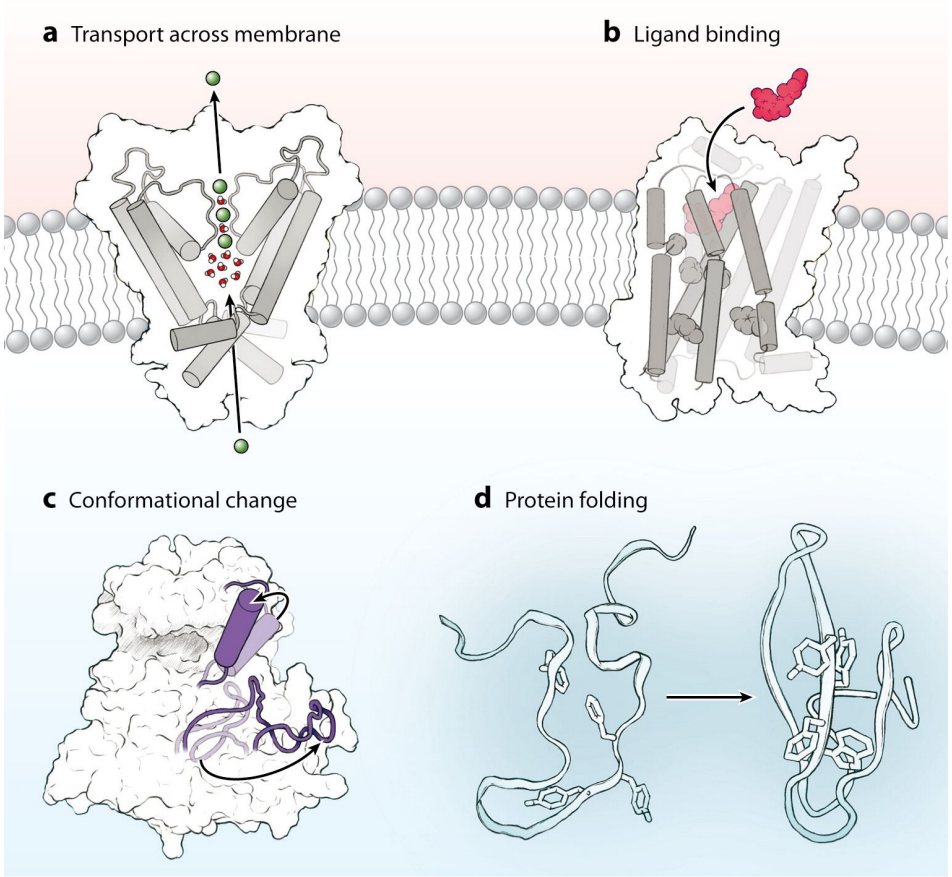
Lecture 10: Molecular dynamics

- MD simulation
- Applications

Molecular dynamics (MD) simulations = Computational microscope

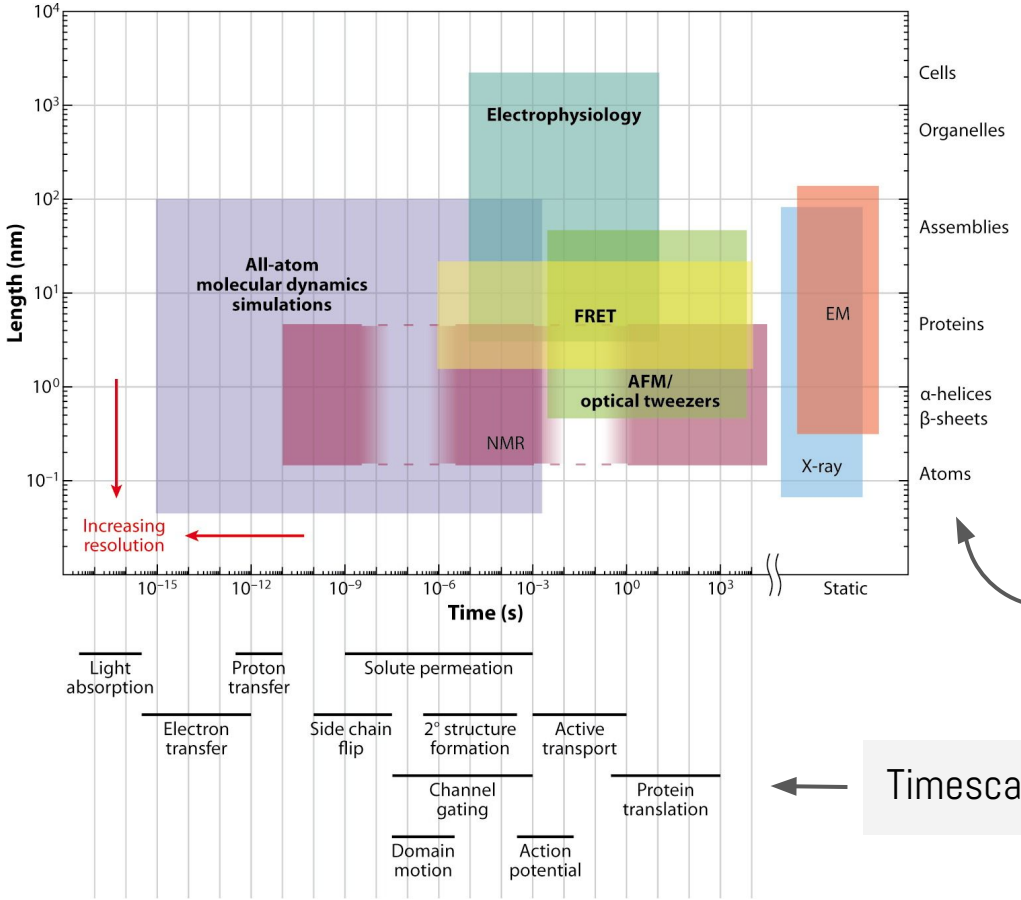


MD simulations reveal the workings of biomolecular systems at a spatial and temporal resolution that is often difficult to access experimentally.

- Positions and velocities of atoms are computed using Newton's laws of motion.

