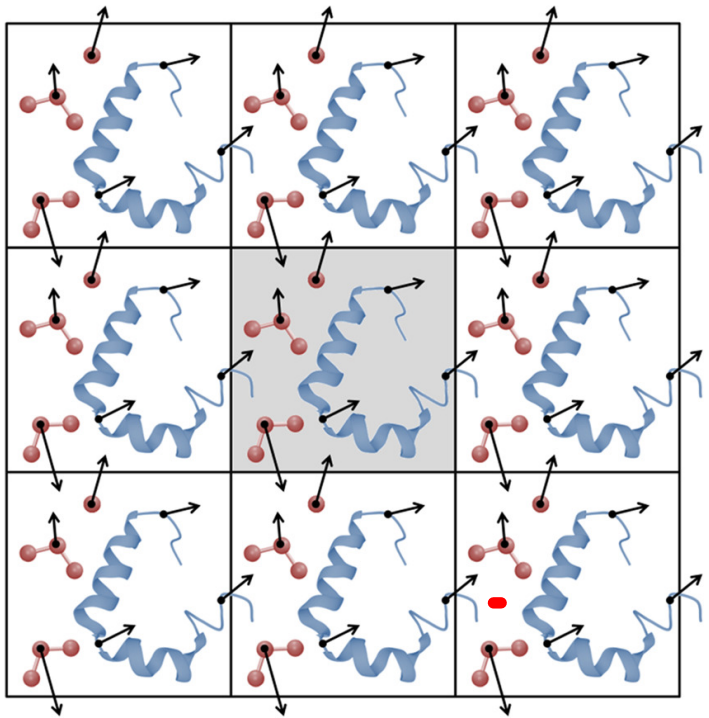
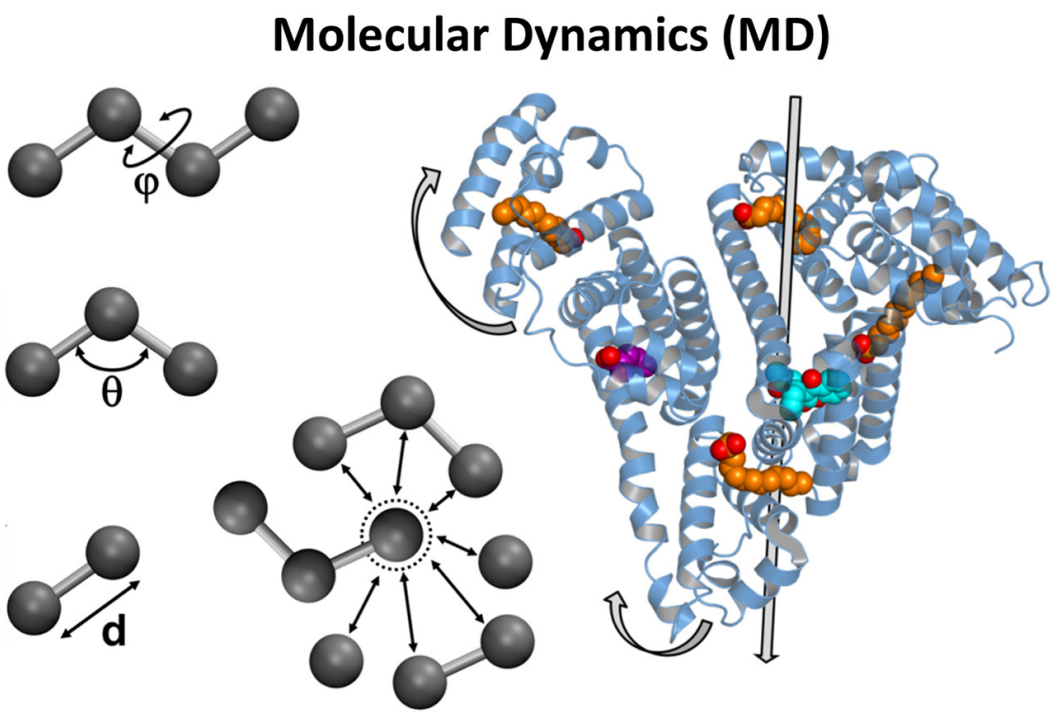
Preparation of structures for molecular dynamics

