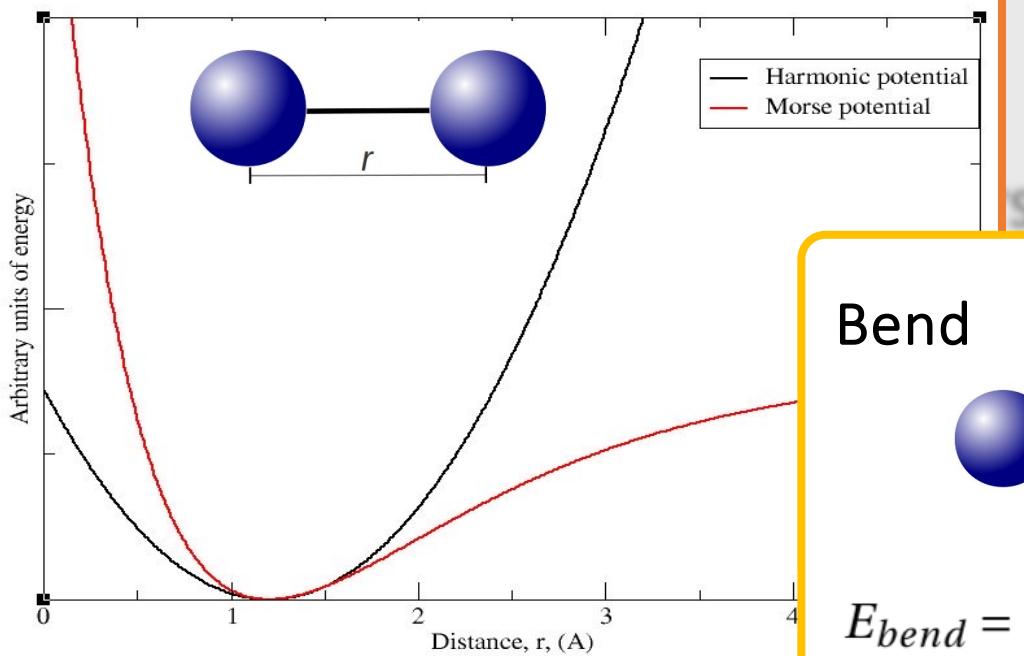
**Force Field** - set of parameters used in classical mechanical calculations

**Potential Energy** - the sum of all the interactions in it

$$E_{FF} = E_{str} + E_{bend} + E_{tors} + E_{VdW} + E_{el}$$



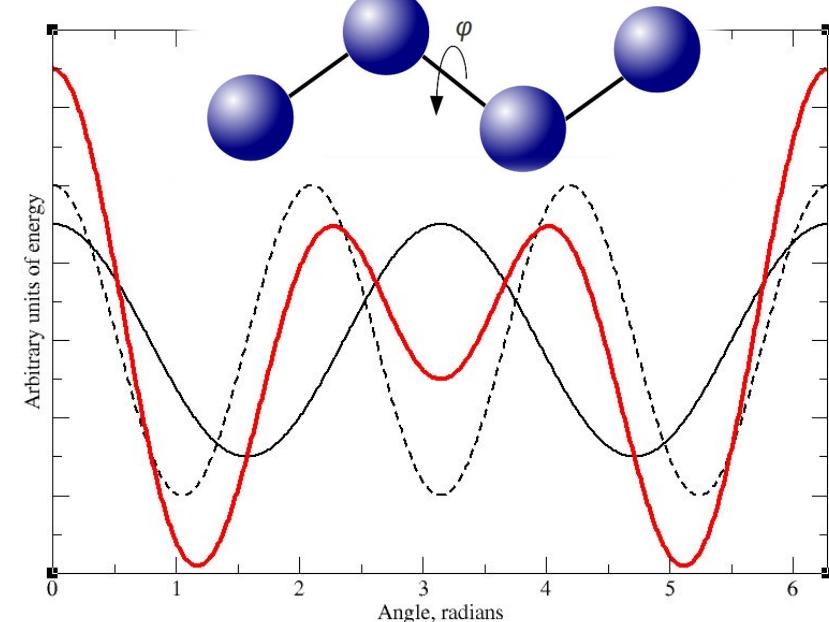
**Bond Stretch**  $E_{str} = \frac{1}{2} k^{AB} (r^{AB} - r_0^{AB})^2$



**Bend**

$$E_{bend} = \frac{1}{2} k^{ABC} (\theta^{ABC} - \theta_0^{ABC})^2$$

**Torsion**  $E_{tors} = \sum \frac{1}{2} V_n \cos n\phi$



$$E_{FF} = E_{str} + E_{bend} + E_{tors} + E_{VdW} + E_{el}$$

bonded

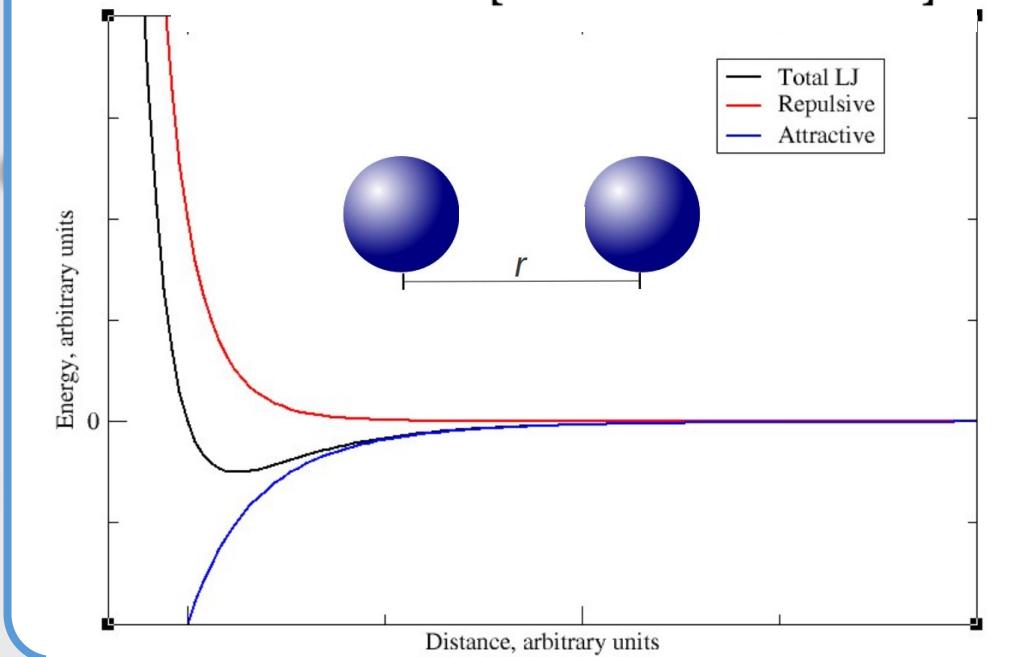
non-bonded

Force Field = set of

Potential Energy

## Lennard-Jones

$$E_{VdW}^{LJ} = 4\epsilon^{AB} \left[ \left( \frac{\sigma^{AB}}{r^{AB}} \right)^{12} - \left( \frac{\sigma^{AB}}{r^{AB}} \right)^6 \right]$$



