

Molecular Dynamics Simulations: Theory and Applications

DSc. Conrado Pedebos
DSc. Pablo Ricardo Arantes

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Molecular Dynamics Simulations: Theory and Applications

Summary of Course Flow:

Day 1: Introduction to Molecular Dynamics

Day 2: Protein-ligand complex simulations (**Pablo**)

Day 3: Coarse-grained and Membrane Proteins

Day 4: Molecular Dynamics simulations alternatives (**Pablo**)

Day 5: Enhanced sampling approaches

Introduction to Molecular Dynamics

Static (adj.)

Motionless, fixed, unchanging

Dynamics (noun)

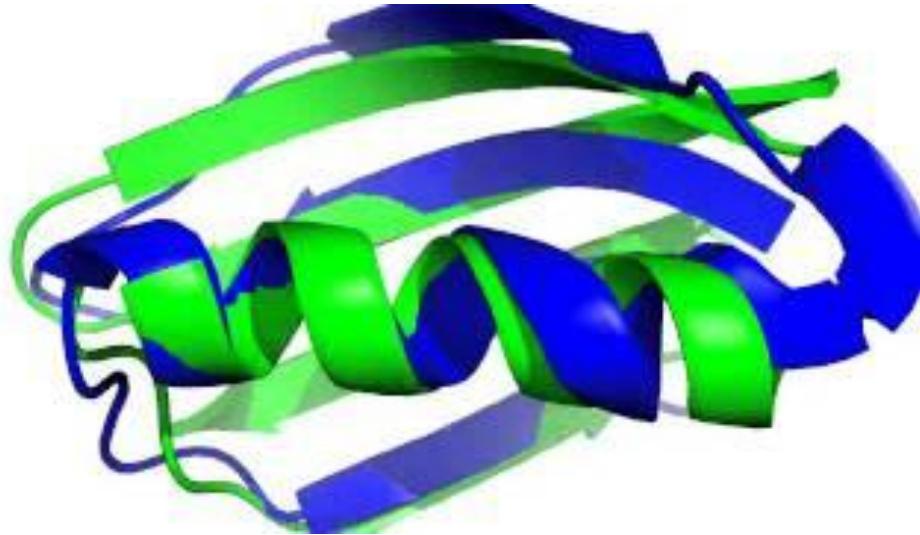
Deals with forces and their
relation primarily to the motion

1D the components

2D the sequences

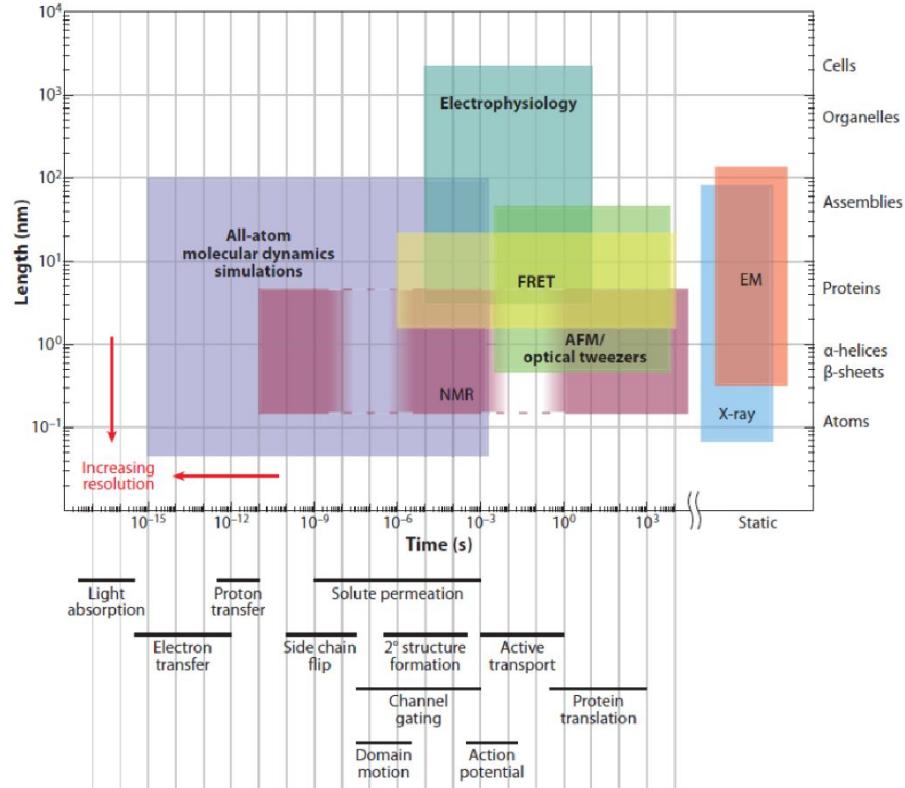
3D the structures

4D the trajectories



Introduction to Molecular Dynamics

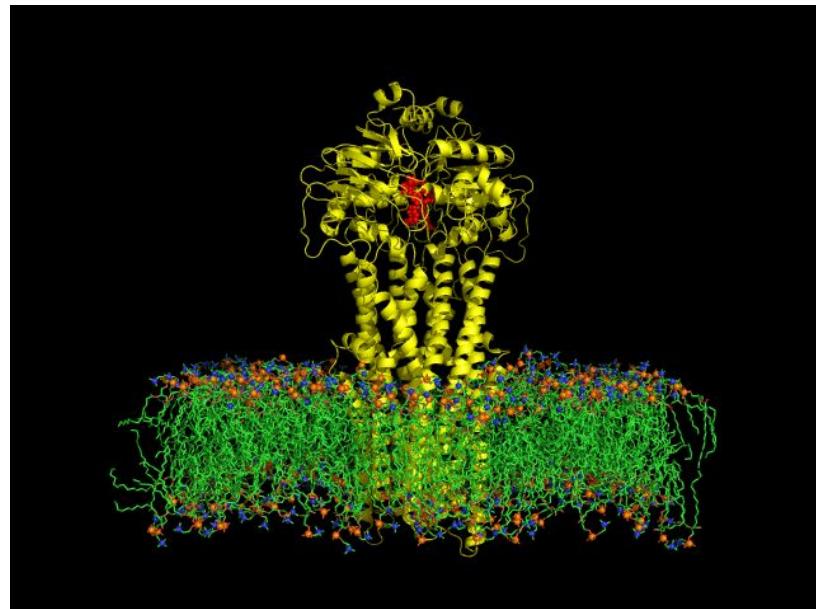
- Each experimental technique studies phenomena of different sizes and timescales.
- NMR has the greatest reach among the experimental methods, but it has considerable limitations (size and concentration)
- MD simulations cover a wide range of what the other methods misses.



Introduction to Molecular Dynamics

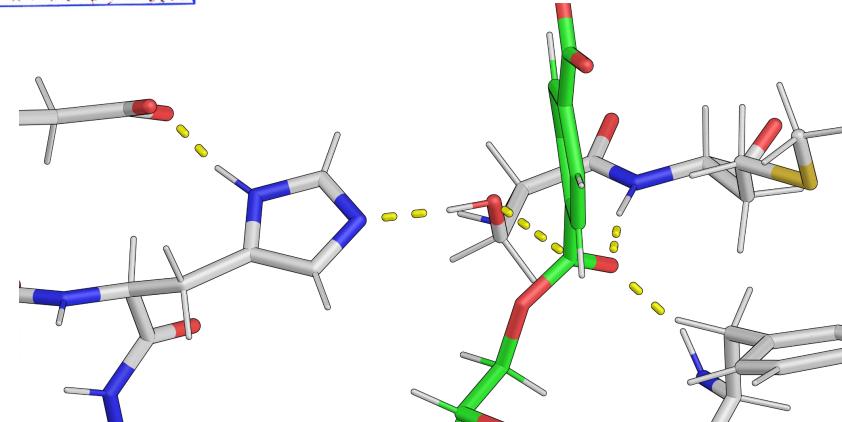
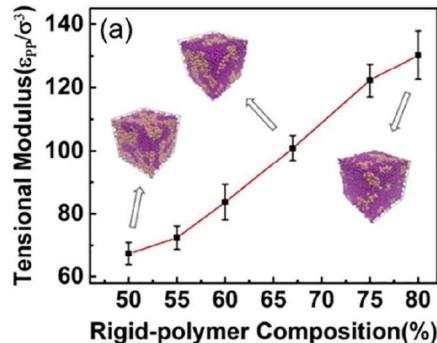
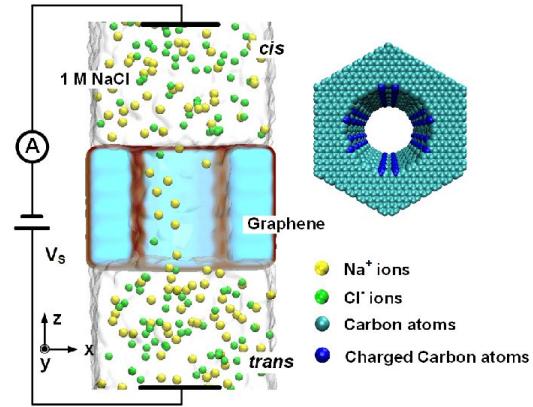
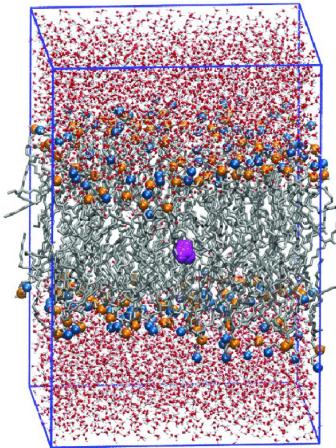
A computational molecular simulation method employed to analyze the physics of **atomic and molecular motion** in a given system. Its main goal is to predict, analyse, imitate, study molecular behaviour.