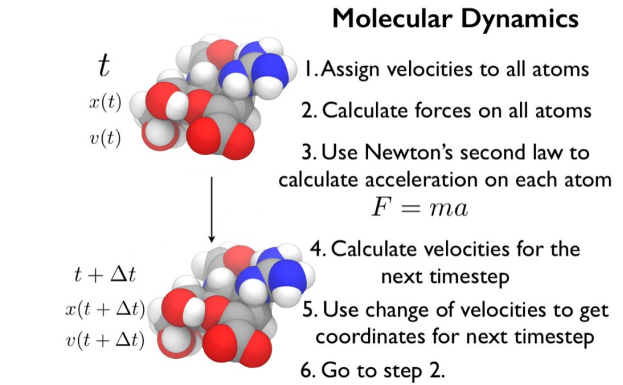


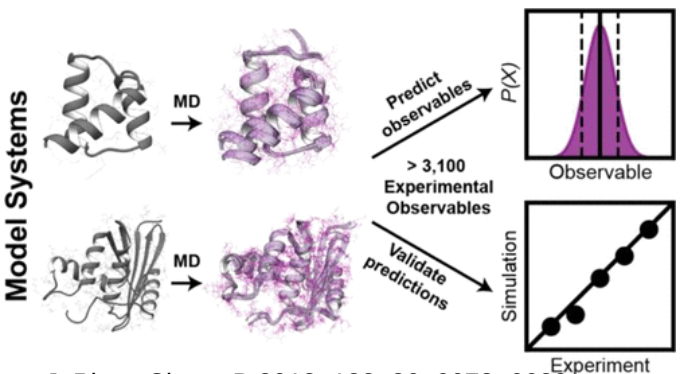


BBA-Proteins Proteomics, Volume 1870, Issue 3, 1 March 2022, 140757

What is Molecular dynamics (MD)?

- MD is a computational method to simulate atomic motion based on Newton's laws
- Provides atomic-level insight into biomolecular dynamics
- Complements experimental techniques like X-ray, cryo-EM, NMR





J. Phys. Chem. B 2018, 122, 26, 6673–6689

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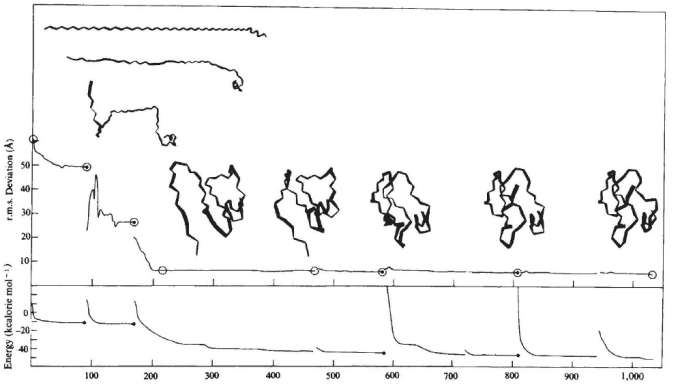
Origins of MD

- 1950s: Hard-sphere fluids (Alder & Wainwrigth, 1959)
- 1975: First protein folding simulation (Levitt & Warshel)
- 1977: First all-atom MD of a protein (McCammon, Gelin & Karplus)



Levitt M et al. (1975) Nature 253, 694–698

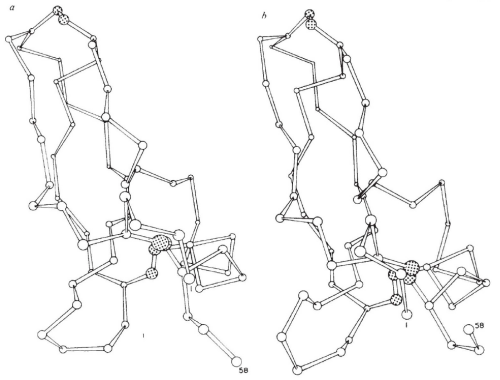


Fig. 1 The peptide backbone (α carbons) and disulphide bonds of PTI. *a*, X-ray structure[11]. *b*, Time evolved structure after 3.2 ps of dynamical simulation.