## Coulomb

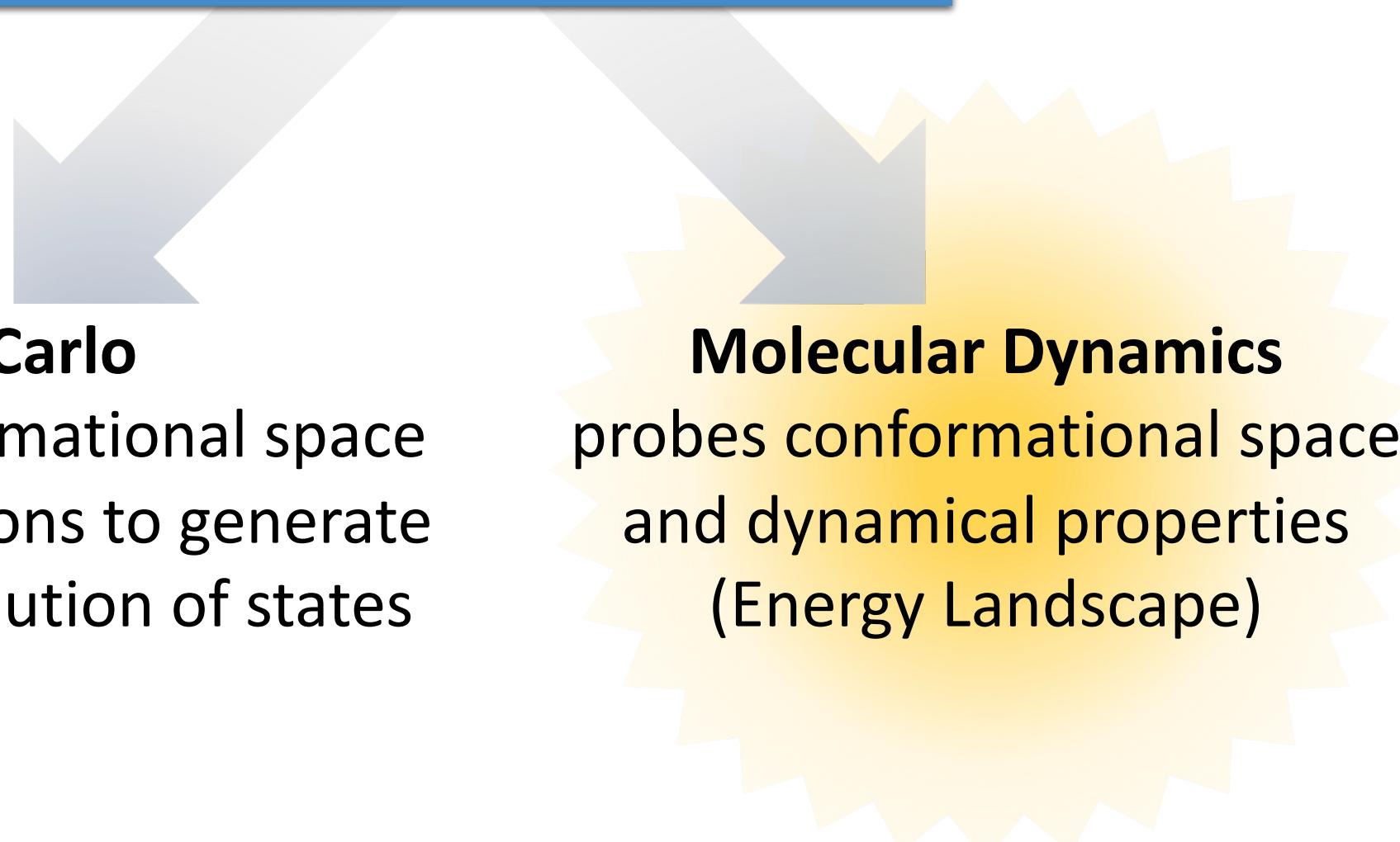
$$E_{el} = \frac{1}{4\pi\epsilon_0} \frac{Q^A Q^B}{r^{AB}}$$