- Biophysics/Biochemistry (protein folding/conformation)
- Chemistry (enzyme reactions - not explicitly)
- Physics (phase transition)
- Material Sciences (polymer properties)
- Pharmacology (drug-receptor interactions)
- Astrophysics (interstellar particles)
- Geology (Mineral Dynamics)
- Food Science (emulsion stability)
- Nanotechnology (drug delivery, molecular self-assembly)

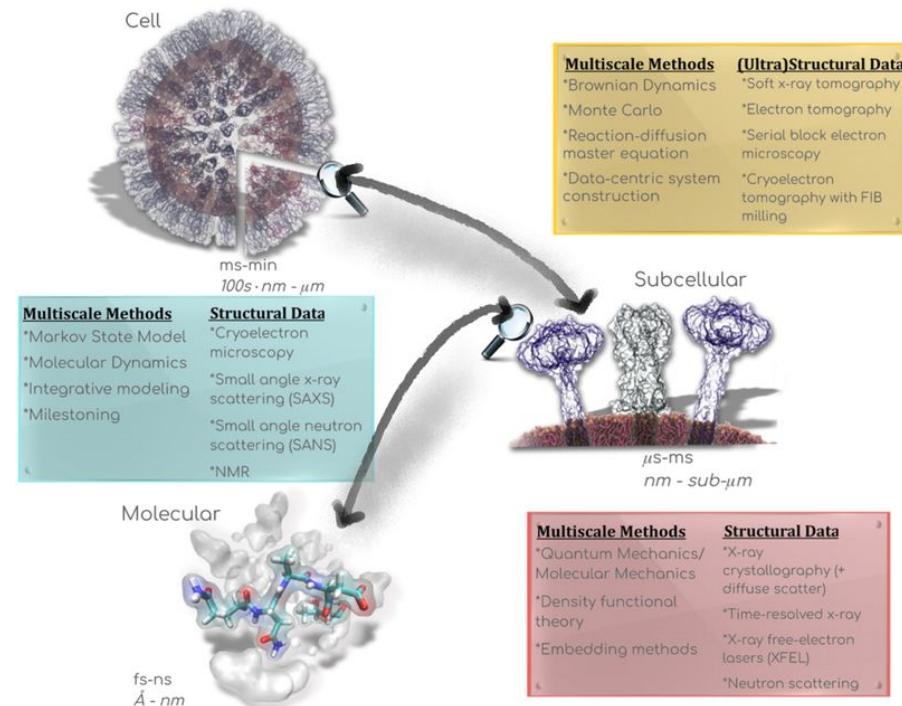
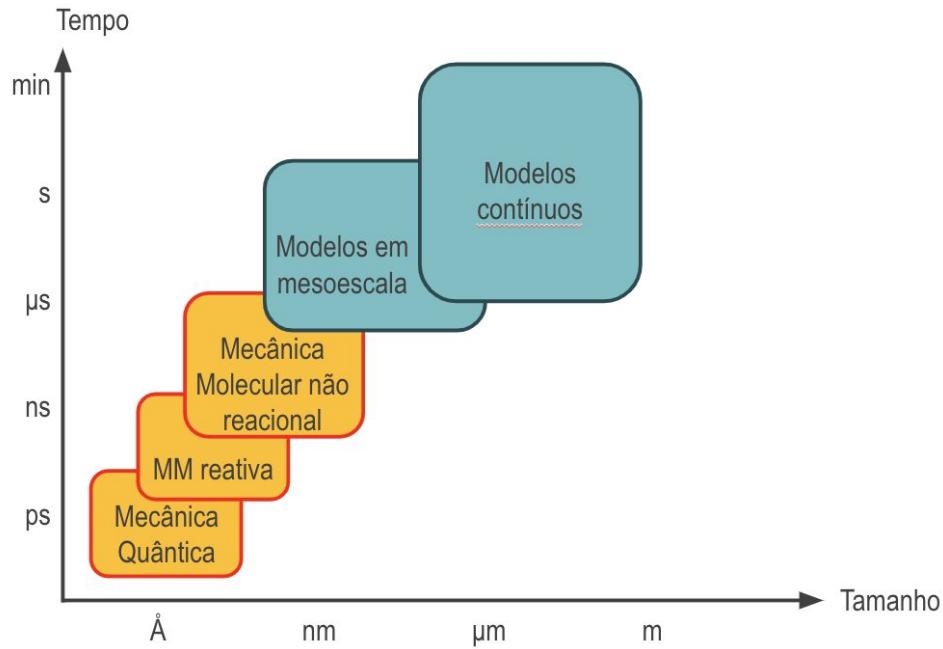


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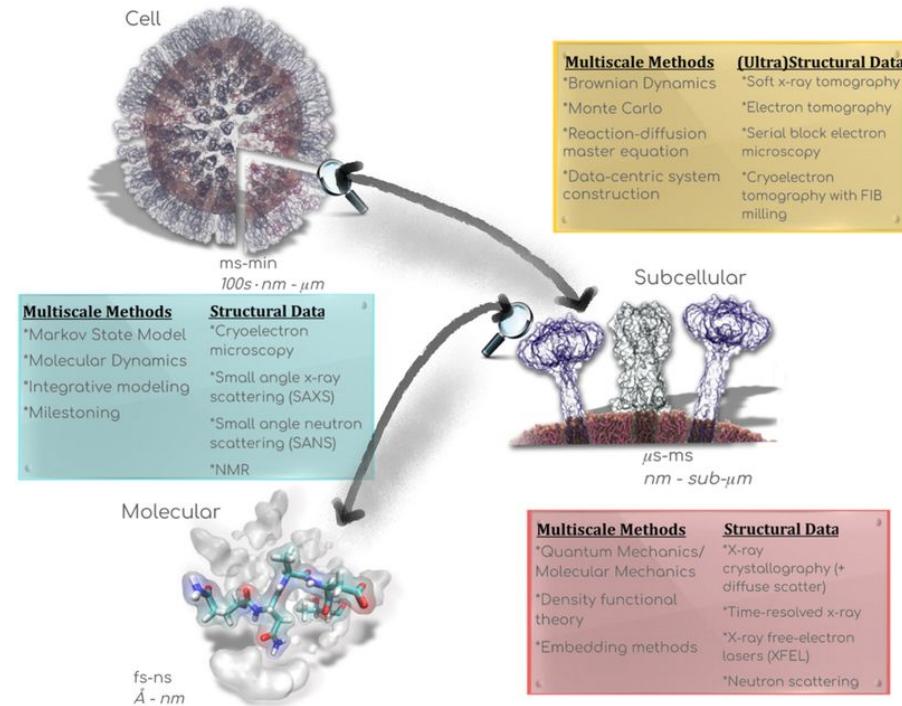
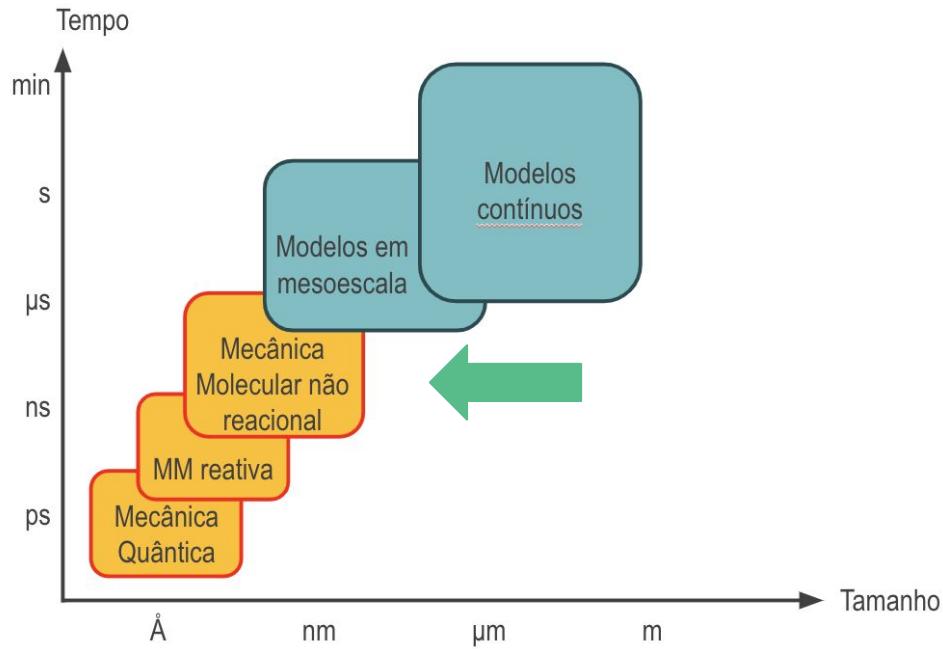
- Conformational changes in proteins
- Drugs interactions to receptors
- Compound permeability in membranes
- Mechanical properties in materials
- Enzymatic reactions
- Molecular transportation in nanopores
(Oxford Nanopore)