McCammon JA et al. (1977) Nature 267, 585–590.

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How MD works

- Newton's second law: F = ma
- Force fields: bonded and nonbonded terms
- Time integration: femtosecond timesteps (1-4 fs)

$$U(R) = \sum_{bonds} k_r (r - r_{eq})^2 \quad \textit{bond}$$

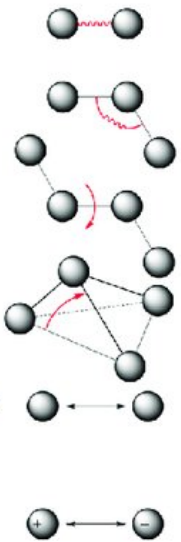
$$+ \sum_{angles} k_\theta (\theta - \theta_{eq})^2 \quad \textit{angle}$$

$$+ \sum_{dihedrals} k_\phi (1 + \cos[n\phi - \gamma]) \quad \textit{dihedral}$$

$$+ \sum_{impropers} k_\omega (\omega - \omega_{eq})^2 \quad \textit{improper}$$

$$+ \sum_{i<j}^{atoms} \varepsilon_{ij} \left[\left(\frac{r_m}{r_{ij}} \right)^{12} - 2 \left(\frac{r_m}{r_{ij}} \right)^{6} \right] \quad \textit{van der Waals}$$

$$+ \sum_{i<j}^{atoms} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \quad \textit{electrostatic}$$



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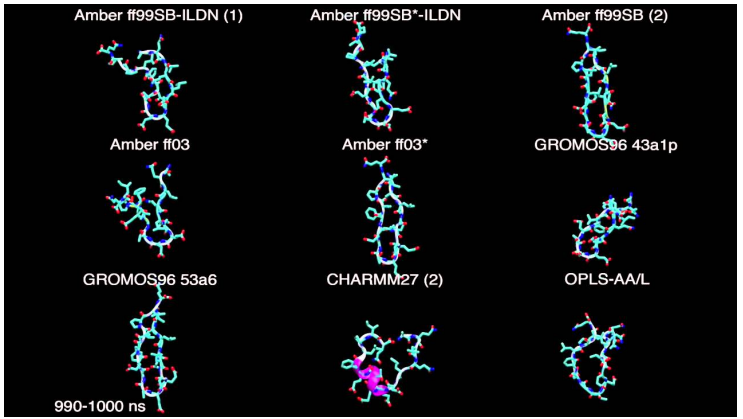
Force Fields in Biomolecular MD

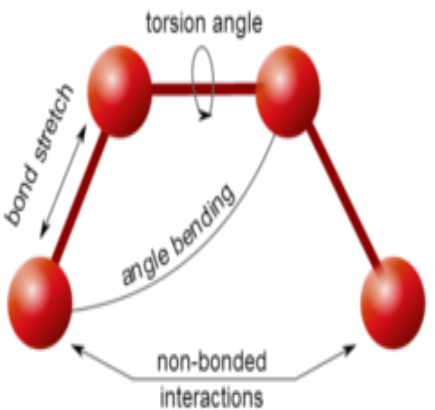
- AMBER, CHARMM, OPLS, GROMOS
- Parameters: bond lengths, angles, partial charges
- Limitations: classical approximation (no bond-breaking)