$$E_{FF} = E_{str} + E_{bend} + E_{tors} + E_{VdW} + E_{el}$$

bonded

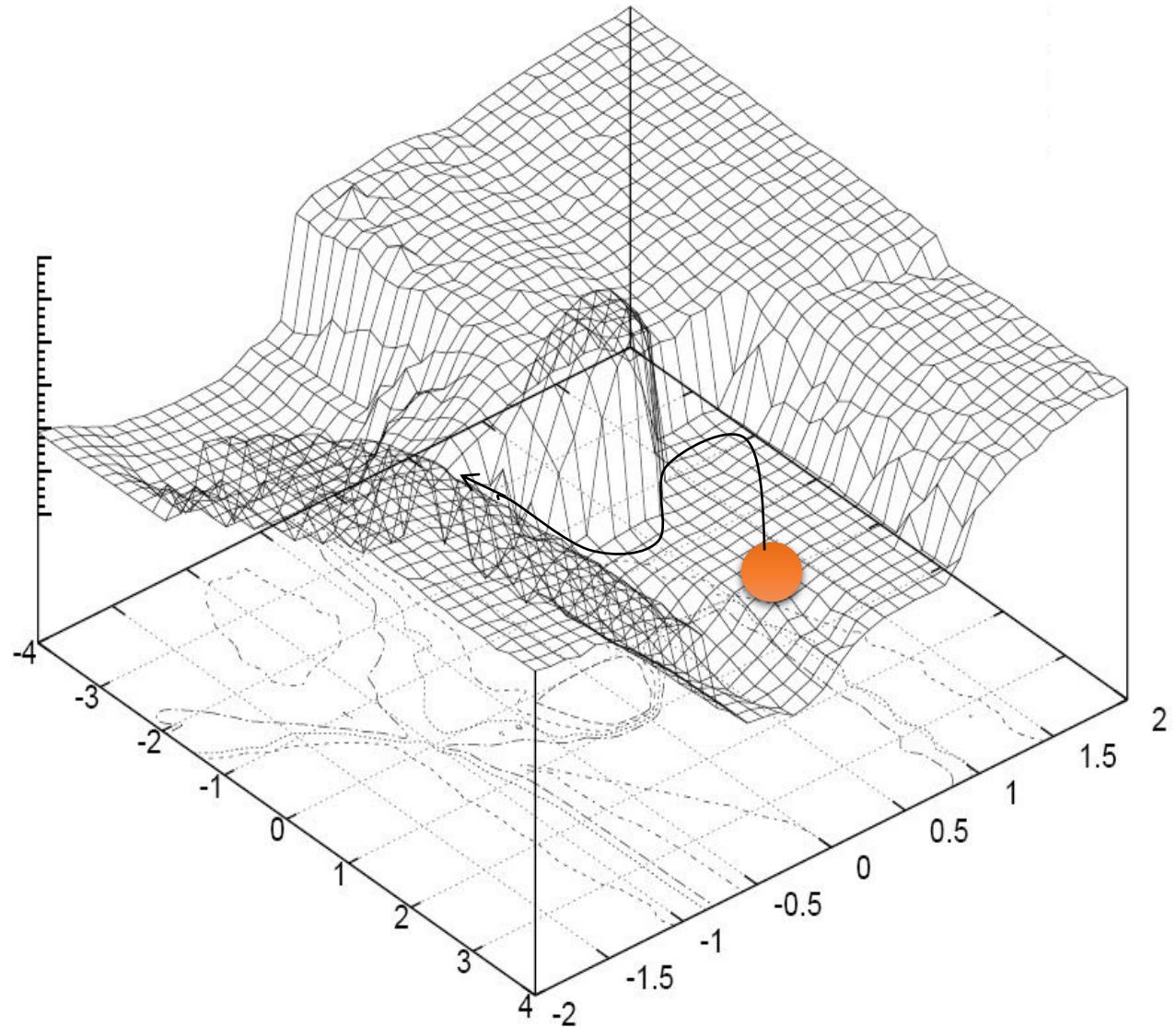
non-bonded

# Force Field Methods



# Energy Landscape

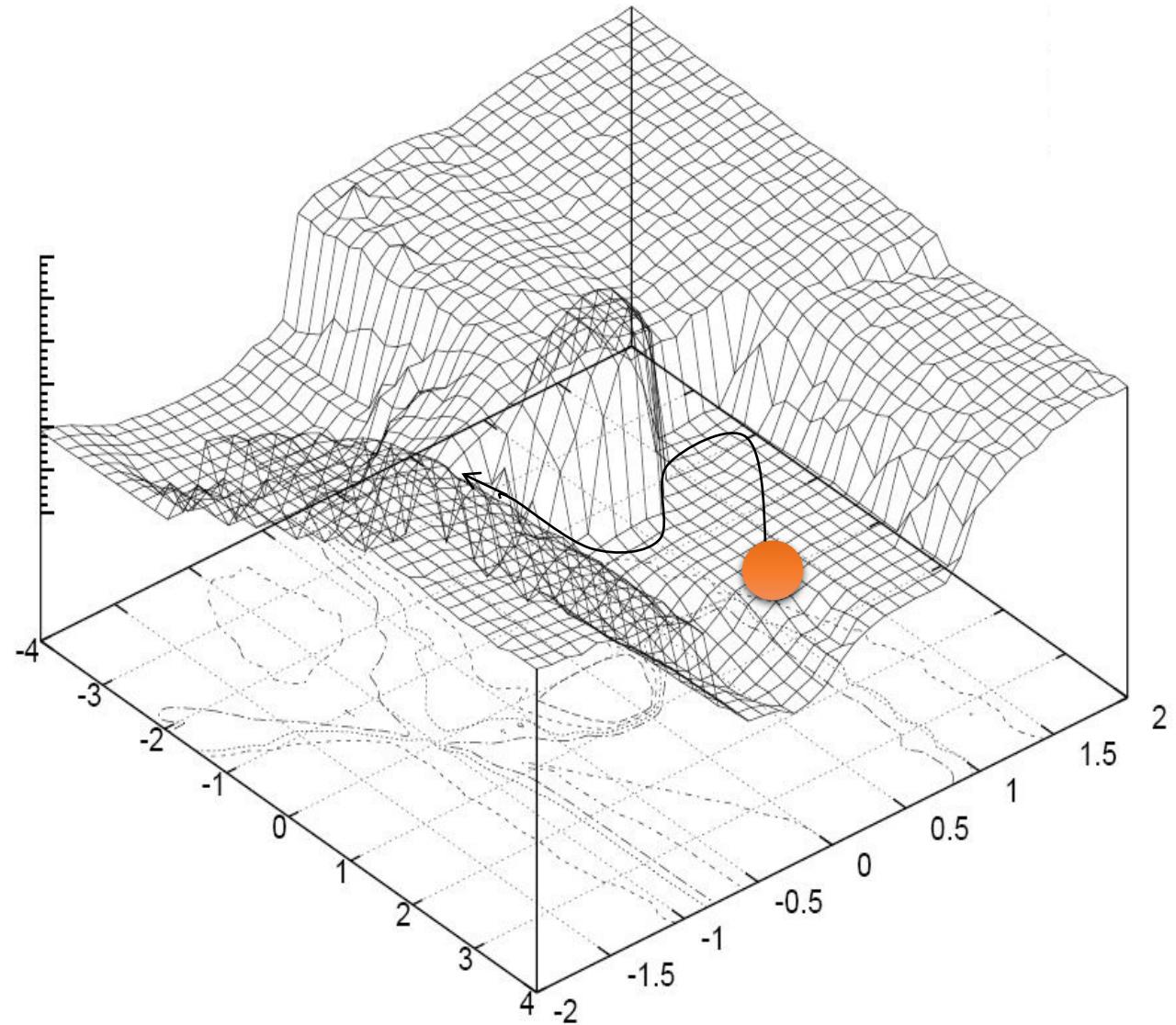
- Atoms interact, generate forces
- Sum of all interactions generates an **energy landscape**
- Energy landscape determines **atoms motion**



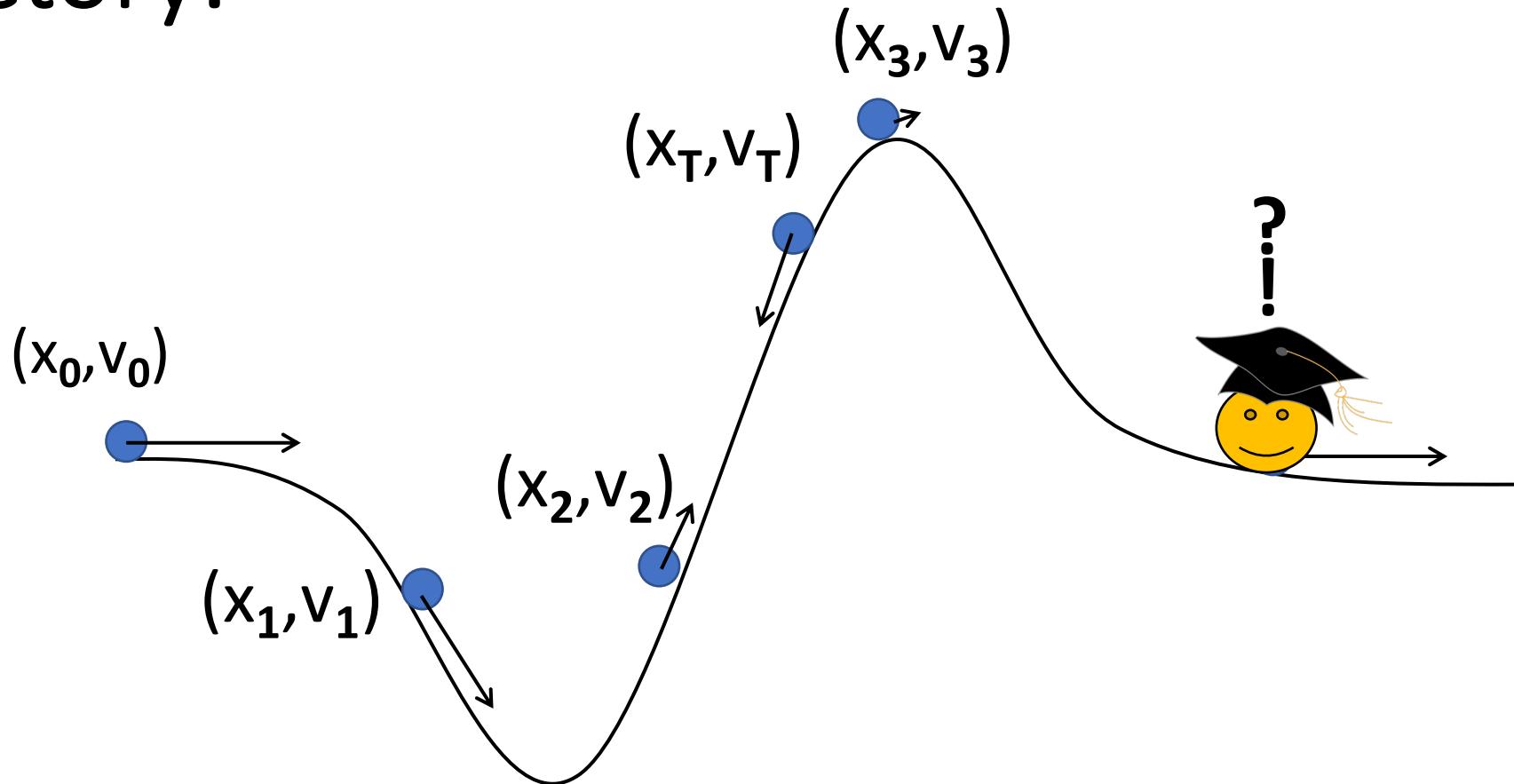
# Energy Landscape

- Classical equations of motion are solved step-by-step, by a *finite difference algorithm*
- **Newton's II law of motion** for a simple system is:

$$m_i \ a = F_i \quad F_i = -\frac{\partial E}{\partial r_i}$$



# Trajectory:



- A trajectory can be decomposed in **small uniform steps**
- **Step size** depends on energy landscape *steepness*

# How to choose this sampling time?

sharpest gradient = highest frequency

Highest frequencies:

- Covalent bond hydrogen - heavy atom ( $10^{14}$  Hz): **0.5 fs**
- Covalent bond heavy atom - heavy atom: **1 fs**
- Angles fluctuations: **2 fs**

Restraining covalent bonds or angles allows to increase timesteps

- SHAKE, RATTLE, LINCS,...