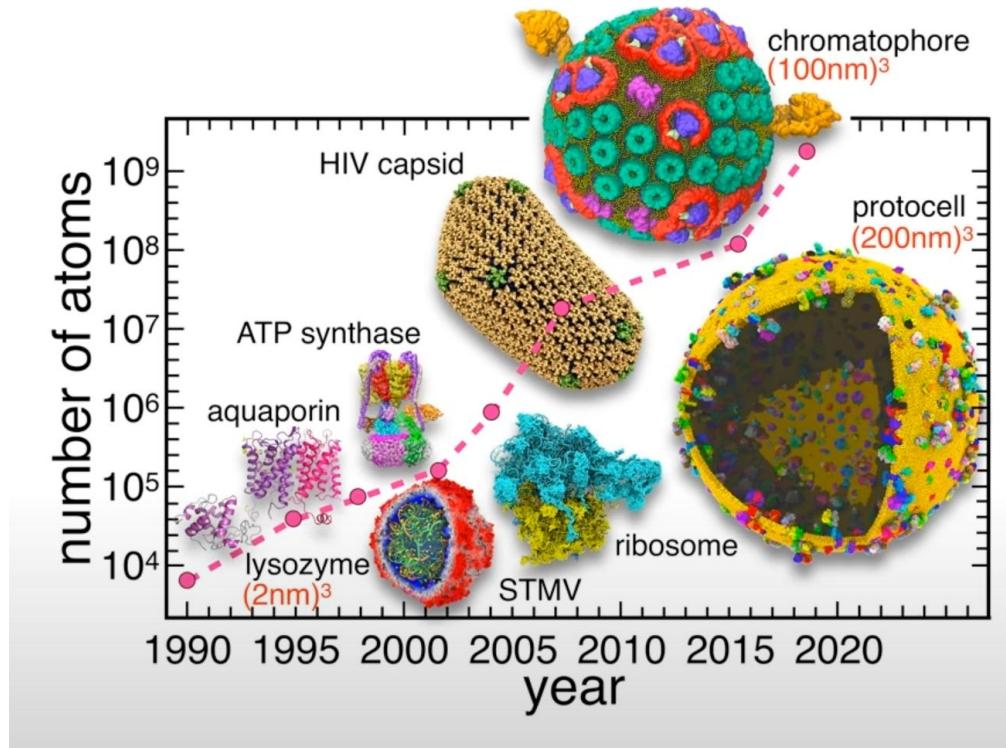
Introduction to Molecular Dynamics



Introduction to Molecular Dynamics



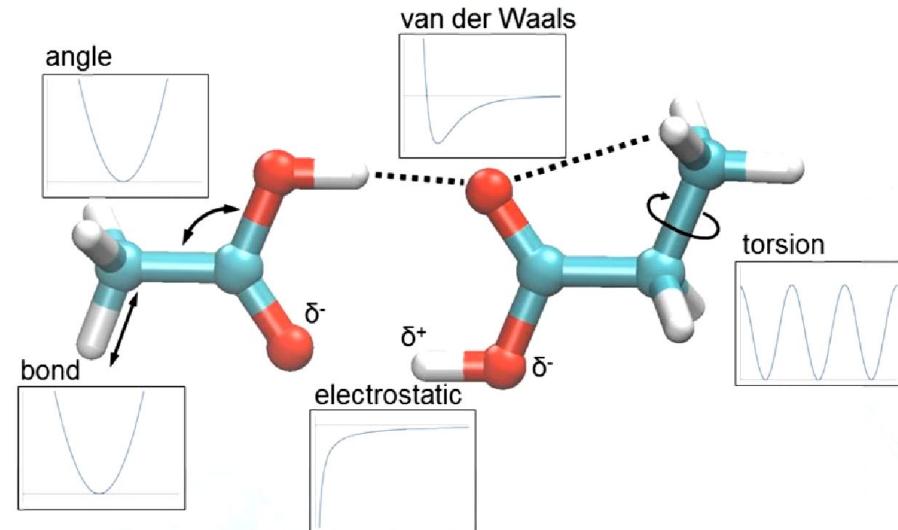
Introduction to Molecular Dynamics



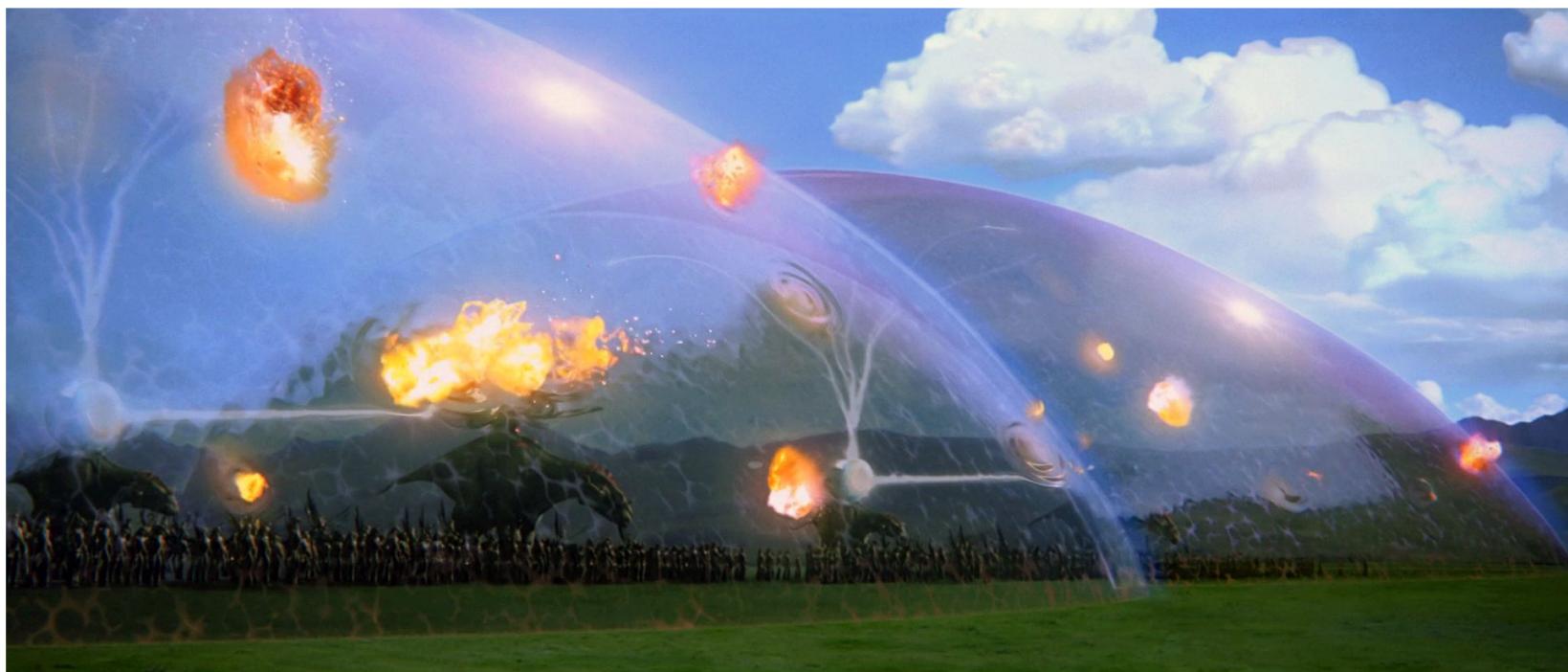
<https://www.youtube.com/watch?v=EIReA3s1Nwk>

Introduction to Molecular Dynamics

- Main points:
 - Principles from **Molecular Mechanics**
 - Governed by Newton's second law of motion ($F = m \cdot a$)
 - Covalent and non-covalent bonds are considered
 - Covalent bonds can not be broken (but they may contract/stretch)
 - Electronic properties are not modeled (ex.: can not observe chemical reactions in MD)



Introduction to Molecular Dynamics



Set of parameters and equations that describes atom types and the interactions between them

Introduction to Molecular Dynamics

$$E_{\text{ligados}} = E_{\text{ligação}} + E_{\text{ângulo}} + E_{\text{diedro}}$$

$$E_{\text{não-ligados}} = E_{\text{Coulomb}} + E_{\text{Lennard-Jones}}$$

$$E_{\text{total}} = E_{\text{ligados}} + E_{\text{não-ligados}}$$

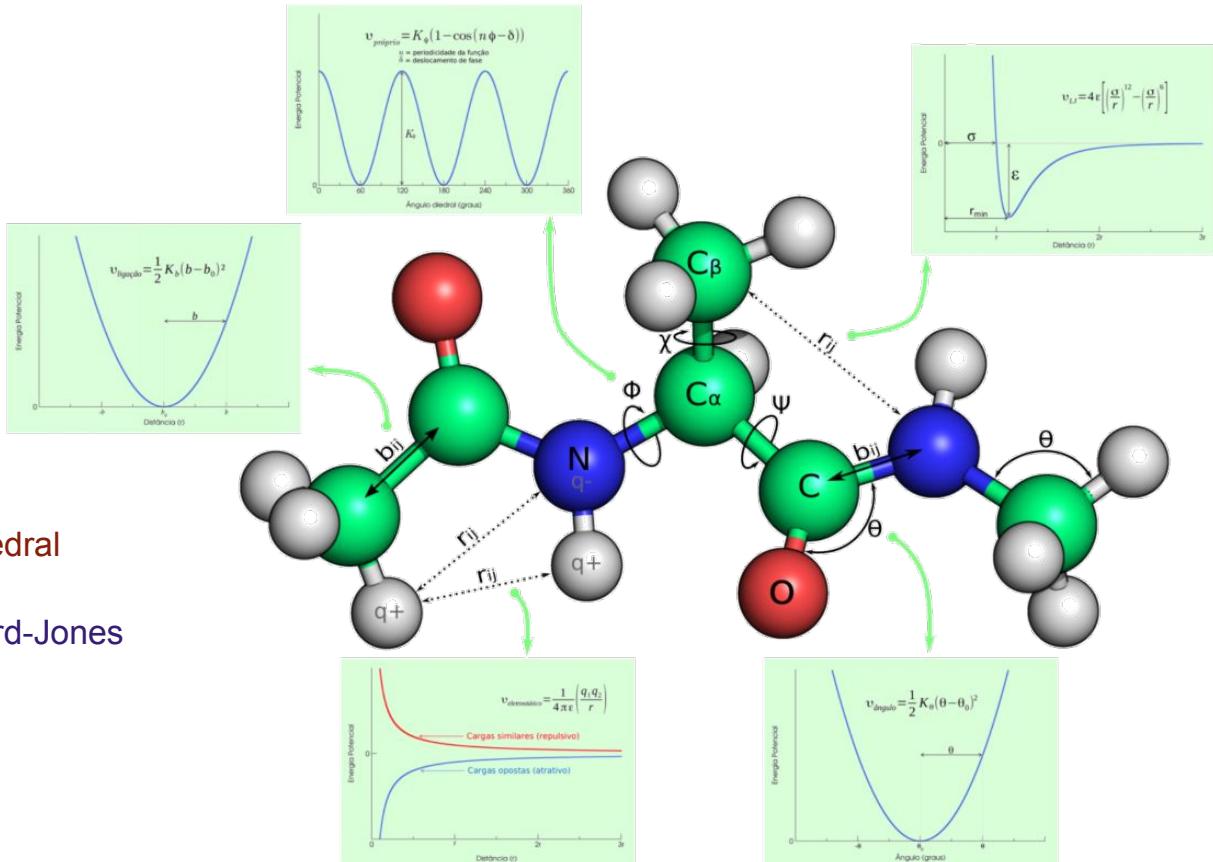
Set of parameters and equations that describes atom types and the interactions between them

Introduction to Molecular Dynamics

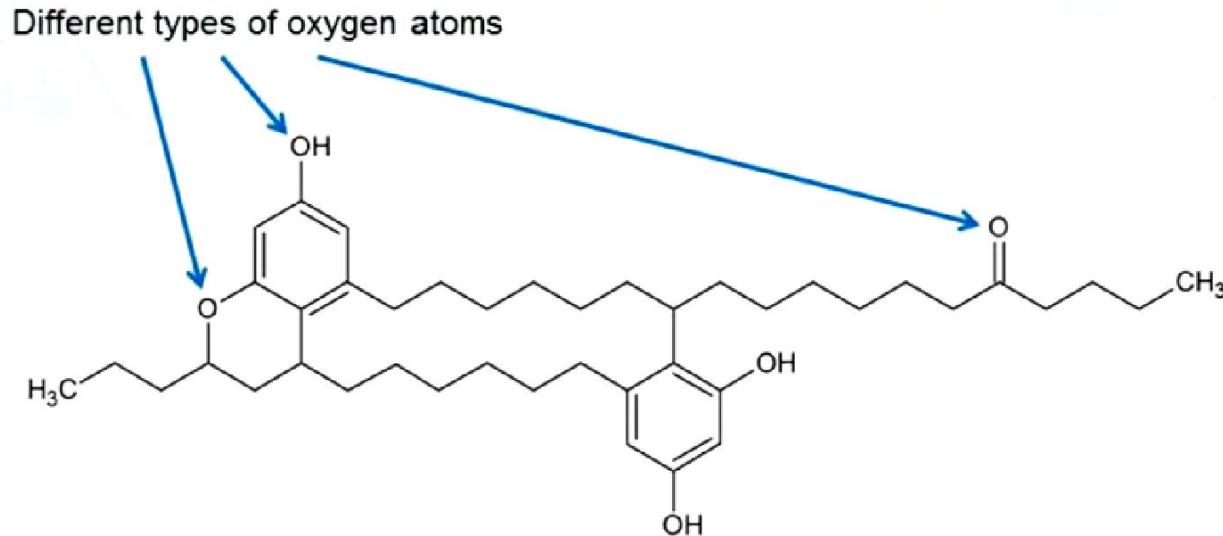
$$E_{\text{bonded}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{dihedral}}$$

$$E_{\text{non-bonded}} = E_{\text{Coulomb}} + E_{\text{Lennard-Jones}}$$

$$E_{\text{total}} = E_{\text{bonded}} + E_{\text{non-bonded}}$$



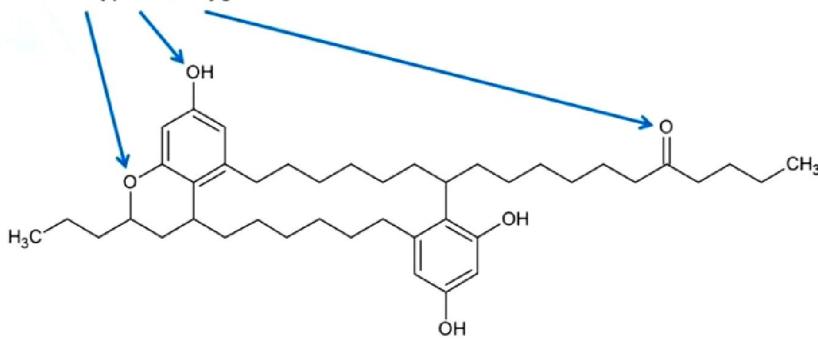
Introduction to Molecular Dynamics



Set of parameters and equations that describes atom types and the interactions between them