https://www.youtube.com/watch?v=AtDOJnVNC18

$$k_\psi(\psi - \psi_0)^2$$

$$\sum_{\text{on-bonded pairs}(i,j)} \frac{q_i q_j}{\varepsilon_D r_{ij}}.$$



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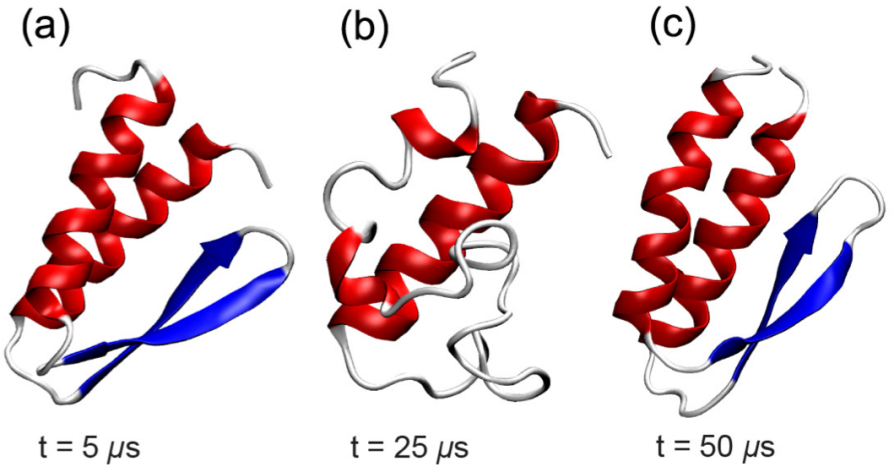
MacKerell AD Jr et al. (1998) J. Phys. Chem. B 102, 3586–3616.

Historical Milestones in MD

- 1980s-1990s: software (CHARMM, AMBER), electrostatics (PME)
- 1990s-2000s: GROMACS, Anton (ms-scale)
- 2010s-presents: GPU accelerarion, enhanced sampling



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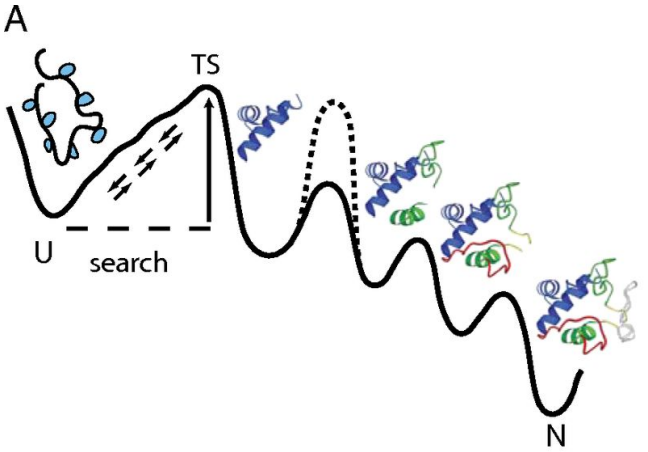
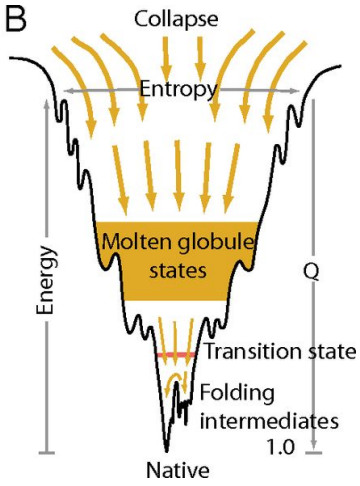
Shaw DE et al. (2010) Science 330, 341–346.

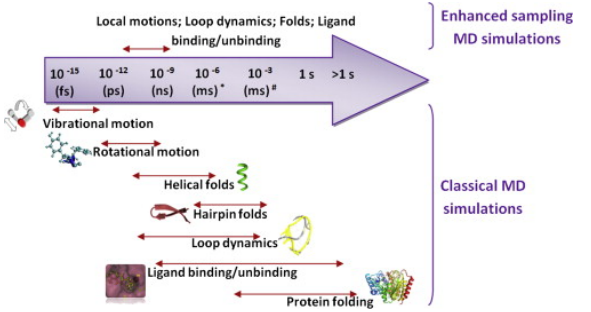
Applications: Protein folding

- MD reveals folding pathways, transition states
- Validation with experimental phi-values and kinetics
- Timescales: microseconds to milliseconds simulations needed





