MD Simulations with OpenMM

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Thesis projects available

github.com/giorginolab/
OpenMM-UniPd-2023

University of Padova c/o Prof. Fuxreiter
Mar 16, 2023

This class

- Molecular dynamics is a powerful tool for studying molecular systems
- OpenMM is a software package that allows for efficient and customizable molecular dynamics simulations
- It has C++ and Python bindings. We'll use the latter, testing *live* on Google Colab.

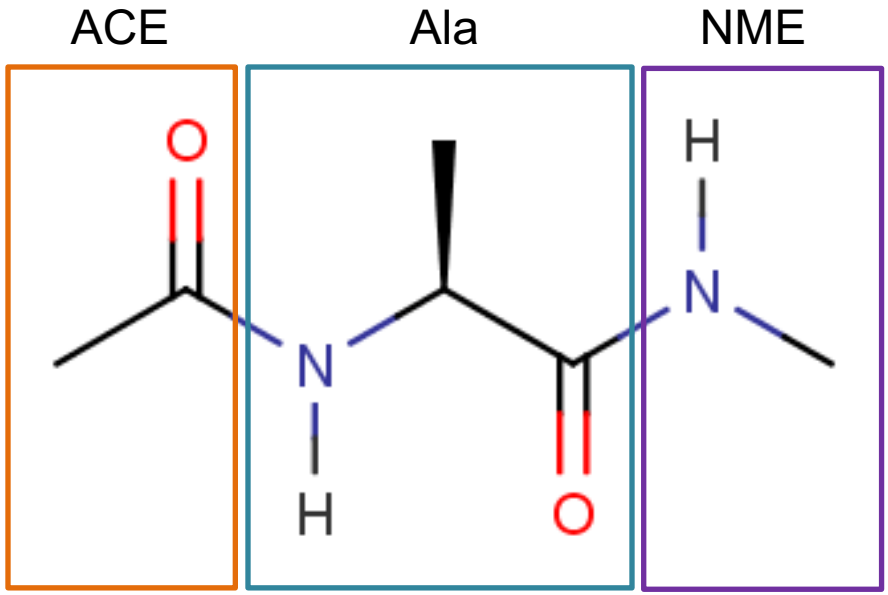
Molecular Dynamics

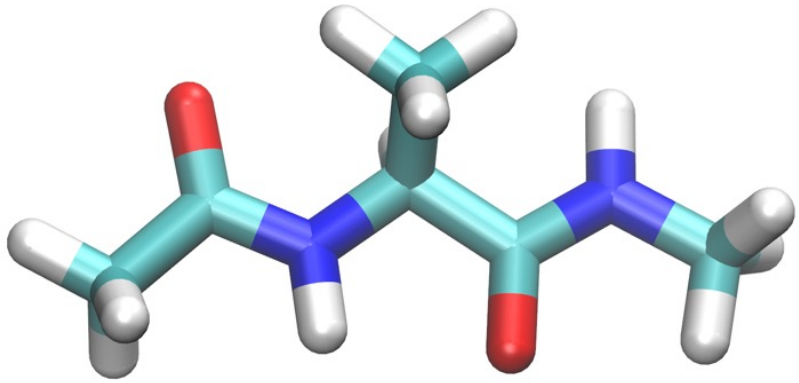
What is MD?

- Attempt the most detailed description of a system which is
  1. atomistic
  2. classical
- Model the internal *forces*…
- …in order to *integrate* the motion
- Hope in convergent *sampling*

$$\vec{F}_i(\mathbf{x}) = m_i \ddot{\mathbf{x}}_i$$

Alanine “dipeptide”