Introduction to Molecular Dynamics

Different types of oxygen atoms

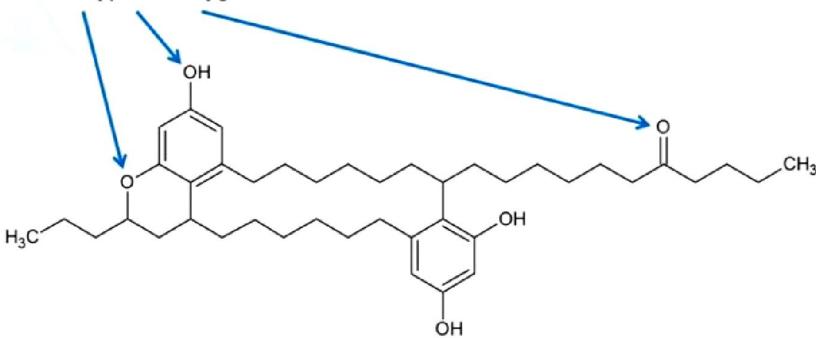


<chem>H_:</chem>	hydrogen
<chem>H_d[a]:</chem>	hydrogen attached to F/Cl/Br/I/N/O/S atom
<chem>C_3:</chem>	tetrahedral (sp^3) carbon
<chem>C_3x1[a]:</chem>	tetrahedral (sp^3) carbon attached to one F/Cl/Br/I/N/O/S atom
<chem>C_3x2[a]:</chem>	tetrahedral (sp^3) carbon attached to two F/Cl/Br/I/N/O/S atoms
<chem>C_3x3[a]:</chem>	tetrahedral (sp^3) carbon attached to three or more F/Cl/Br/I/N/O/S atoms
<chem>C_2:</chem>	trigonal (sp^2) carbon
<chem>C_2x1[a]:</chem>	trigonal (sp^2) carbon attached to one F/Cl/Br/I/N/O/S atom
<chem>C_2x2[a]:</chem>	trigonal (sp^2) carbon attached to two or more F/Cl/Br/I/N/O/S atoms
<chem>C_1:</chem>	linear (sp) carbon
<chem>C_1x[a]:</chem>	linear (sp) carbon attached to F/Cl/Br/I/N/O/S atom
<chem>C_r:</chem>	resonant (aromatic) carbon
<chem>C_rx[a]:</chem>	resonant (aromatic) carbon attached to F/Cl/Br/I/N/O/S atom(s)
<chem>O_3:</chem>	tetrahedral (sp^3) oxygen
<chem>O_3o[a]:</chem>	tetrahedral (sp^3) oxygen in carboxyl group
<chem>O_2:</chem>	trigonal (sp^2) oxygen
<chem>O_2am[a]:</chem>	oxygen in amide group
<chem>O_2n[a]:</chem>	oxygen in nitro group
<chem>N_3:</chem>	tetrahedral (sp^3) nitrogen
<chem>N_3am[a]:</chem>	nitrogen in amide group
<chem>N_2:</chem>	trigonal (sp^2) nitrogen
<chem>N_1:</chem>	linear (sp) nitrogen
<chem>N_n[a]:</chem>	nitrogen in nitro group
<chem>N_r5[a]:</chem>	resonant (aromatic) nitrogen in five membered ring
<chem>N_r6[a]:</chem>	resonant (aromatic) nitrogen in six membered ring
<chem>S_32:</chem>	tetrahedral (sp^3) sulfur with two valence bonds
<chem>P_33:</chem>	tetrahedral (sp^3) phosphorous with three valence bonds
<chem>F_, Cl, Br, I_:</chem>	halogens
<chem>F_c[a], Clc[a], Brc[a], I_c[a]:</chem>	halogens attached to carbon

[a] new atom type

Introduction to Molecular Dynamics

Different types of oxygen atoms



Bond parameters

Bond	K_r^a	r^b
C–O	656	1.250
C–N	424	1.383
HN–N	434	1.010

Angle parameters

Angle	K_θ^c	θ^d
N–C–O	80	120.9
C–N–HN	30	120.0
HN–N–HN	35	120.0
N–C–N	70	118.6

Dihedral parameters

Torsion	No. of paths ^e	$V_n/2^f$	γ^g	n^h
HN–N–C–O	1	2.5	180	-2
HN–N–C–O	1	2.0	0	1

Improper dihedral parameters

Torsion	$V_n/2^f$	γ^g	n^h
N–N–C–O	10.5	180	2
C–HN–N–HN	1.1	180	2

Nonbonding parameters

Atom type	σ (Å)	ε (kcal mol ⁻¹)
HN	0.6000	0.0157
O	1.6612	0.2100
C	1.9080	0.0860
N	1.8240	0.1700

^a Force constant (kcal mol⁻¹ Å⁻²). ^b Bond distance (Å).

^c Force constant (kcal mol⁻¹ radian⁻²). ^d Angle (°).

^e Number of bond paths that the total $\frac{V_n}{2}$ is divided into.

^f Magnitude of torsion (kcal mol⁻¹).

^g Phase offset (°).

Introduction to Molecular Dynamics

- How do you obtain force field parameters?
- Experimental measurements:
 - Infrared (IR) spectroscopy: bond vibration.
 - Conformations obtained by high resolution X-ray crystallography
 - Lipid phase behaviour
 - n-octanol-water partition
- High level quantum mechanics calculations (computational):
 - Calculates the electrostatic potential with QM, then adjust the partial charges to reproduce the data in MM

Introduction to Molecular Dynamics

Force field = $\frac{-dE_{total}}{dx}$

acceleration of atom i $\leftarrow \frac{d^2\mathbf{r}_i(t)}{dt^2} = \frac{\mathbf{F}_i}{m_i}$

force acting on atom i

$m_i \rightarrow$ mass of atom i

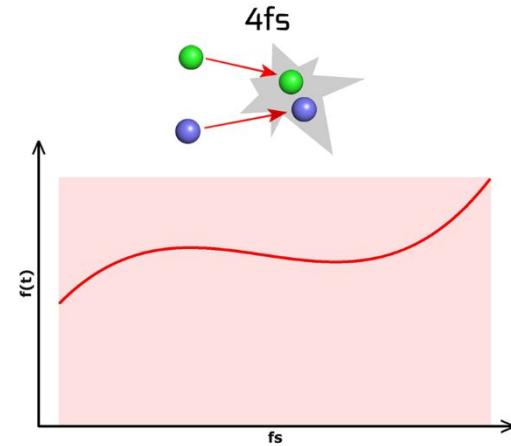
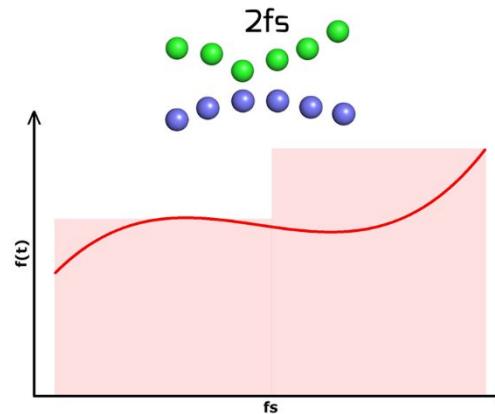
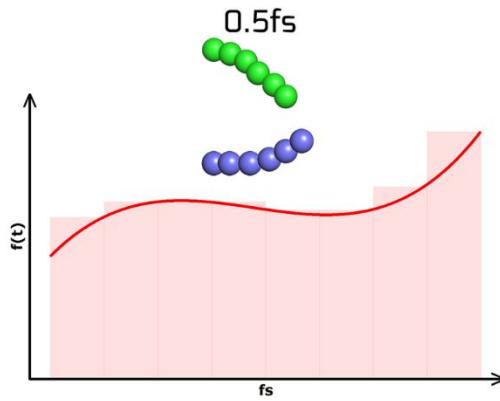
velocities
calculation

$$v(t + \frac{\Delta t}{2}) = v(t) + a(t) \cdot \frac{\Delta t}{2}$$

positions
calculation

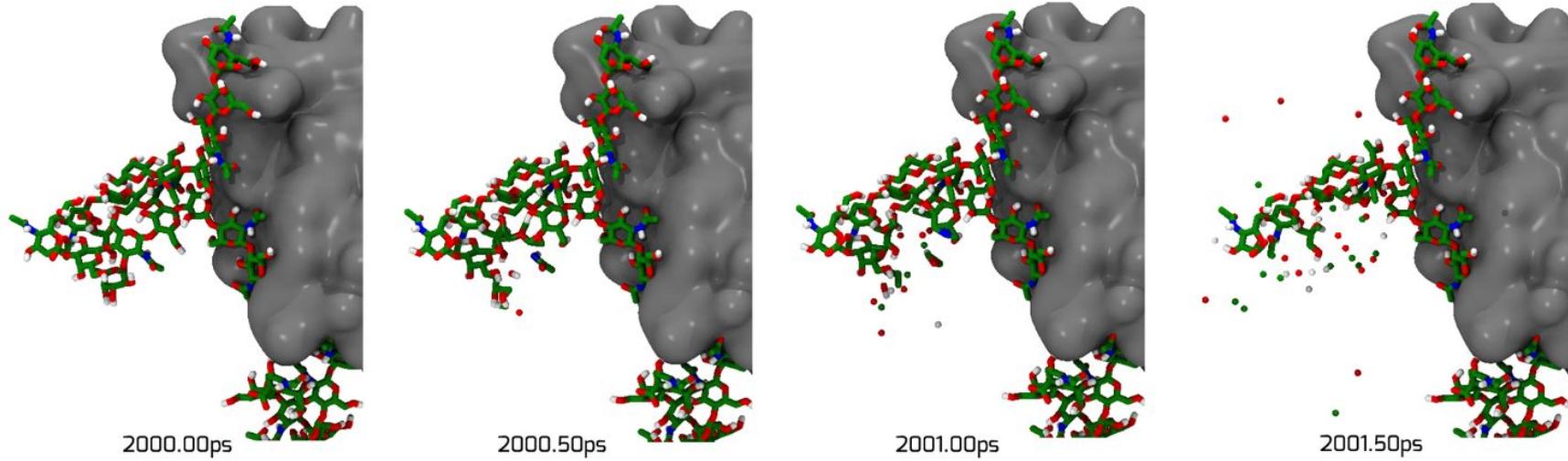
$$\mathbf{r}(t + \Delta t) = \mathbf{r}(t) + v(t + \frac{\Delta t}{2}) \cdot \Delta t$$