Proc. Natl. Acad. Sci. U.S.A. 111 (45) 15873-15880



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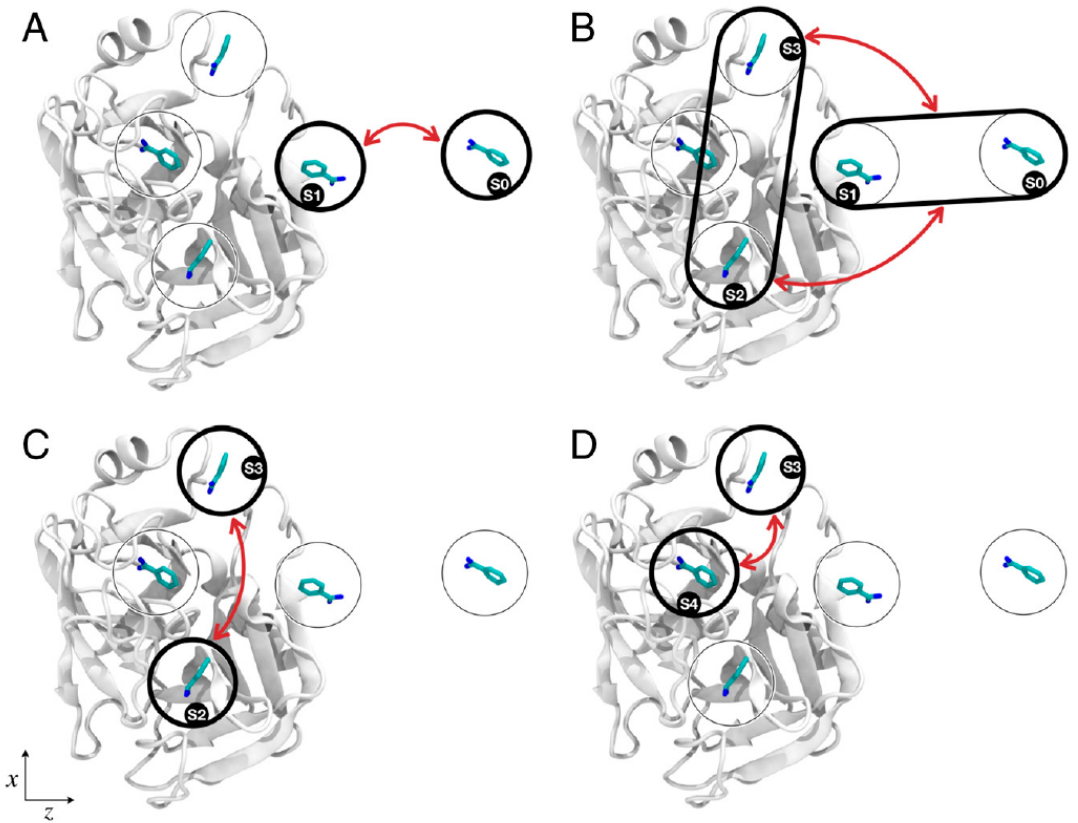
Applications: Ligand binding

- MD tracks ligand entry, exit, and binding modes
- Captures kinetic data: on/off rates, pathways
- Useful in drug discovery



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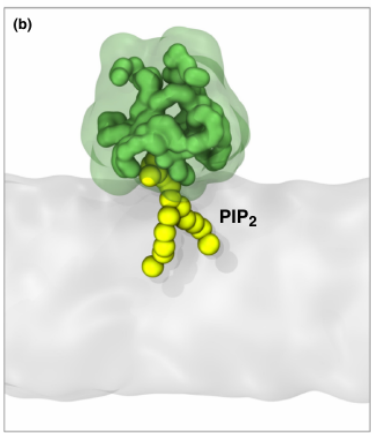
Dror RO et al. (2012) Annu. Rev. Biophys. 41, 429–452.