# How to control temperature and pressure?

Simulations can replicate a specific *thermodynamic ensemble*  
typically *NVT* or *NPT*

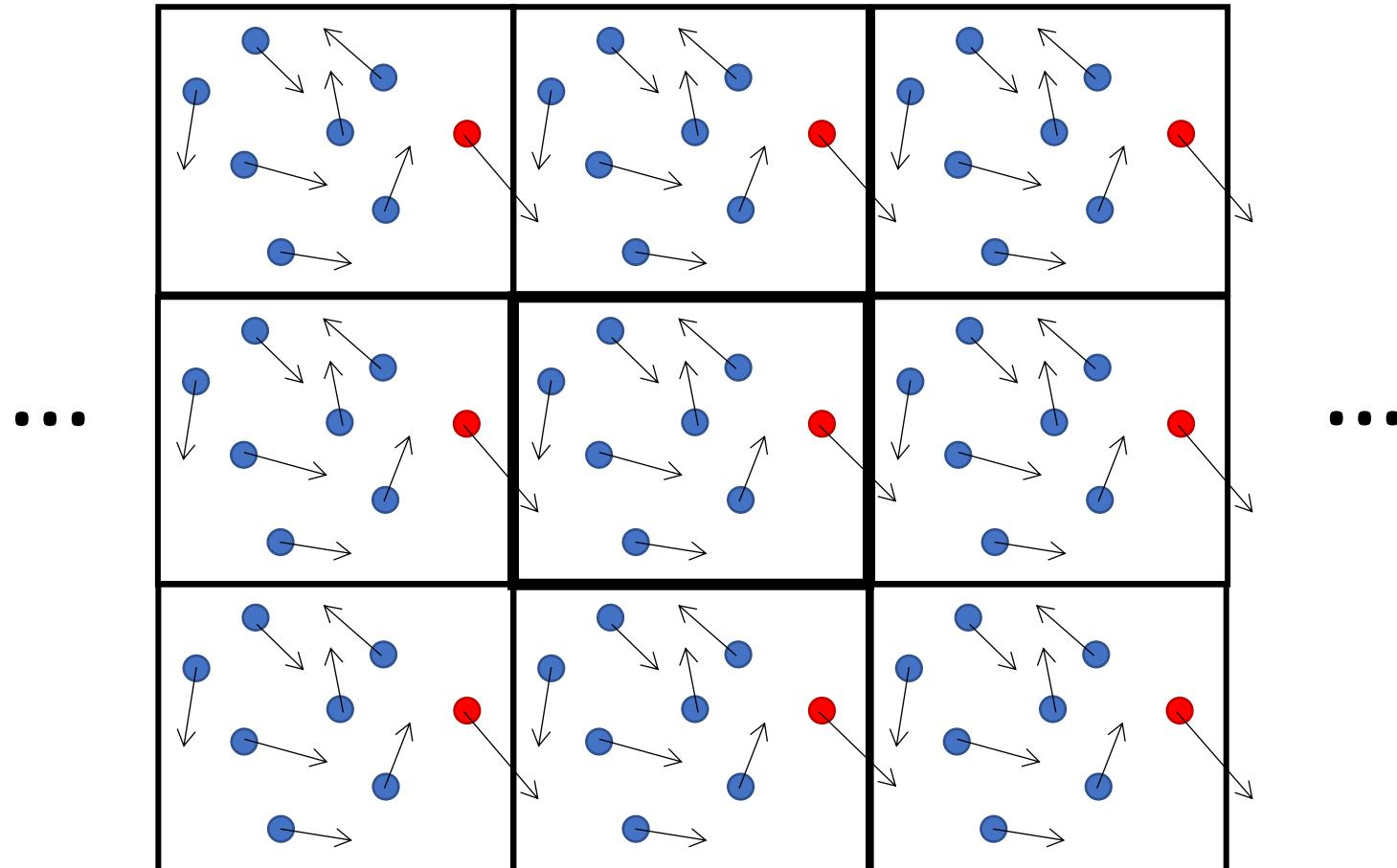
Addition of equations acting as  
***thermostats*** (scaling atom velocities)  
***barostats*** (scaling positions)

e.g.: Berendsen, Nose-Hoover, Parrinello-Rahman, ...

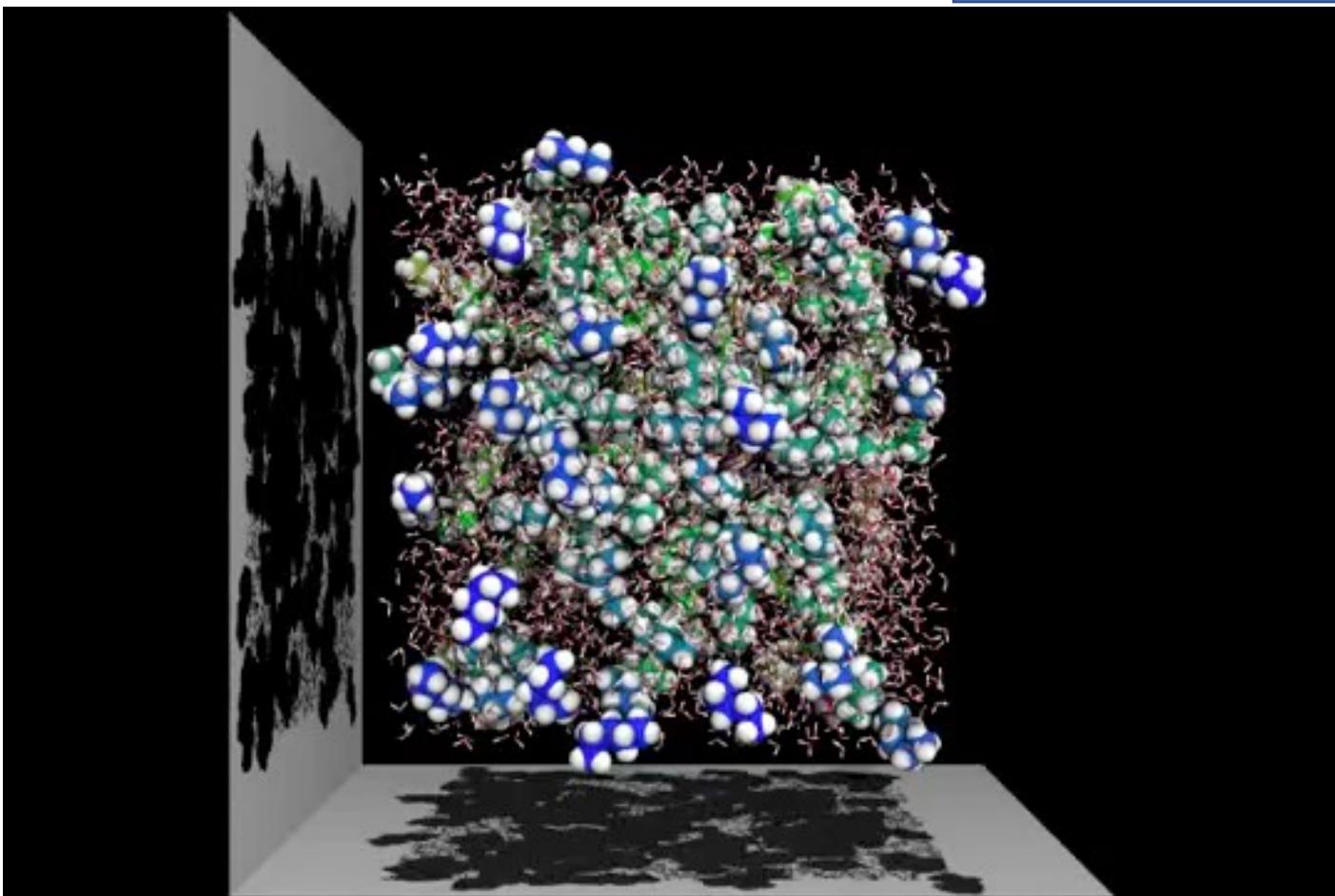
# Is the simulation box finite?