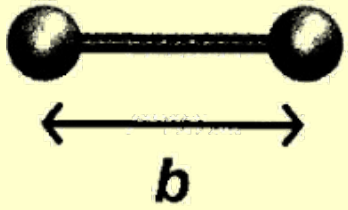


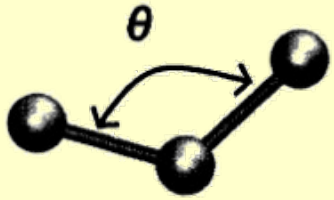


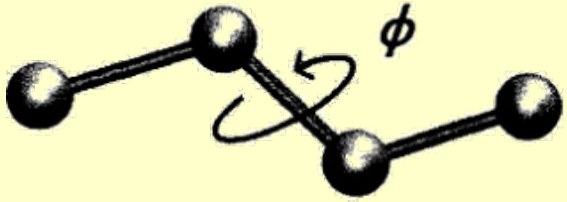
Bonded energy terms

+ Electrostatics

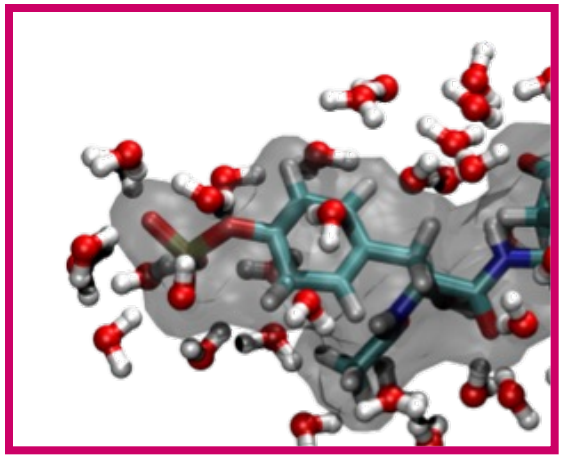
+ VdW



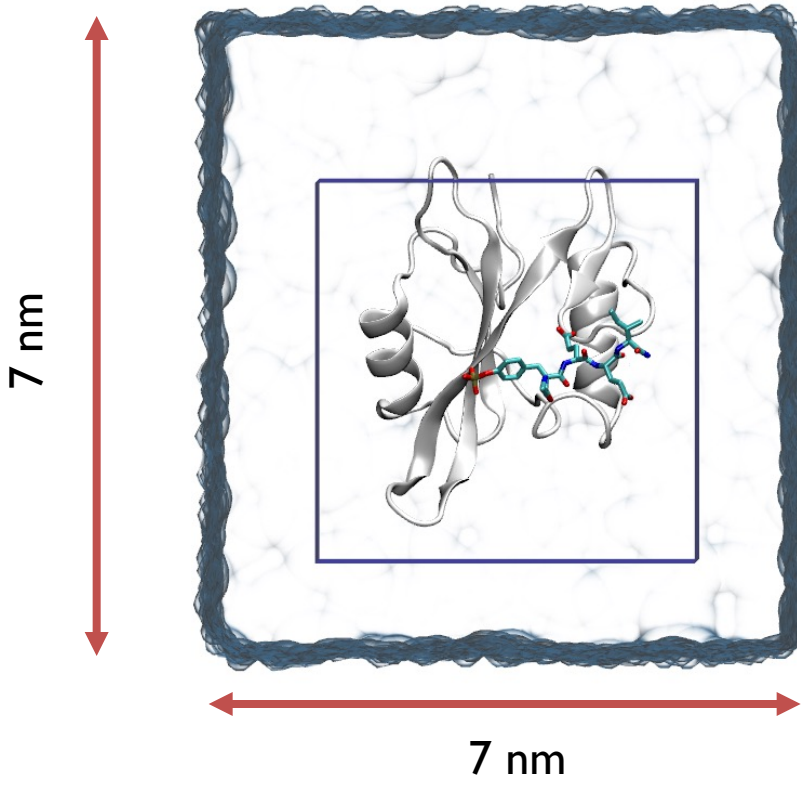


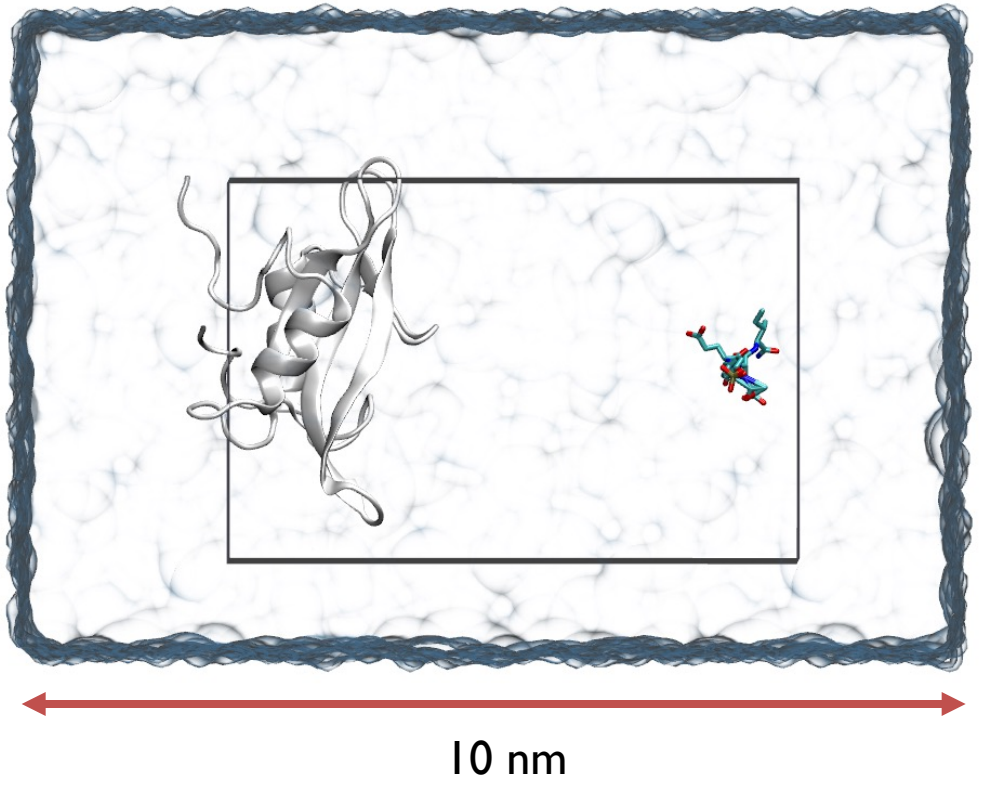


The forcefield is a database of interatomic parameters



- **Explicit solvation**
- → O(10^5) atoms
- **Unbiased dynamics**
- Update every 10^{-15} s (1 fs)





***Event* ≡ Binding / Unbinding / Folding / Unfolding / …**

* $1/t_{on}$ = association rate of SH2-pYEEI × [pYEEI]