Applications: Membranes and complexes

- Simulations of lipid bilayers, membrane proteins
- Protein-membrane interactions, permeability
- Membrane dynamics and domain formation



Marrink SJ et al. (2007) J Phys Chem B. 12, 111(27).

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MD in drug discovery

- Predict binding affinies (FEP, MM/PBSA)
- Discover allosteric sites and cryptic pockets
- Model target flexibility explicitly

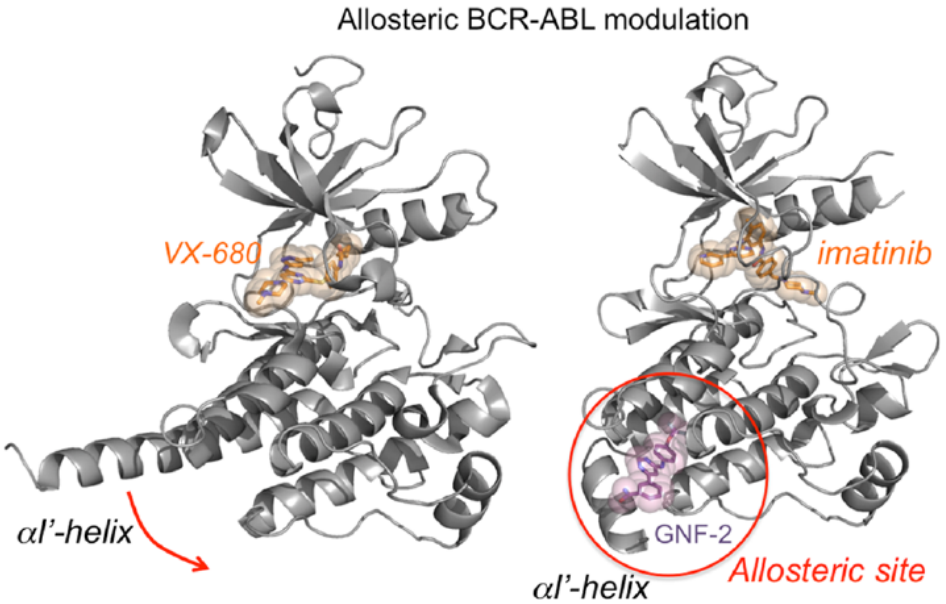

Figure 9. Allosteric modulation in BCR-ABL (PDB codes 2f4j and 3k5v). The ligand GNF-2 binds to the myristate pocket (red circle, allosteric site) concomitantly to the bending of the αI′-helix and induces a c-ABL-like autoinhibited conformation of BCR-ABL that has reduced kinase activity.

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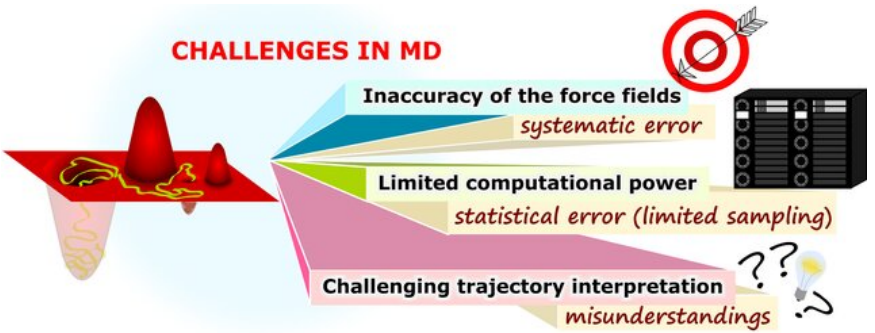
Limitations of MD

- Time scales (microseconds-miliseconds still challenging)
- Force field inaccuracies
- Computational cost
- Sampling limitations