For **bulk properties** use *periodic boundary conditions* (PBC)

For **boundary effects** use wall, PBC in xy-direction, vacuum in NVT, ...



# In each timestep...



Set initial  
conditions for  $x$ ,  
 $v$  and box size

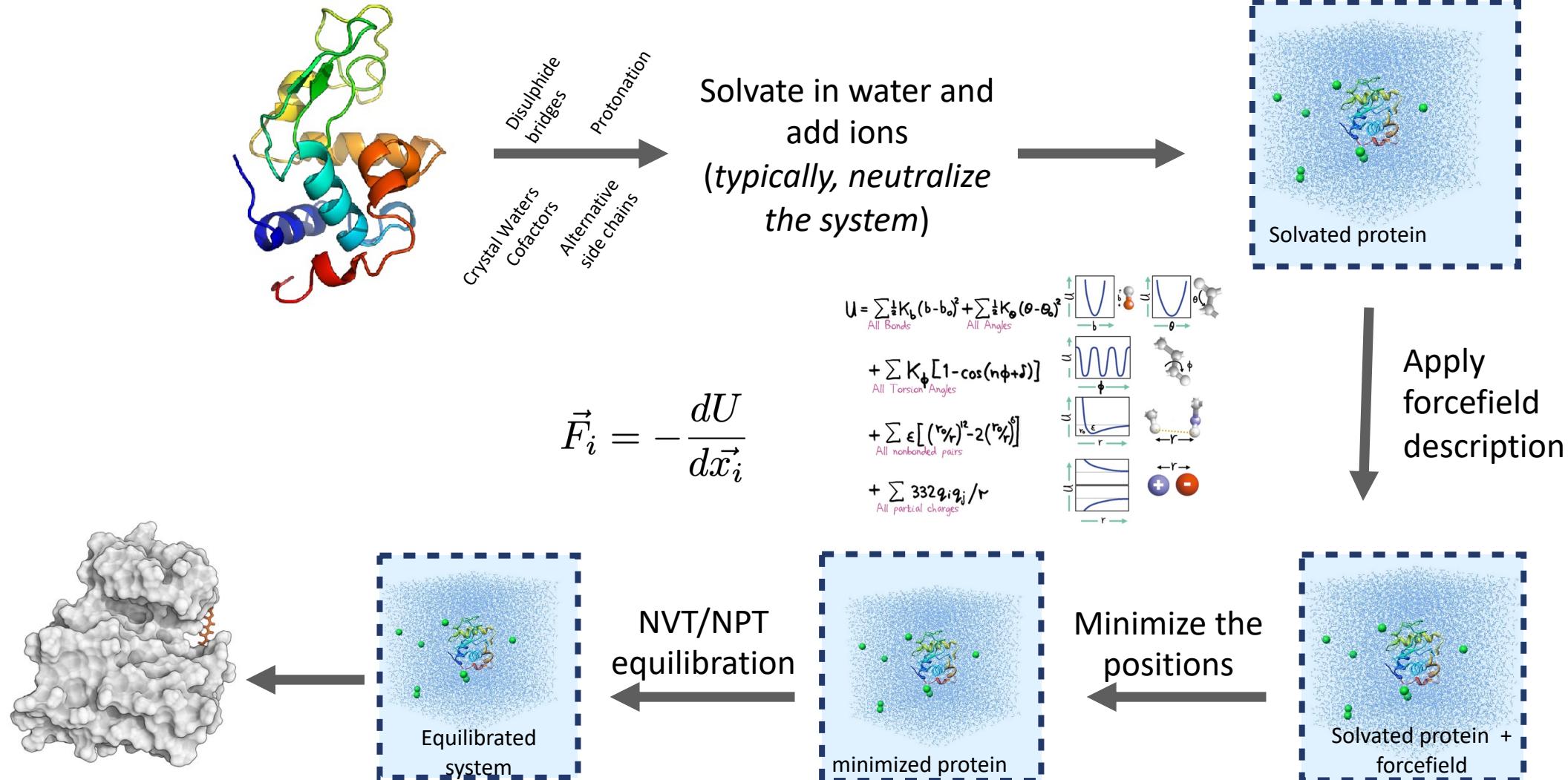
Compute forces

Compute new  $x'$   
and  $v'$  for all atoms

Scale  $x'$  and  $v'$   
with  
thermo/barostat

Update  $x'$  and  $v'$   
(with pbc)