Large gain

Ability to "play" biomolecular processes at *all-atom* resolution *in silico*

Molecular bases of folding, binding, selectivity, gating…

Large cost

E.g.*: t_{on} ~ 30 μs →

→ **10^{10}** integration timesteps →

→ 15 years single-CPU compute time

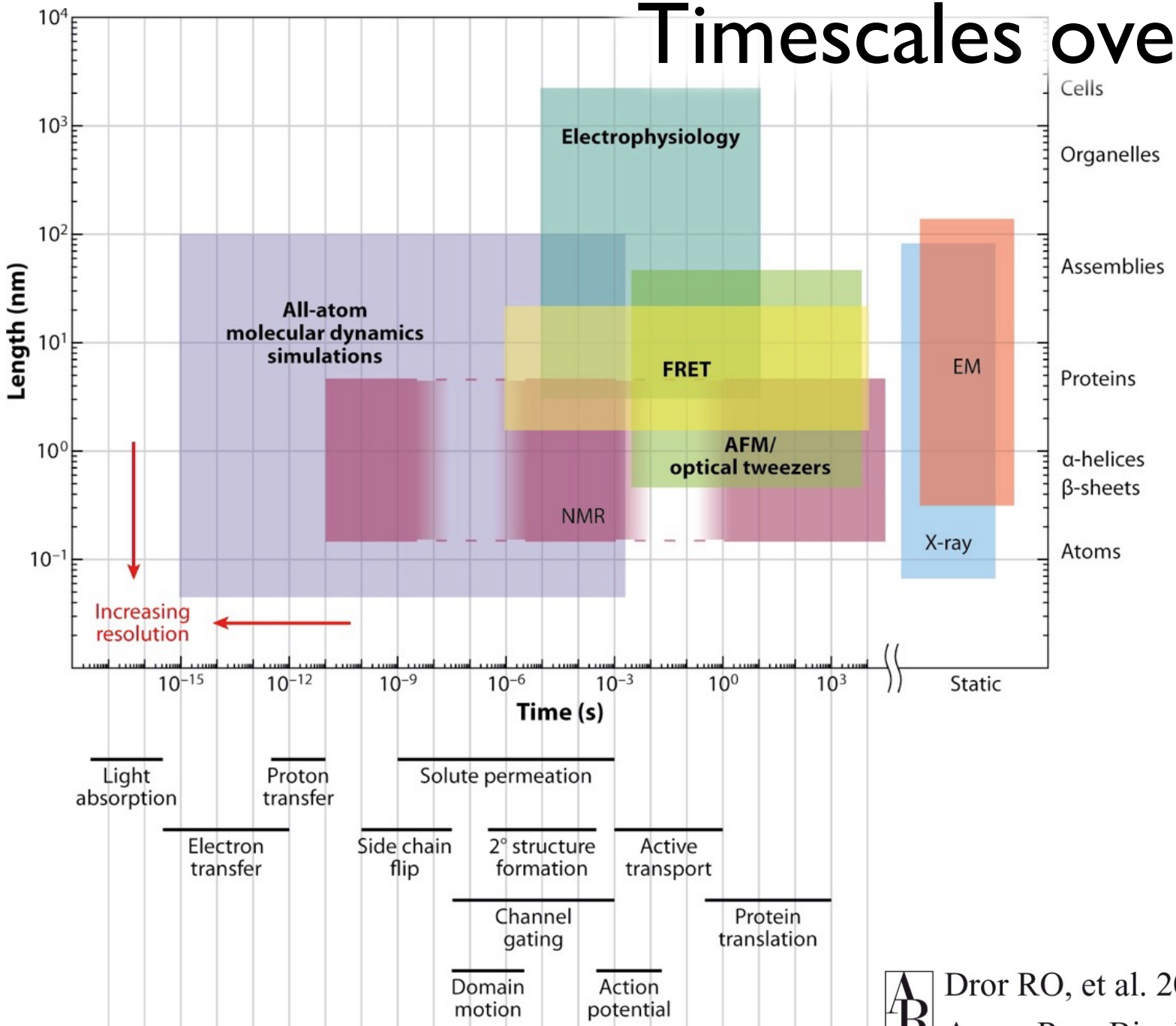
Assumptions

- In this tutorial we shall deal with **unbiased** sampling approaches with **explicit** solvent, i.e.
  - no added forces except the "physical" ones in your system;
  - all of the system (including water molecules) have atomic resolution.
- Also, current classical MD does not address, by design, the following:
  - Chemical reactions, e.g. catalysis, phosphorylation, ubiquitination etc.
  - Protonation changes
- Finally, small molecules pose distinct challenges and need a separate, expensive **parameterization** step.

MD is entirely about timescales

- Your ability to obtain quantitative results is severely limited by the sampling ability you have. You will only be able to reach phenomena occurring on the sampled timescales, or shorter.
  - Sidechain rearrangements, diffusion-limited processes: usually possible *
  - Local flexibility: usually possible *
  - Membrane environments: ok-ish
  - Binding: hard but not impossible
  - Folding: very hard but not impossible
    - [*] Unless there are significant barriers.