Introduction to Molecular Dynamics



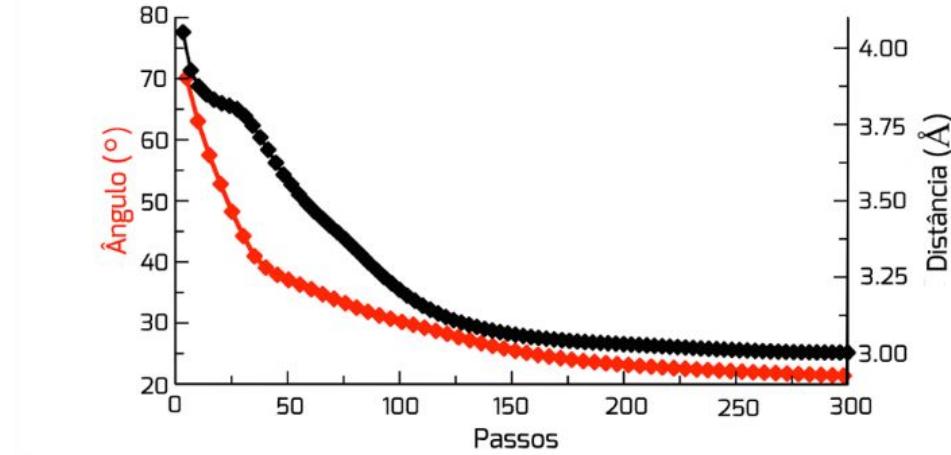
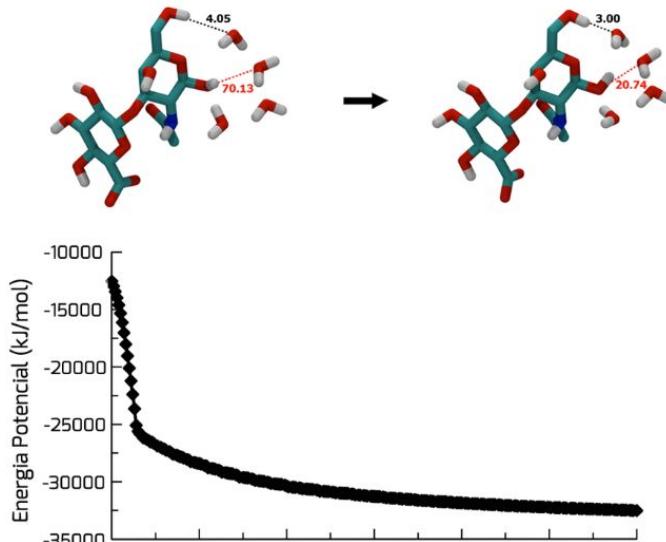
Introduction to Molecular Dynamics

System Explosion!



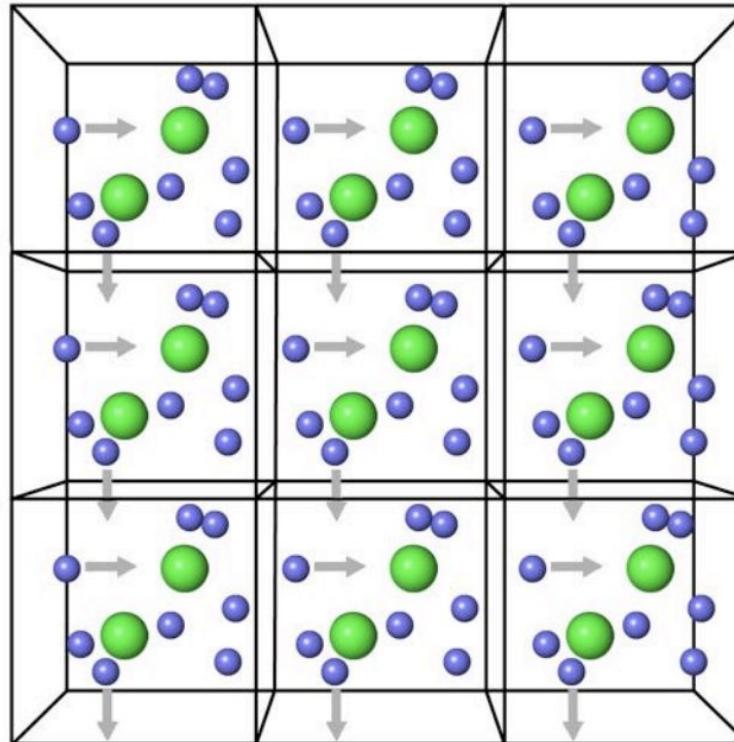
Introduction to Molecular Dynamics

Energy Minimization can fix a bad starting configuration



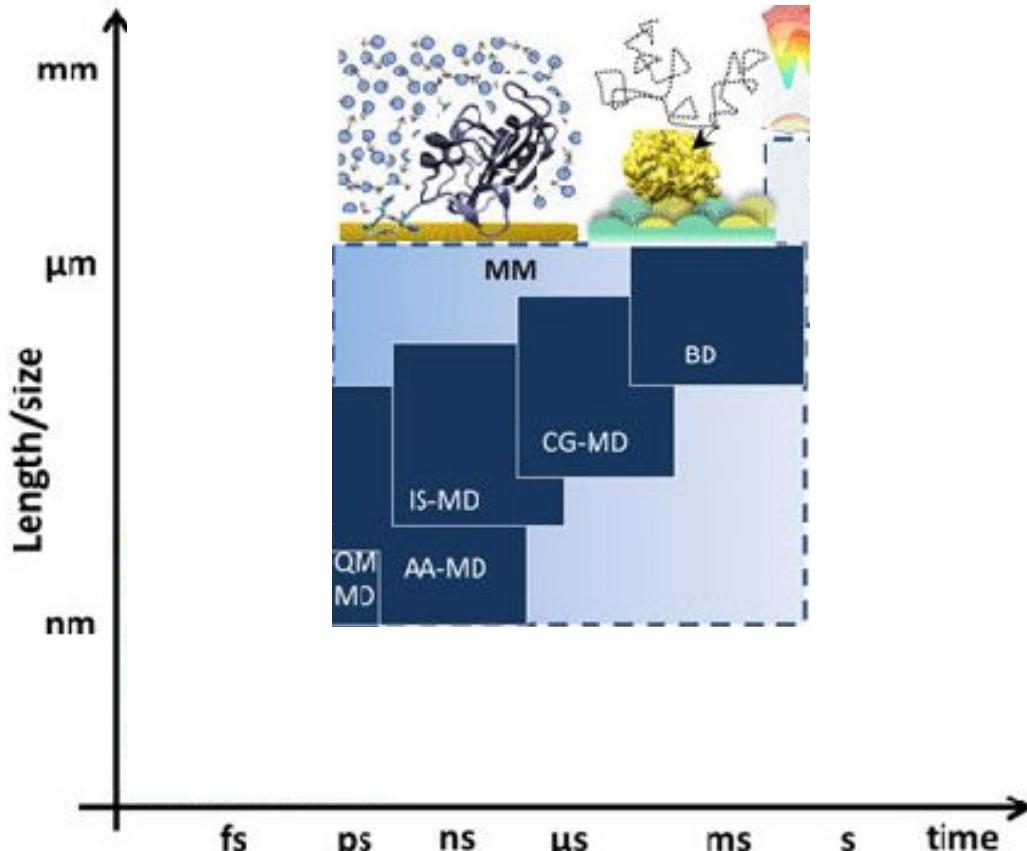
Introduction to Molecular Dynamics

Periodic
Boundary
Conditions



Introduction to Molecular Dynamics - Reminders

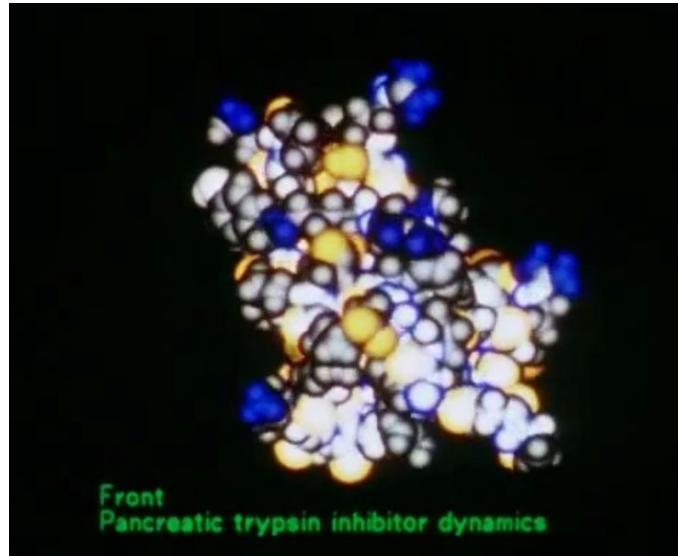
- Atoms move in a specific scale of time.
- It is **IMPERATIVE** to keep in mind the scale of the motions we are interested to observe while designing an MD experiment.
- The timescale accessible by atomistic resolution MD is at the millisecond level (ms).
- **IMPORTANT:** have a clear hypothesis to test or a relevant biological/chemical/physical question to answer



Introduction to Molecular Dynamics

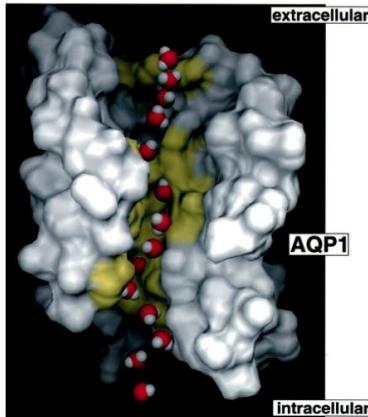
For simple systems (gas solutions), employed since the ~1960s.

Around ~1970 starts to be employed to study small proteins.

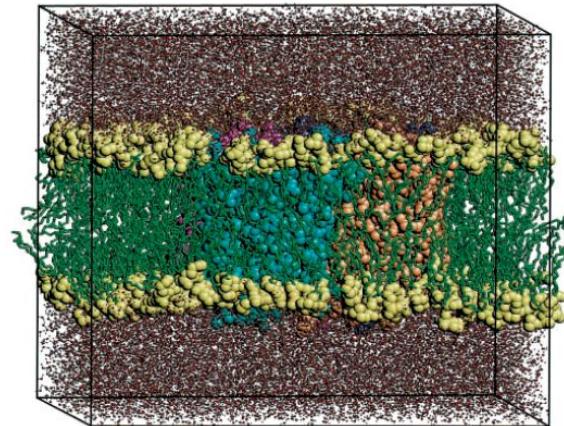


https://youtu.be/_hMa6G0ZoPQ

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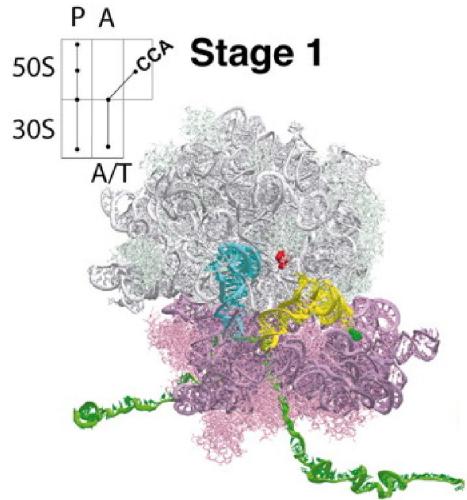


Aquaporinas
de Groot BL & Grubmüller H,
Science (2001), 294:2353-2357.