# Molecular dynamics require multiple steps for the setup of simulations



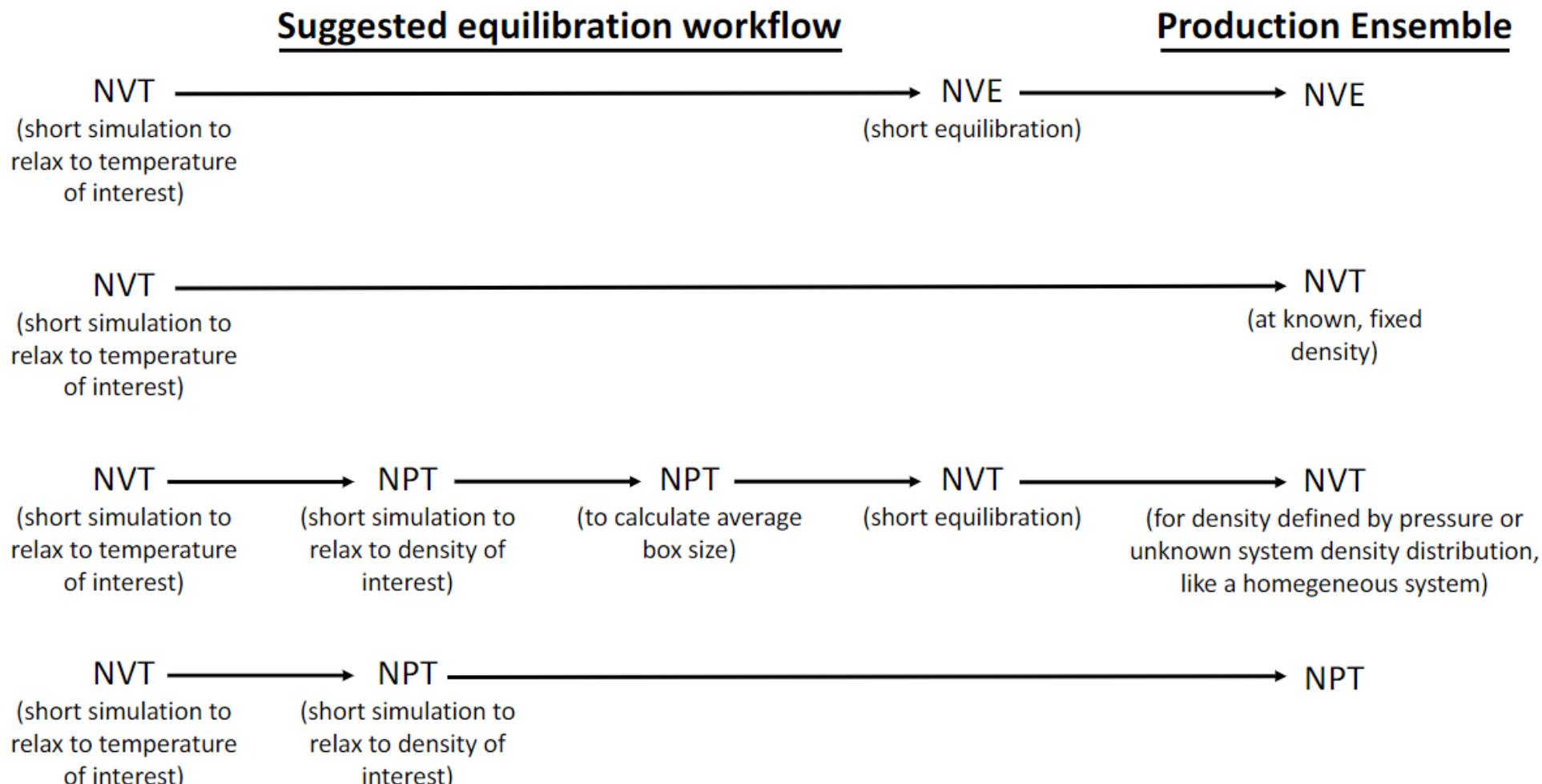
Production simulation

[http://www.bevanlab.biochem.vt.edu/Pages/Personal/justin/gmx-tutorials/lysozyme/01\\_pdb2gmx.html](http://www.bevanlab.biochem.vt.edu/Pages/Personal/justin/gmx-tutorials/lysozyme/01_pdb2gmx.html)

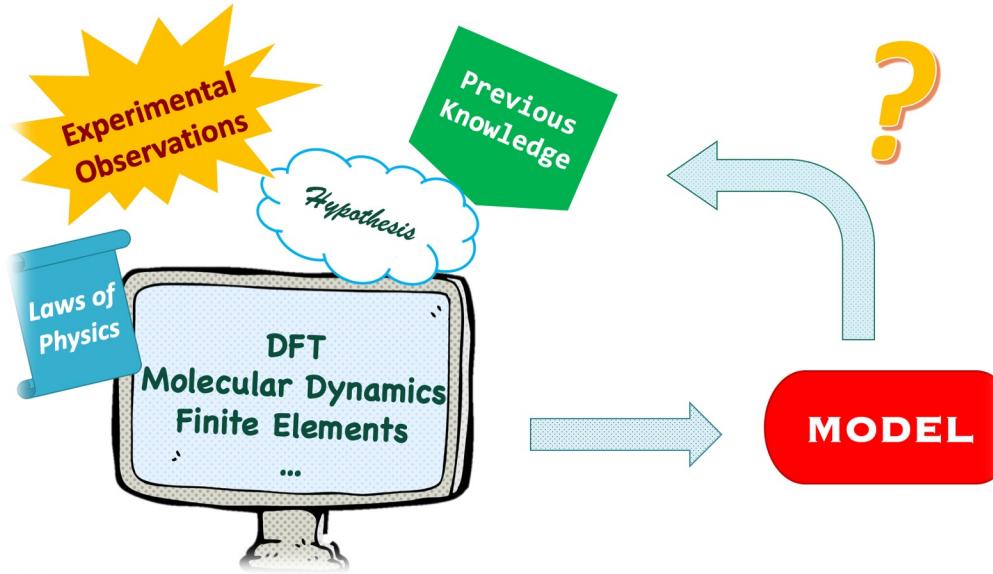
Levitt, *Nature Struct. Biol.*, 2001

# Example equilibration protocols

**YOU WANT:** constant energy, volume, pressure, temperature, no exotic chemistry, ...



# What do I need to MD?



## RESOURCES

- Computational Power
  - MD Software
  - Force Fields

## INFORMATION

- Hypothesis!
- What is the Process?  
Chemical/Physical
- Timescales of this Process
- Molecular Structures

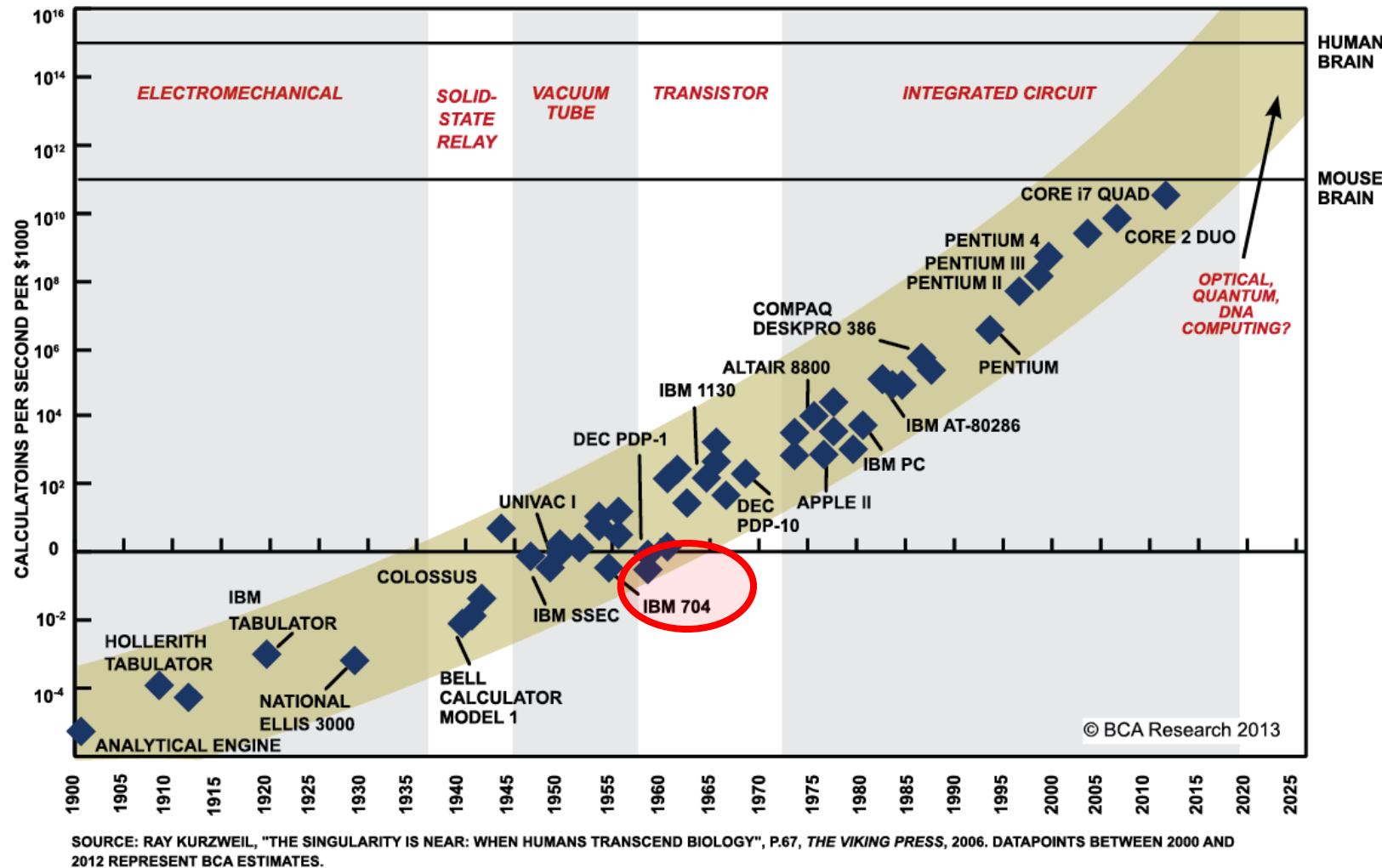
# Computational Power *on a supercomputer 24/7 for several weeks*