Timescales overview



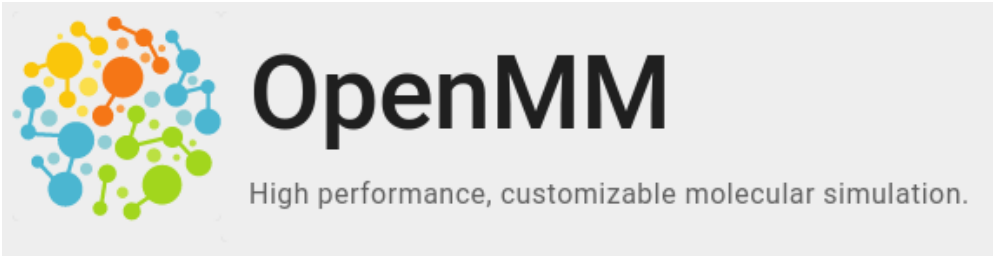
Dror RO, et al. 2012.
Annu. Rev. Biophys. 41:429–52

Patience and limits

- The following factors affect the running speed (usually expressed in ns per simulation day, ns/day)
  - System size. Reasonable is 100 AA ~ 30,000 atoms.
  - Computer speed. Forget laptops.
  - Definitely use GPUs.
  - Software.

OpenMM

OpenMM.org



- OpenMM is a molecular dynamics simulation toolkit that allows for high-performance simulations of biomolecules.
- Allows for simulation of a variety of molecular systems, including proteins, nucleic acids, and small molecules
- OpenMM supports a wide range of force fields and integrators and can run on CPUs and GPUs.
- Open source, written in C++ with Python and other language bindings available

Basic Workflow

- Define the **system** object.
- Define the **integrator** object.
- Add custom **forces** to the system if needed.
- Define the **simulation** object.
- Set the initial positions and velocities.
- Run the simulation.
- Analyze the results.

Integrators

- Integrators are algorithms that solve the equations of motion for a system
- OpenMM includes several integrators, such as Langevin dynamics, Verlet integrator, and Monte Carlo barostat
- Different integrators are appropriate for different types of simulations and systems

Simulating a system

- Once a system has been defined and the force field and integrator selected, it can be simulated using OpenMM
- The simulation involves running a series of steps, where each step involves calculating the forces on each atom, integrating the equations of motion, and updating the system's coordinates
- After the simulation, data analysis can be performed to obtain information about the system's behavior and properties

In practice

6H1F: Gelsolin G2+nanobody

Structure Summary | 3D View | Annotations | Experiment | Sequence | Genome | Versions

Biological Assembly 1

3D View: Structure | 1D-3D View | Electron Density | Validation Report | Ligand Interaction

Global Symmetry: Asymmetric - C1
Global Stoichiometry: Hetero 2-mer - A1B1

Find Similar Assemblies

Biological assembly 1 assigned by authors and generated by PISA (software)

Biological Assembly Evidence: gel filtration

Macromolecule Content

- Total Structure Weight: 28.49 kDa
- Atom Count: 1,896
- Modelled Residue Count: 229
- Deposited Residue Count: 259
- Unique protein chains: 2

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6H1F

Structure of the nanobody-stabilized gelsolin D187N variant (second domain)

PDB DOI: 10.2210/pdb6H1F/pdb

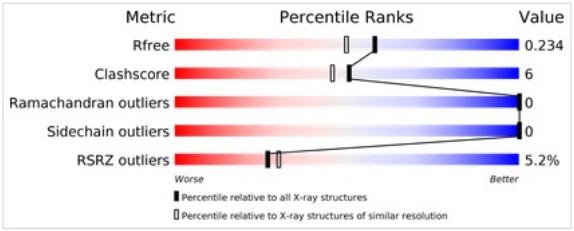
Classification: STRUCTURAL PROTEIN
Organism(s): Lama glama, Homo sapiens
Expression System: Escherichia coli
Mutation(s): Yes

Deposited: 2018-07-11 **Released:** 2019-01-23
Deposition Author(s): Hassan, A., Milani, M., Mastrangelo, E., de Rosa, M.
Funding Organization(s): Amyloidosis Foundation

Experimental Data Snapshot

Method: X-RAY DIFFRACTION
Resolution: 1.90 Å
R-Value Free: 0.233
R-Value Work: 0.199
R-Value Observed: 0.202

wwPDB Validation | 3D Report | Full Report



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Literature | Download Primary Citation

Nanobody interaction unveils structure, dynamics and proteotoxicity of the Finnish-type amyloidogenic gelsolin variant.