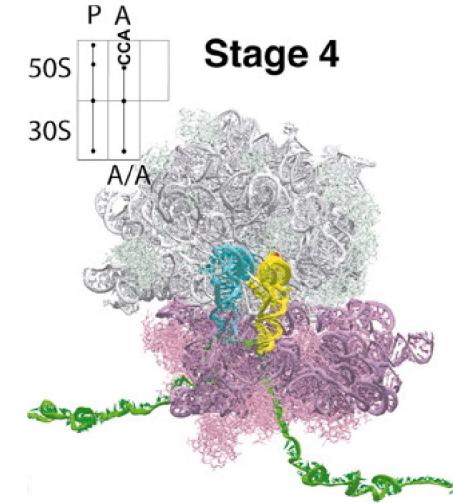


<https://www.youtube.com/watch?v=1Uw6u0fzNsE>

Introduction to Molecular Dynamics



tRNA inside the ribosome
Sanbonmatsu et al.,
PNAS (2005), 102:15854-15859.



<https://www.youtube.com/watch?v=KVFKk2d2IV0>

Introduction to Molecular Dynamics

The Nobel Prize in Chemistry 2013

The Nobel Prize in Chemistry 2013

Martin Karplus, Michael Levitt, Arieh Warshel



Photo: A. Mahmoud
Martin Karplus
Prize share: 1/3



Photo: A. Mahmoud
Michael Levitt
Prize share: 1/3

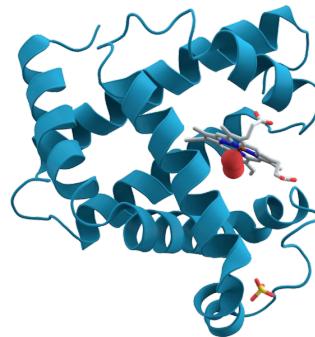


Photo: A. Mahmoud
Arieh Warshel
Prize share: 1/3

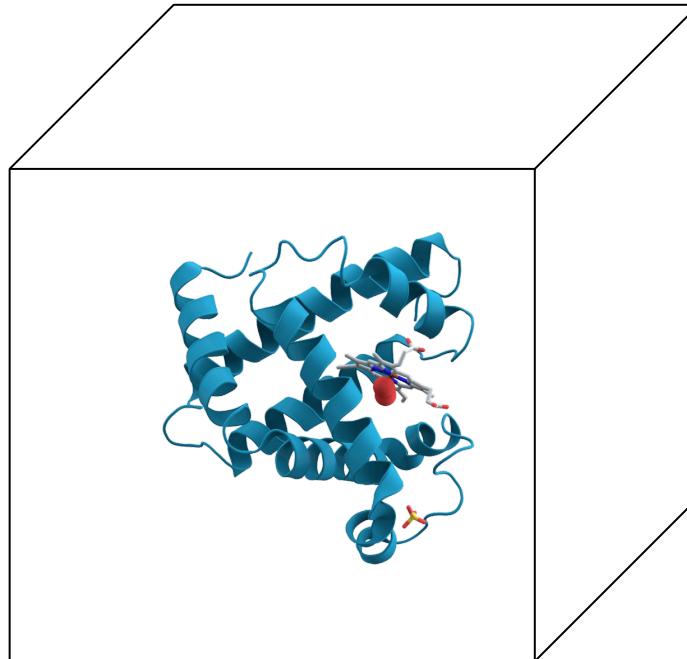
The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.



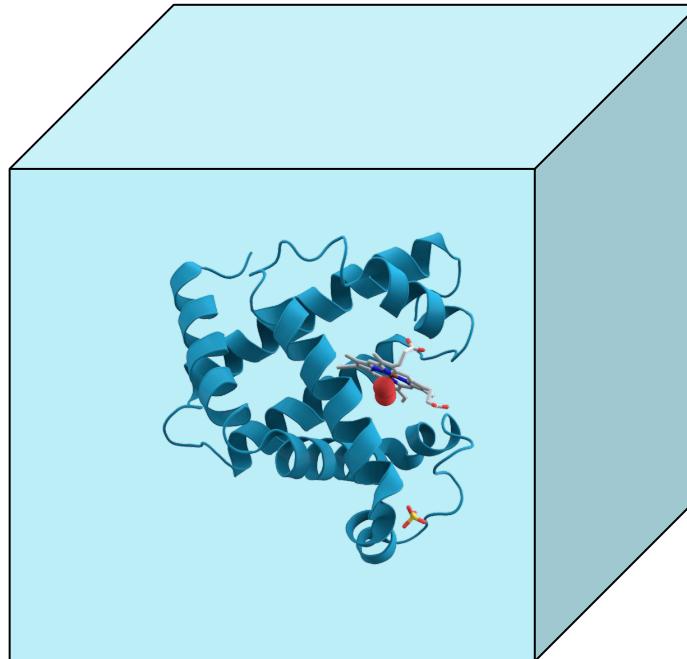
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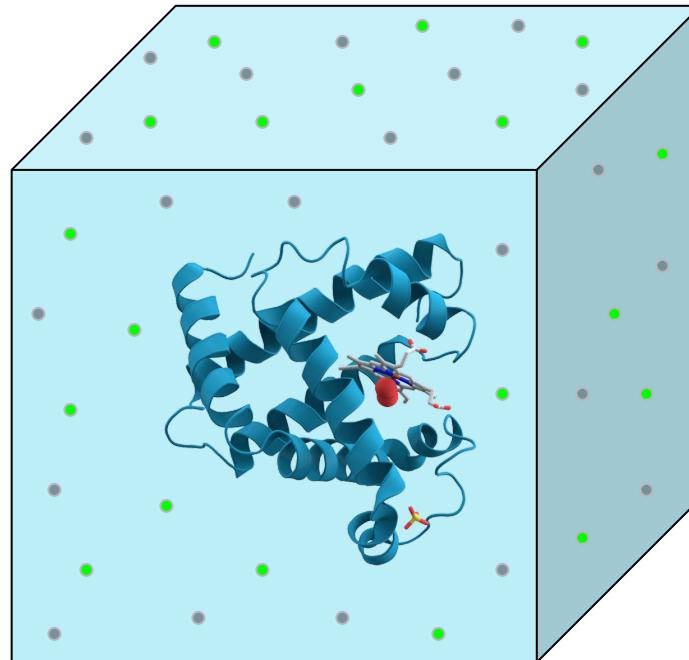
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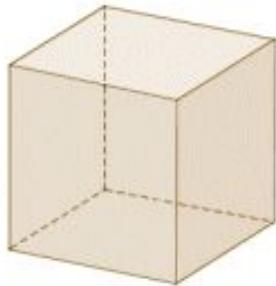
Introduction to Molecular Dynamics



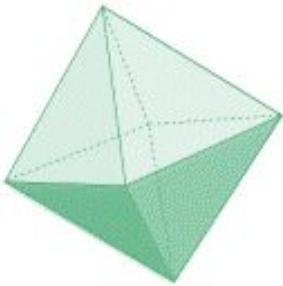
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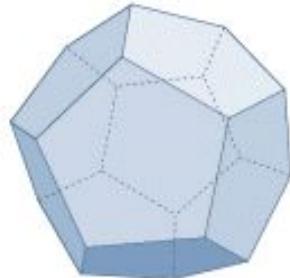
Introduction to Molecular Dynamics



Hexahedron



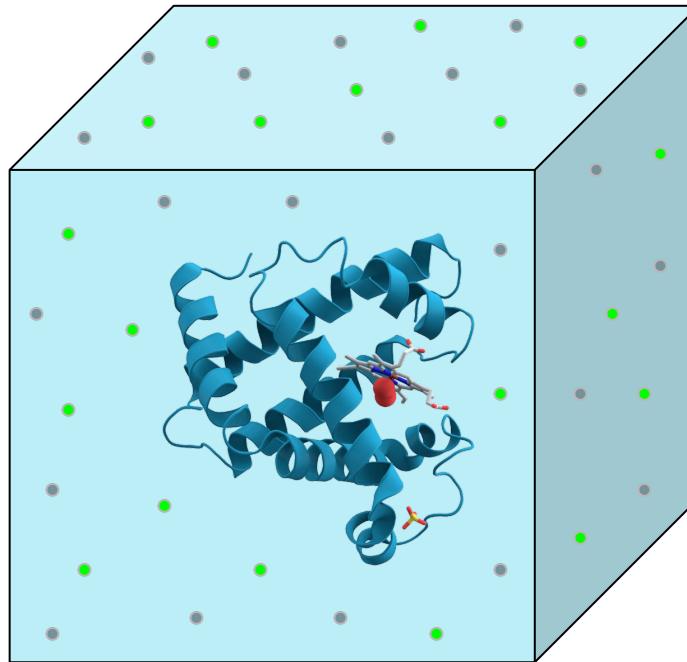
Octahedron



Dodecahedron



Icosahedron

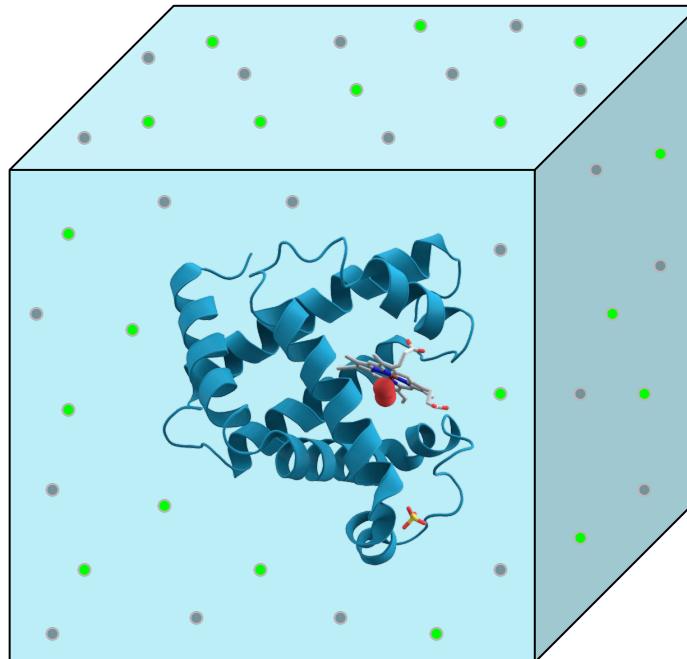


Introduction to Molecular Dynamics

- 1) Provide starting velocities for each atom of the system
- 2) Calculate force and acceleration of each atom using Newton's second law of motion:

$$F = m * a$$

- 3) Calculate new coordinates (step t+1) based on the acceleration.
- 4) Update atomic velocities at step (t+1)
- 5) Go back to 2) to reach step (t+2) and execute for N steps.