Calculation time affected by:

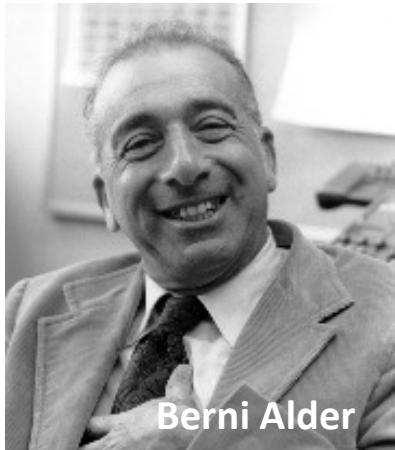
- Processor power
- Number of processors
- Interconnect speed



IBM 704



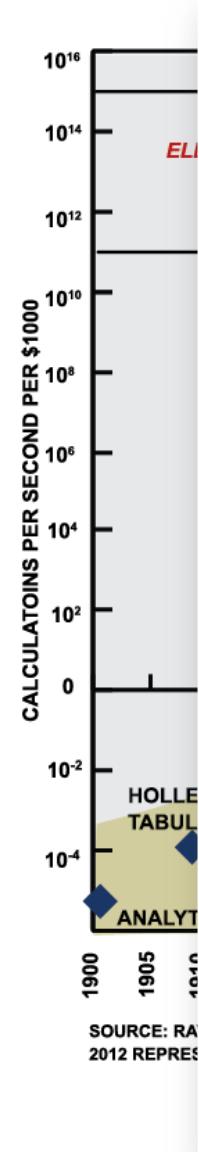
# Computational Power *on a supercomputer 24/7 for several weeks*



Berni Alder



IBM 704



SOURCE: RA  
2012 REPRES

## Phase Transition for a Hard Sphere System

B. J. ALDER AND T. E. WAINWRIGHT

*University of California Radiation Laboratory, Livermore, California*

(Received August 12, 1957)

A CALCULATION of molecular dynamic motion has been designed principally to study the relaxations accompanying various nonequilibrium phenomena. The method consists of solving exactly (to the number of significant figures carried) the simultaneous classical equations of motion of several hundred particles by means of fast electronic computers. Some of the details as they relate to hard spheres and to particles having square well potentials of attraction have been described.<sup>1,2</sup> The method has been used also to calculate equilibrium properties, particularly the equation of state of hard spheres where differences with previous Monte Carlo<sup>3</sup> results appeared.

HUMAN BRAIN

MOUSE BRAIN

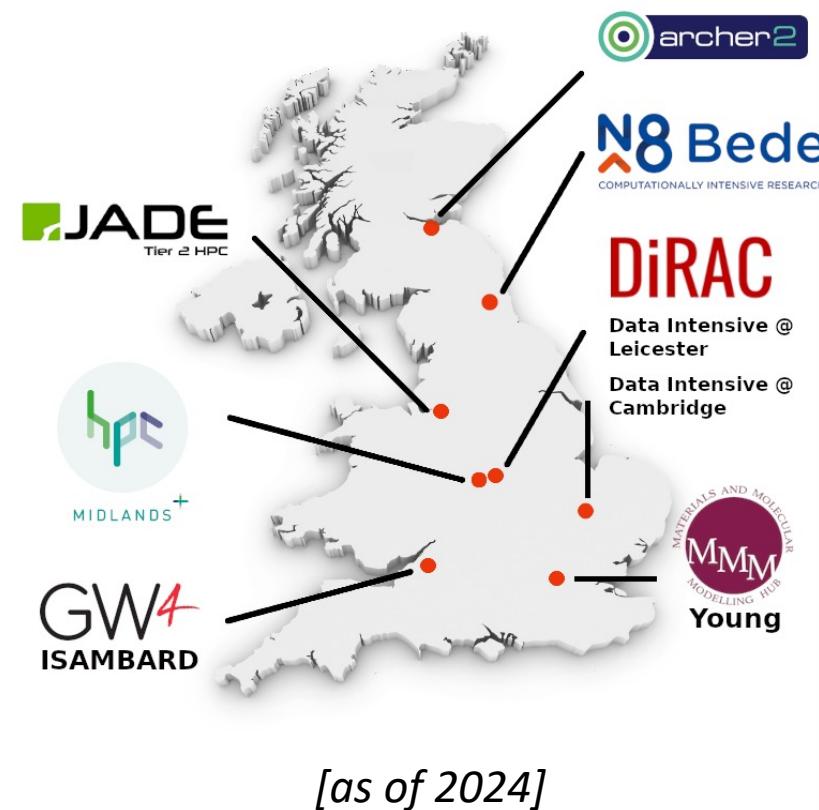
ICAL,  
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UTING?

2013

2020

2025

# Calculating runtimes: example on UK Tier 2 systems



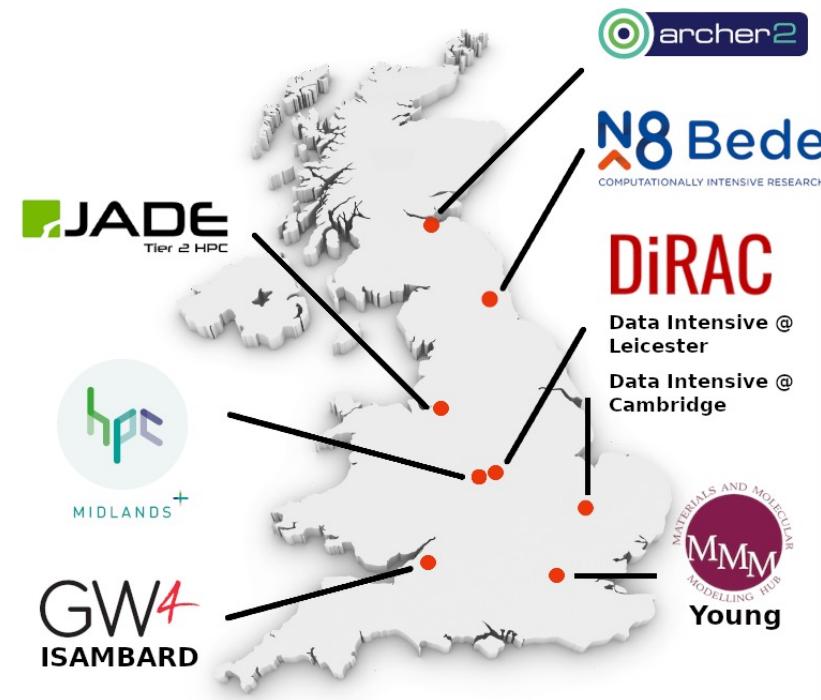
The screenshot shows the HECTime Calculator page on the HECBioSim website (<https://www.hecbiosim.ac.uk/access-hpc/hpc-calculator>). The page features a banner with molecular models and a search bar. The main content area is titled "The HECTime Calculator" and instructs users to enter information about their simulation. A form contains the following input fields:

JADE2
1000
100000
GROMACS 2020.4

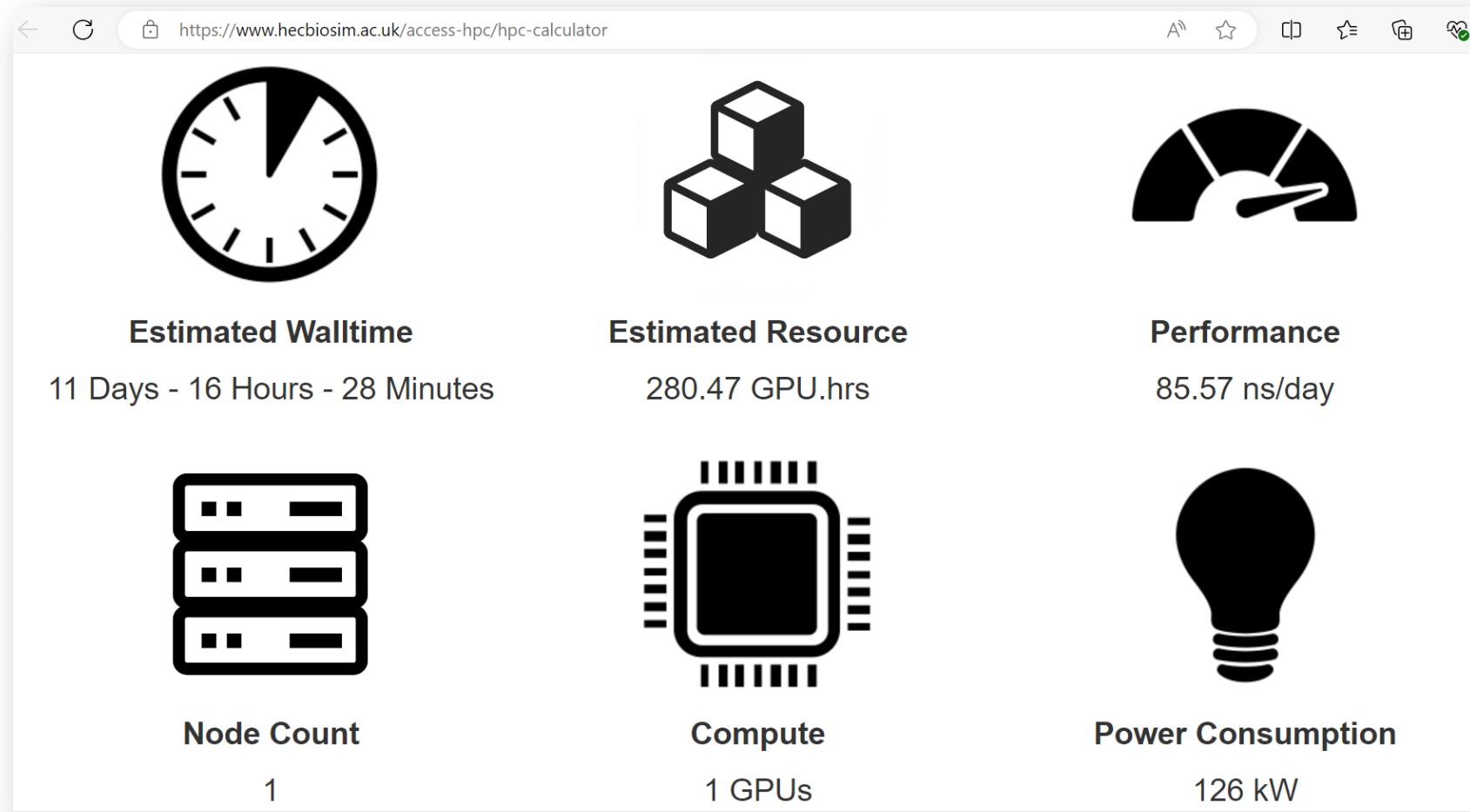
At the bottom are "Reset" and "Calculate" buttons.

<https://www.hecbiosim.ac.uk/access-hpc/hpc-calculator>

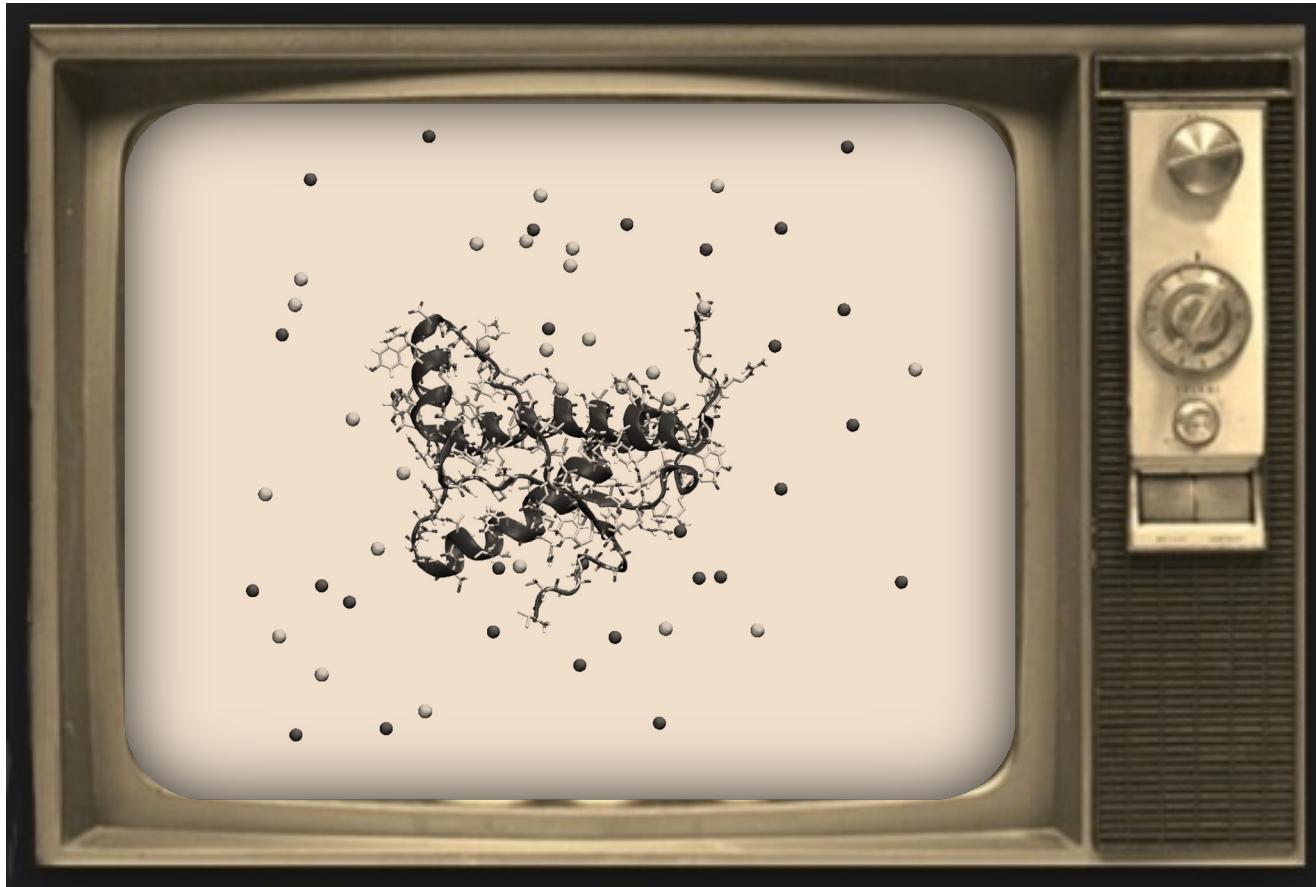
# Calculating runtimes: example on UK Tier 2 systems



[as of 2024]



<https://www.hecbiosim.ac.uk/access-hpc/hpc-calculator>



Now let's start with setting  
up your first simulation!