Dror (2012) Annu. Rev. Biophys.

Spatiotemporal resolution of various techniques



Data on single molecules (as opposed to only on ensembles) are in boldface.

- AFM, atomic force microscopy
- EM, electron microscopy
- FRET, Forster resonance energy transfer
- NMR, nuclear magnetic resonance

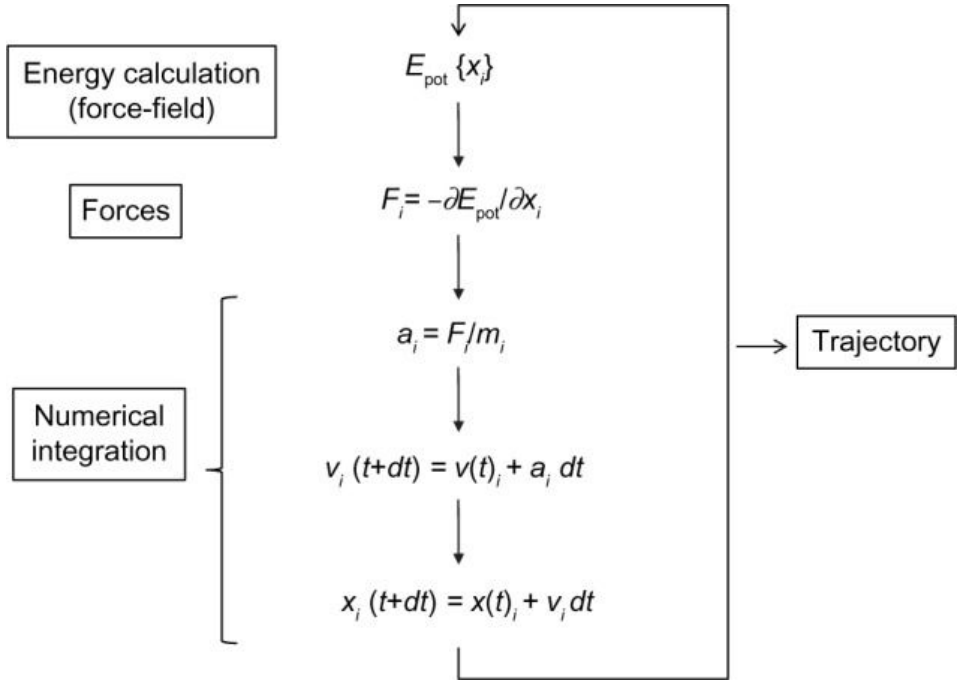
Spatial resolution of biological features

Timescales of molecular processes

Dror (2012) Annu. Rev. Biophys.