Giorgino, T., Mattioni, D., Hassan, A., Milani, M., Mastrangelo, E., Barbiroli, A., Verhelle, A., Gettemans, J., Barzago, M.M., Diomede, L., de Rosa, M.
(2019) Biochim Biophys Acta Mol Basis Dis **1865**: 648-660

PubMed: 30625383 Search on PubMed
DOI: 10.1016/j.bbadis.2019.01.010
Primary Citation of Related Structures:

3D Protein Feature View: 6H1F

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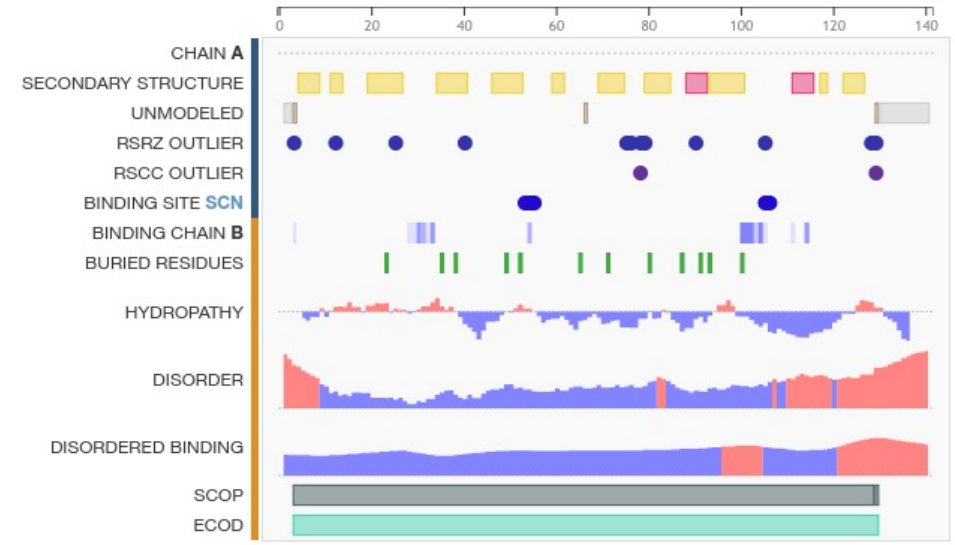
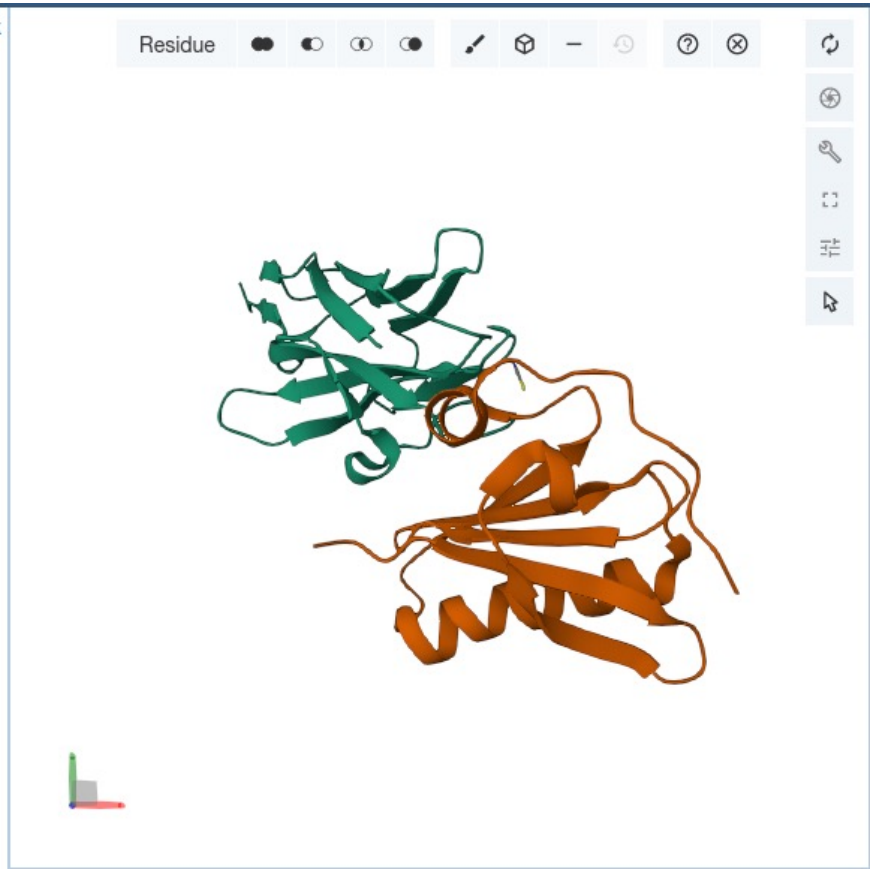
Structure of the nanobody-stabilized gelsolin D187N variant (second domain)