Introduction to Molecular Dynamics - Water Models

- There are at least 45 different water models.
 - Just a few of them are used for biomolecular simulations.
- The main ones are:
 - SPC (Pullman (ed.), Intermolecular Forces (Reidel, Dordrecht, 1981) p331)
 - SPC/E (Berendsen et al. J. Phys. Chem. 91 (1987) 6269-6271)
 - TIP3P (Jorgensen. J. Chem. Phys. 79 (1983) 926-935)
 - TIP4P (Jorgensen & Madura. Mol. Phys. 56 (1985) 1381-1392)
 - TIP5P (Mahoney & Jorgensen. J. Chem. Phys. 112 (2000) 8910-8922)
 - OPC (Izadi et al. J. Phys. Chem. Lett. 5 (2014) 3863–3871)

Introduction to Molecular Dynamics

1) All-atom:

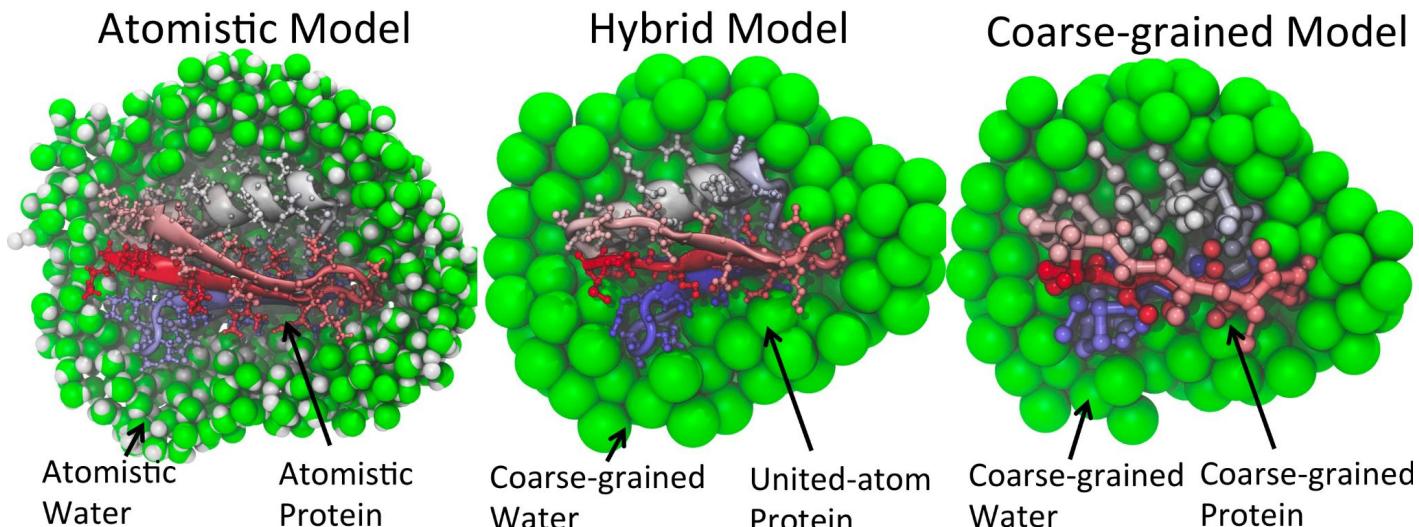
- a) AMBER
- b) CHARMM
- c) OPLS

2) United-atom:

- a) GROMOS

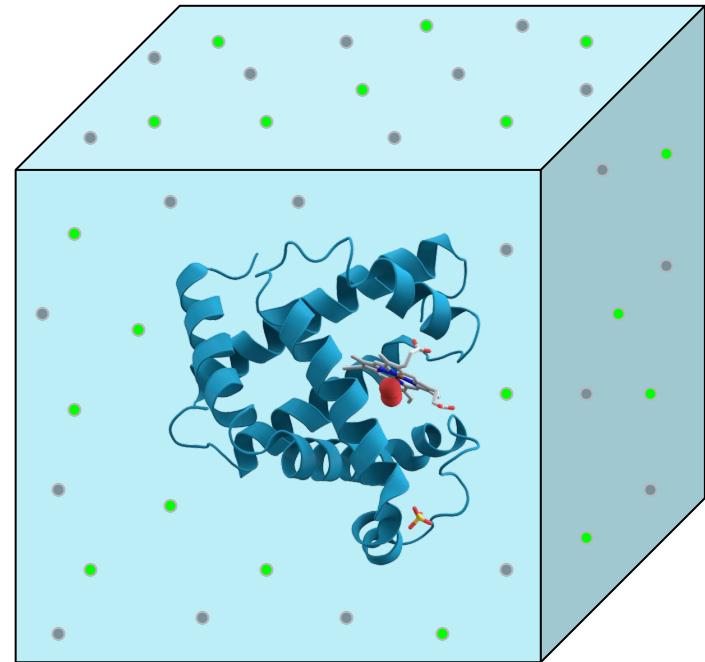
3) Coarse-Grained:

- a) MARTINI
- b) SIRAH



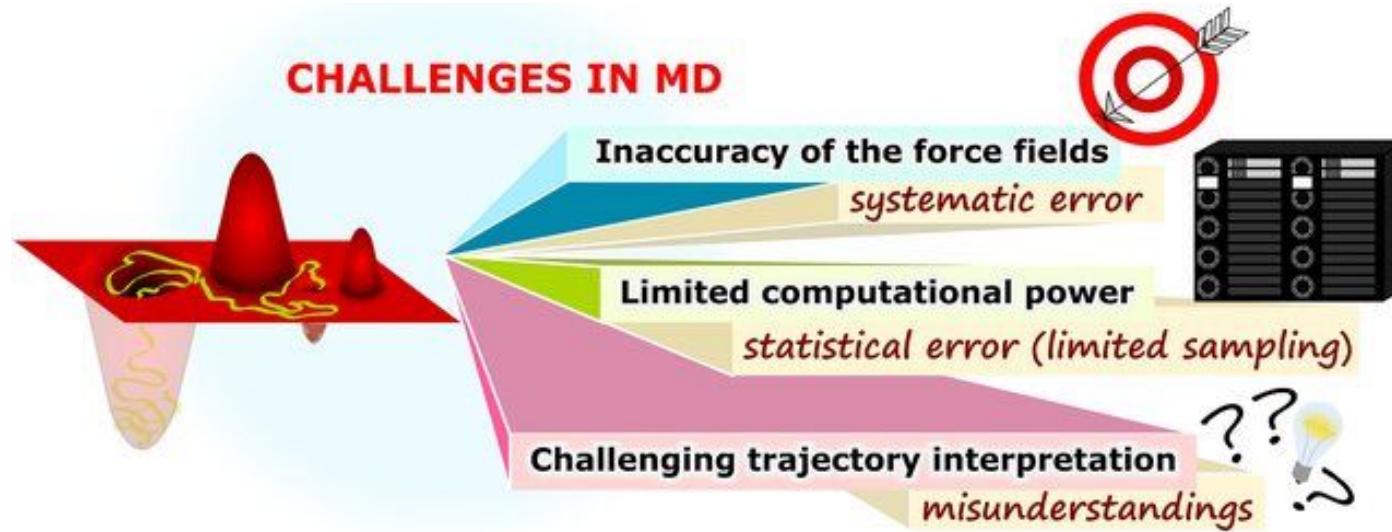
Introduction to Molecular Dynamics

- 1) Obtain the structure of the solute to be studied
- 2) Choose the force field (are there enough parameters for all my solute molecules?)
- 3) Build the solute topology (file containing the parameters of the force field to describe that system, allowing the calculation of Forces and Acceleration.)
- 4) Solvate and neutralize the system
- 5) Minimize the system energy
- 6) Equilibrate the simulation box (temperature, pressure and solvation layers)
- 7) Simulate the unrestrained system (production stage)



Introduction to Molecular Dynamics

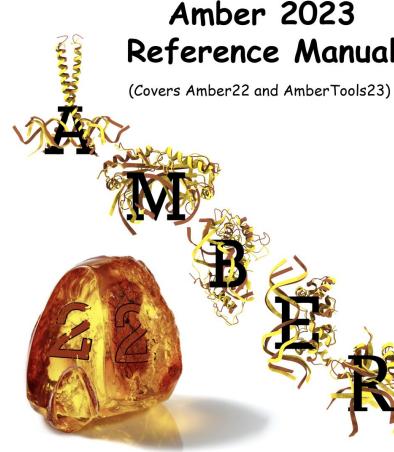
- MD main limitations:



Introduction to Molecular Dynamics

FAST. FLEXIBLE. FREE.
GROMACS

www.gromacs.org



<https://ambermd.org/>

CHARMM
Chemistry at HARvard Macromolecular Mechanics

www.charmm.org



OpenMM

<https://openmm.org/>

Introduction to Molecular Dynamics - Practical Lesson



JOURNAL OF
CHEMICAL INFORMATION
AND MODELING

pubs.acs.org/jcim

Letter

Making it Rain: Cloud-Based Molecular Simulations for Everyone

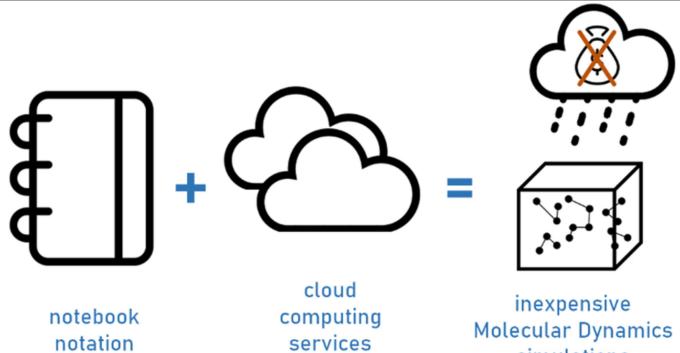
Pablo R. Arantes,* Marcelo D. Polêto, Conrado Pedebos, and Rodrigo Ligabue-Braun



Cite This: *J. Chem. Inf. Model.* 2021, 61, 4852–4856



Read Online



SCAN ME

<https://pablo-arantes.github.io/making-it-rain>

Introduction to Molecular Dynamics - Practical Lesson

How Google Colab works?

Google colab

Blog

Release Notes

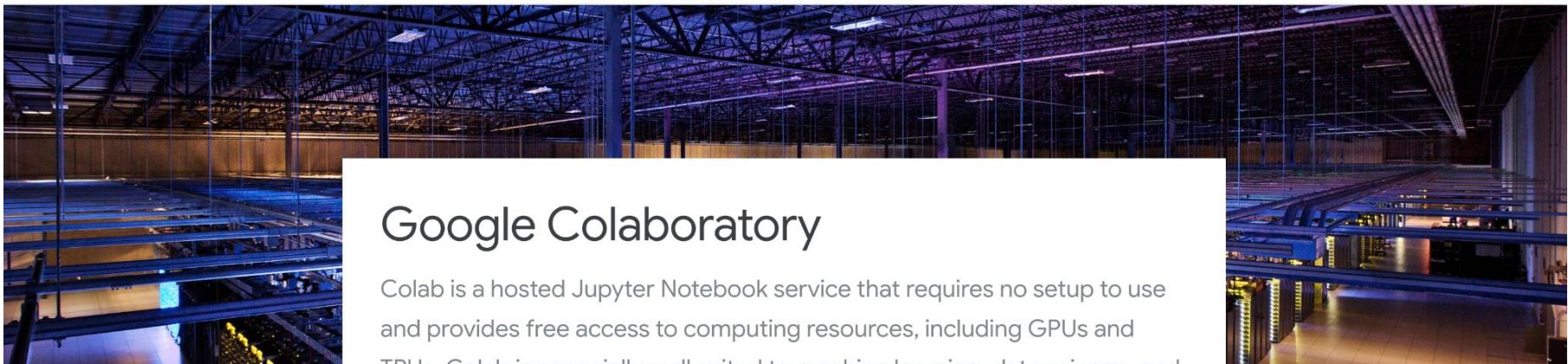
Notebooks

Resources

[Open Colab](#)

[New Notebook](#)

[Sign Up](#)



Google Colaboratory

Colab is a hosted Jupyter Notebook service that requires no setup to use and provides free access to computing resources, including GPUs and TPUs. Colab is especially well suited to machine learning, data science, and education.