Molecular dynamics (MD) simulations = Computational microscope

The basic MD algorithm.



The simulation output – the trajectory – is an ordered list of 3N atom coordinates for each simulation time (or snapshot).

E_{pot}: potential energy

t: simulation time

dt: iteration time

For each spatial coordinate of the N simulated atoms (i):

- x: atom coordinate
- F: forces component
- a: acceleration
- m: atom mass
- v: velocity.

Hospital (2016) Adv. Appl. Bioinform. Chem.

Force field and the energy function

The potential energy of *N* interacting atoms $U(\mathbf{r}_1, \ldots, \mathbf{r}_N)$ is a function of their positions $\mathbf{r}_i = (x_i, y_i, z_i)$.

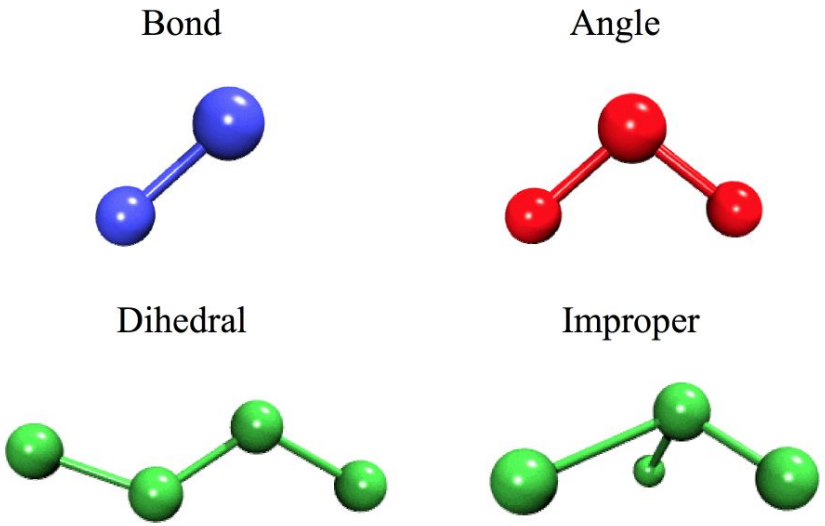
The force acting upon *i*th atom is determined by the gradient (vector of first derivatives) with respect to atomic displacements:

$$\mathbf{F}_i = -\nabla_{\mathbf{r}_i} U(\mathbf{r}_1, \cdots, \mathbf{r}_N) = -\left(\frac{\partial U}{\partial x_i}, \frac{\partial U}{\partial y_i}, \frac{\partial U}{\partial z_i}\right)$$

Find the positions $\mathbf{r}_i(t + \Delta t)$ at time $t + \Delta t$ in terms of the already known positions at time t.

Verlet algorithm:

$$\mathbf{r}_i(t + \Delta t) \cong 2\mathbf{r}_i(t) - \mathbf{r}_i(t - \Delta t) + \frac{\mathbf{F}_i(t)}{m_i}\Delta t^2$$



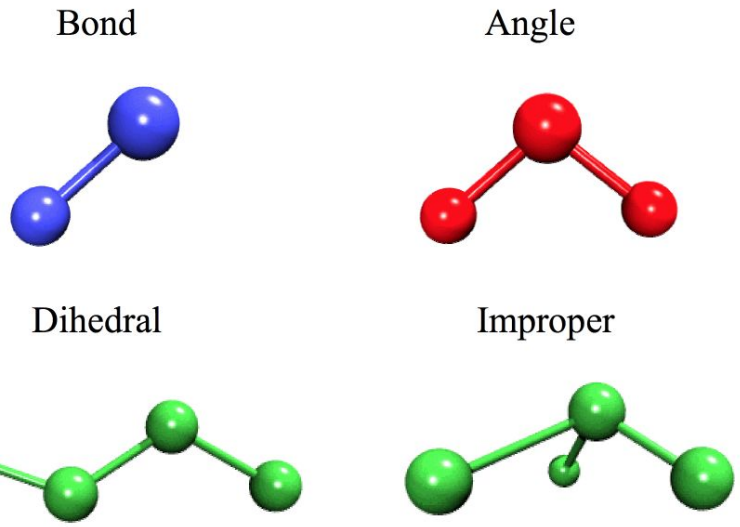
Force field: energy function used to compute the forces acting on atoms (due to interatomic interactions) during an MD simulation.