Chain

A

Gelsolin nanobody - Lama glama





Using OpenMM on Google Colab

- **Google Colab** is a free Jupyter environment that allows you to run Python code in the cloud. GPUs runtimes are available.
- OpenMM can be used on Google Colab to run molecular dynamics simulations without the need for installing any software on your local machine.
- To use OpenMM on Google Colab or locally, open the provided notebook (read the comments)

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OpenMM_2023.ipynb	test editing locally	8 minutes ago
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gsn-nb.py	preview	yesterday
openmm_fuxreiter_2023_r1.pdf	preview	yesterday

README.md

OpenMM-Tutorial-UniPD-2023

OpenMM class, prof. Fuxreiter's course at UniPD

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No packages published
Publish your first package

Languages

Jupyter Notebook 84.4%
Python 15.6%

Visualize

- After you have done the simulation, load the minimized PDB and output.dcd in PyMOL
- What about PBCs? Fix with: `pbc_unwrap` …

Questions

- How many atoms?
- How many residues?
- Disulfide bridges?
- How many trajectory frames?
- Simulation length in *actual* time?

More questions

- Does density change? Should it?
- What is the box size? Is it appropriate?
- Relaxation time?
- Plot the log file

Conclusion

Conclusion

- OpenMM is a powerful tool for molecular dynamics simulations
- Good, if fragmented, documentation
- With its customizable force fields and integrators, it can be used to study a wide range of atomistic systems, e.g.
  - "toy" polymers
  - all-atom MD with major FFs
  - ANN potentials

Resources for learning OpenMM

- OpenMM.org website and documentation
- GitHub repository with examples and tutorials
- Community forums and mailing lists for support and discussion

- See also
  - OpenMMtools
  - https://openforcefield.org/
  - HTMD, ACEMD
  - https://github.com/openmm/pdbfixer
  - Charmm-GUI

PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

OpenMM 7: Rapid development of high performance algorithms for molecular dynamics

Peter Eastman[1]*, Jason Swails[2], John D. Chodera[3], Robert T. McGibbon[1], Yutong Zhao[1], Kyle A. Beauchamp[3¤], Lee-Ping Wang[4], Andrew C. Simmonett[5], Matthew P. Harrigan[1], Chaya D. Stern[3,6], Rafal P. Wiewiora[3,6], Bernard R. Brooks[5], Vijay S. Pande[1,7]

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2 Department of Chemistry and Chemical Biology and BioMaPS Institute, Rutgers University, Piscataway,

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