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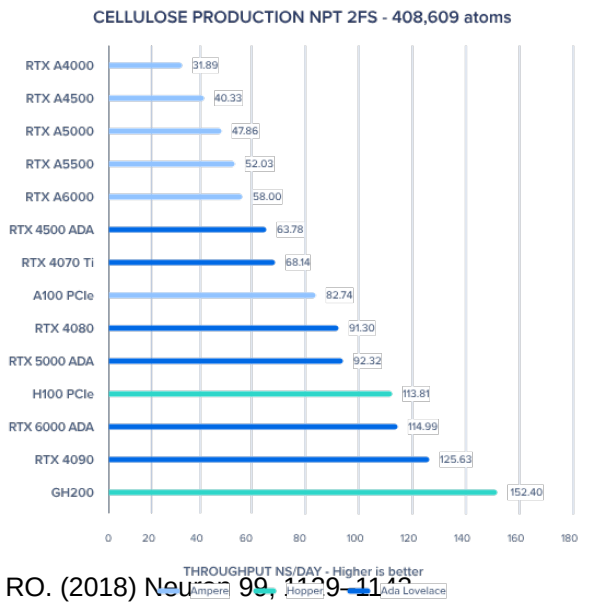

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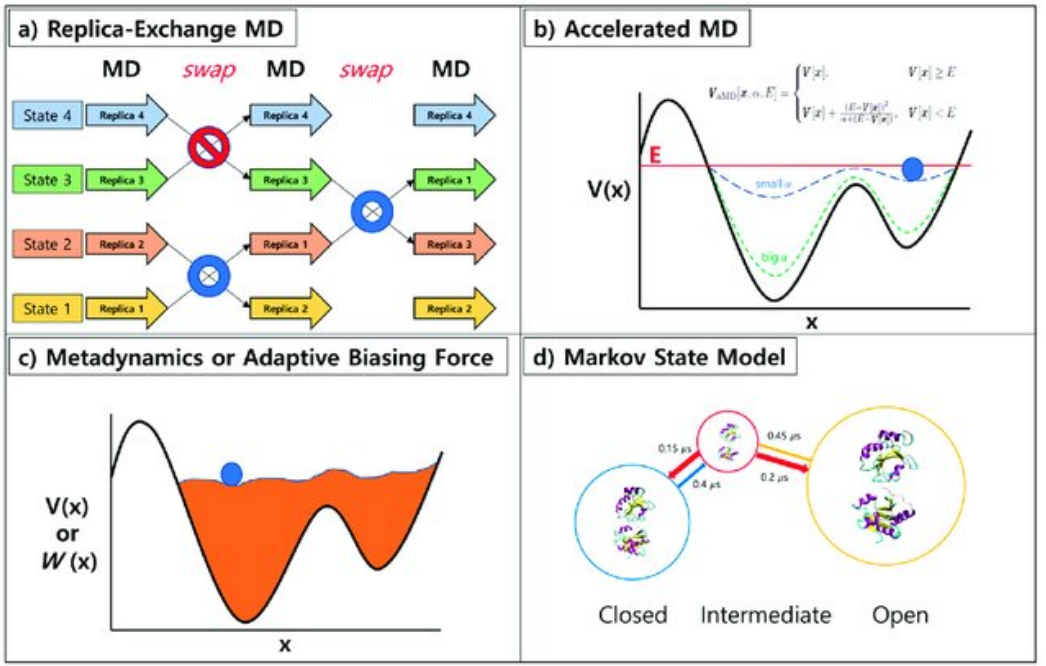
Hollingsworth SA & Dror RO. (2018) Neuron 99, 1129–1143

Addressing limitations

- Enhanced sampling: REMD, metadynamics, aMD
- Coarse-grained models
- Machine learning force fields (e.g., DeepMD)



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Laio 2008 Rep. Prog. Phys. 71 126601

Why modeling is fundamental

- Visualizes the invisible: atomic trajectories
- Complements experiment (e.g. NMR, cryo-EM)
- Enables in silico experiments not feasible in the lab
- Rational design: drug, enzymes, biosensors

Karplus M & Kuriyan J. (2005) PNAS 102, 6679–6685.

Summary

- MD simulates biomolecular dynamics at atomic resolution
- Decades of refinement: from picoseconds to milliseconds
- Limitations remain, but modeling is essential
- Integrative approach: theory + experiment

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