Force field and the energy function

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$



U_{bond}: oscillations about the equilibrium bond length

U_{angle}: oscillations of 3 atoms about an equilibrium angle

$U_{dihedral}$: torsional rotation of 4 atoms about a central bond

$U_{nonbond}$: non-bonded energy terms (electrostatics and Lenard-Jones)

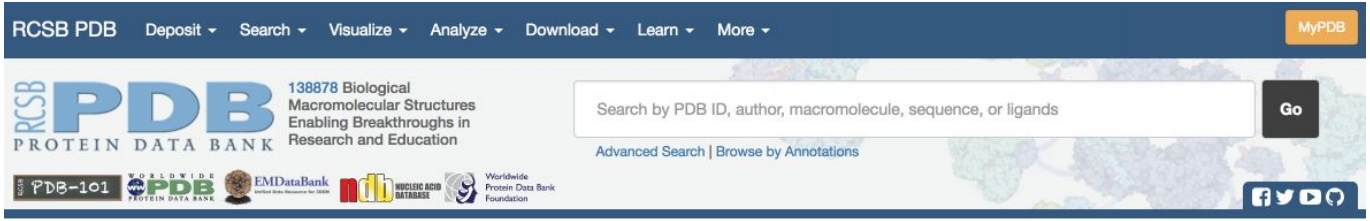
Force field: energy function used to compute the forces acting on atoms (due to interatomic interactions) during an MD simulation.