[Open Colab](#)

[New Notebook](#)

Introduction to Molecular Dynamics - Practical Lesson

Science



AlphaFold

This Colab notebook allows you to easily predict the structure of a protein using a slightly simplified version of AlphaFold v2.3.2.



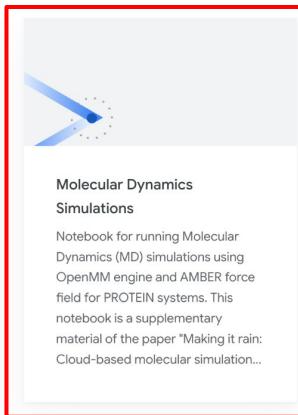
AlphaTensor

This Colab shows how to load the provided .npz file with rank- 49 factorizations of $\mathcal{T}4$ in standard arithmetic, and how to compute the invariants \mathcal{R} and \mathcal{K} in order to demonstrate that these factorizations are mutually...



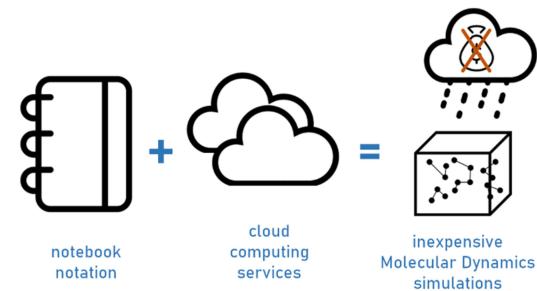
Google Earth API

This notebook demonstrates how to setup the Earth Engine Python API in Colab and provides several examples of how to print and visualize Earth Engine processed data.



Molecular Dynamics Simulations

Notebook for running Molecular Dynamics (MD) simulations using OpenMM engine and AMBER force field for PROTEIN systems. This notebook is a supplementary material of the paper "Making it rain: Cloud-based molecular simulation..."

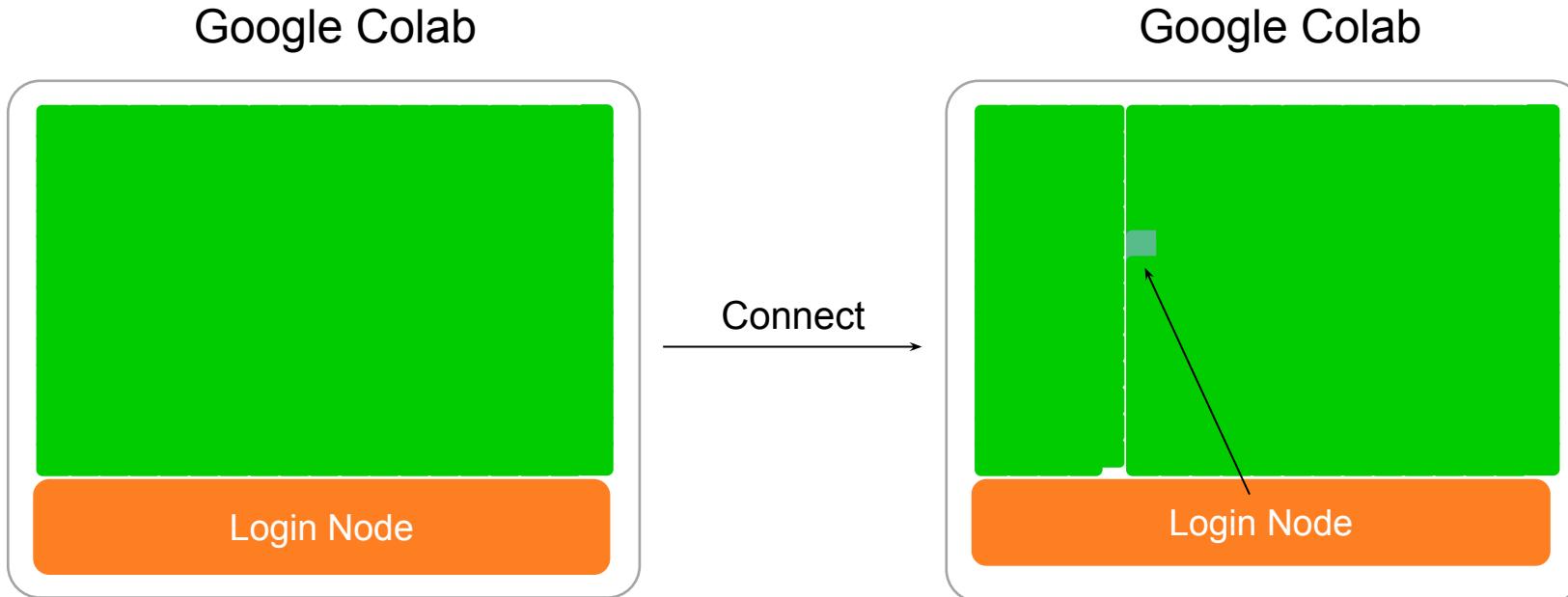


<https://pablo-arantes.github.io/making-it-rain>

<https://colab.google/notebooks/>

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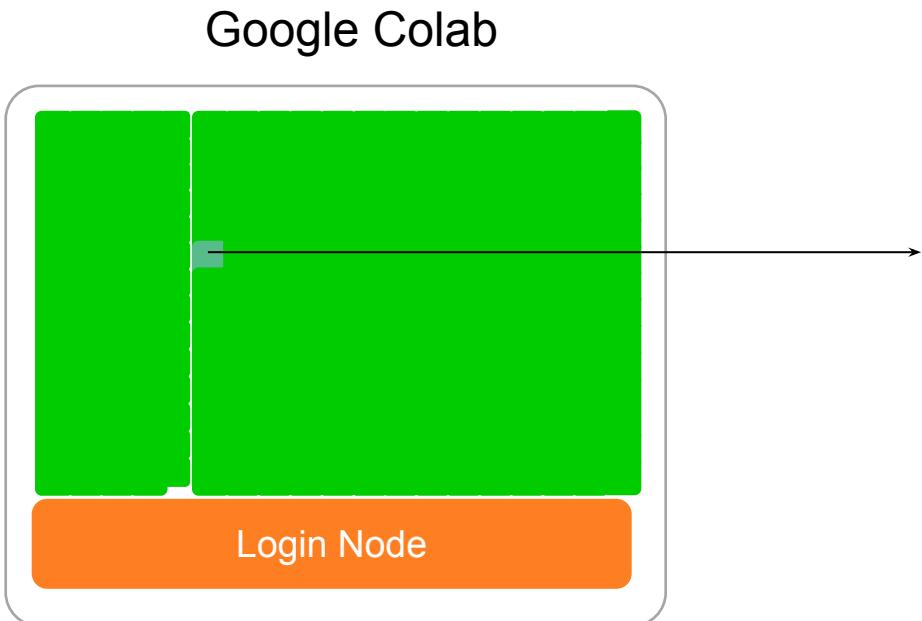
How Google Colab works?



■ = Virtual Machine

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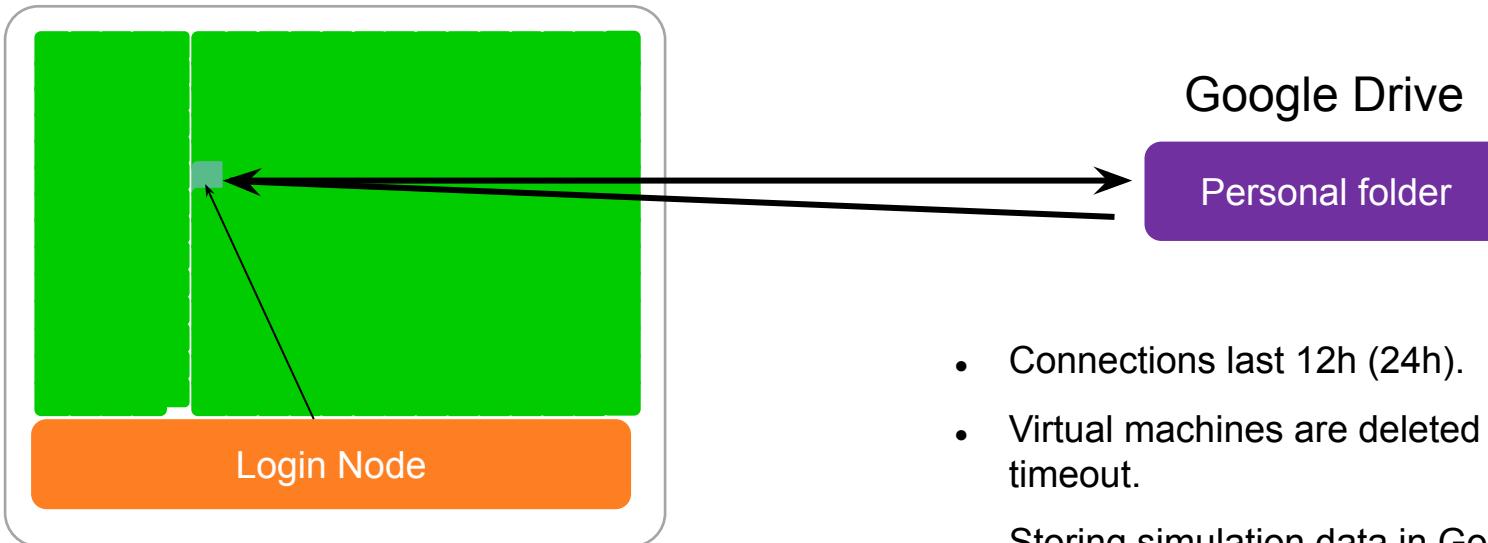


- Colab Free!
 - Colab Pro = USD 9.90 / month
 - Colab Pro+ = USD 49.90 / month
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- All GPU and RAM memory.
 - Free Colab: **Nvidia T4**
 - Pro Colab: **Nvidia T4**, **Nvidia K80**, **Nvidia P100** and **Nvidia V100**

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How Google Colab works?

Google Colab



- Connections last 12h (24h).
- Virtual machines are deleted after timeout.
- Storing simulation data in Google Drive is a workaround but requires **storage space!**

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What are Jupyter notebooks?

- Web-based interactive development environment for code and data.
- They are usually written as actual protocol notebooks that can be ran multiple times to yield results.