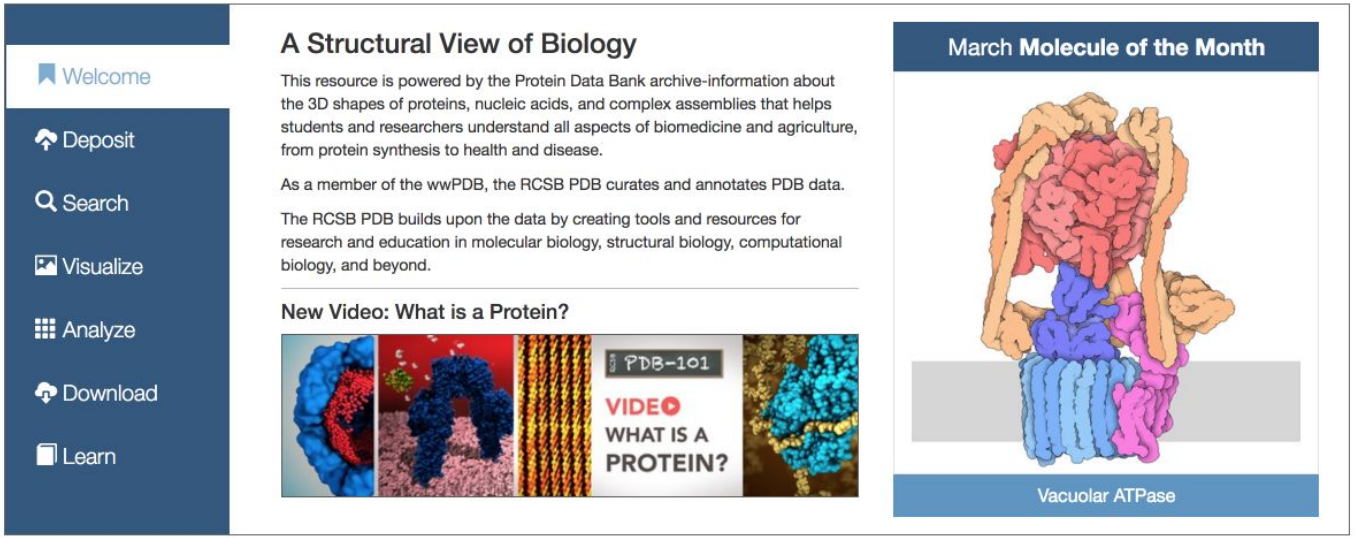
Steps in a typical MD simulation

1. Prepare molecule: Read in pdb and psf file
2. Minimization: Reconcile observed structure with force field used (T = 0)
3. Heating: Raise temperature of the system
4. Equilibration: Ensure system is stable
5. Dynamics: Simulate under desired conditions (NVE, NpT, etc); Collect your data
6. Analysis: Collect your data; Evaluate observables (macroscopic level properties); Or relate to single molecule experiments.

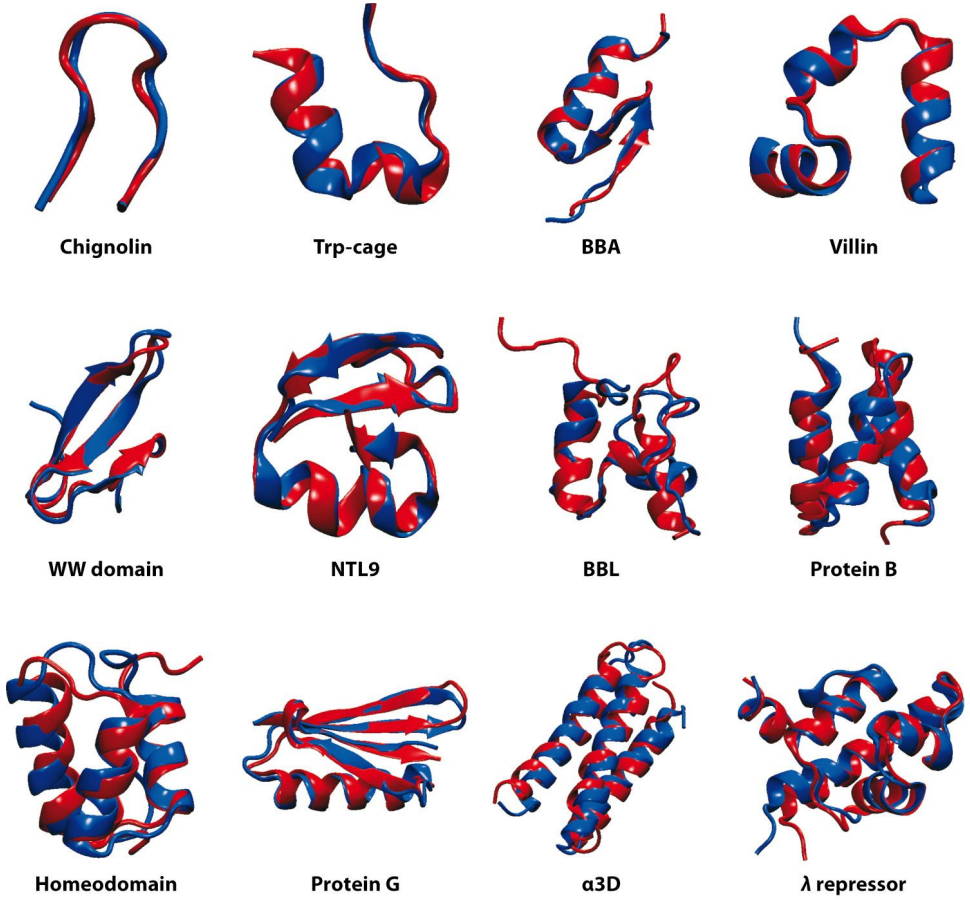
Protein Data Bank (PDB)

www.rcsb.org: 3D shapes of proteins, nucleic acids, and complex assemblies.





Simulations of structurally diverse proteins



Simulations with a single force field.

- 12 structurally diverse proteins fold spontaneously to a structure (blue) closely resembling that determined experimentally (red).
- Simulation snapshots chosen automatically based on a clustering analysis that did not exploit knowledge of the experimental structure.
- Total simulation time per protein: 104 – 2,936 μs – allowing observation of at least 10 folding & 10 unfolding events for each protein.

Dror (2012) Annu. Rev. Biophys.

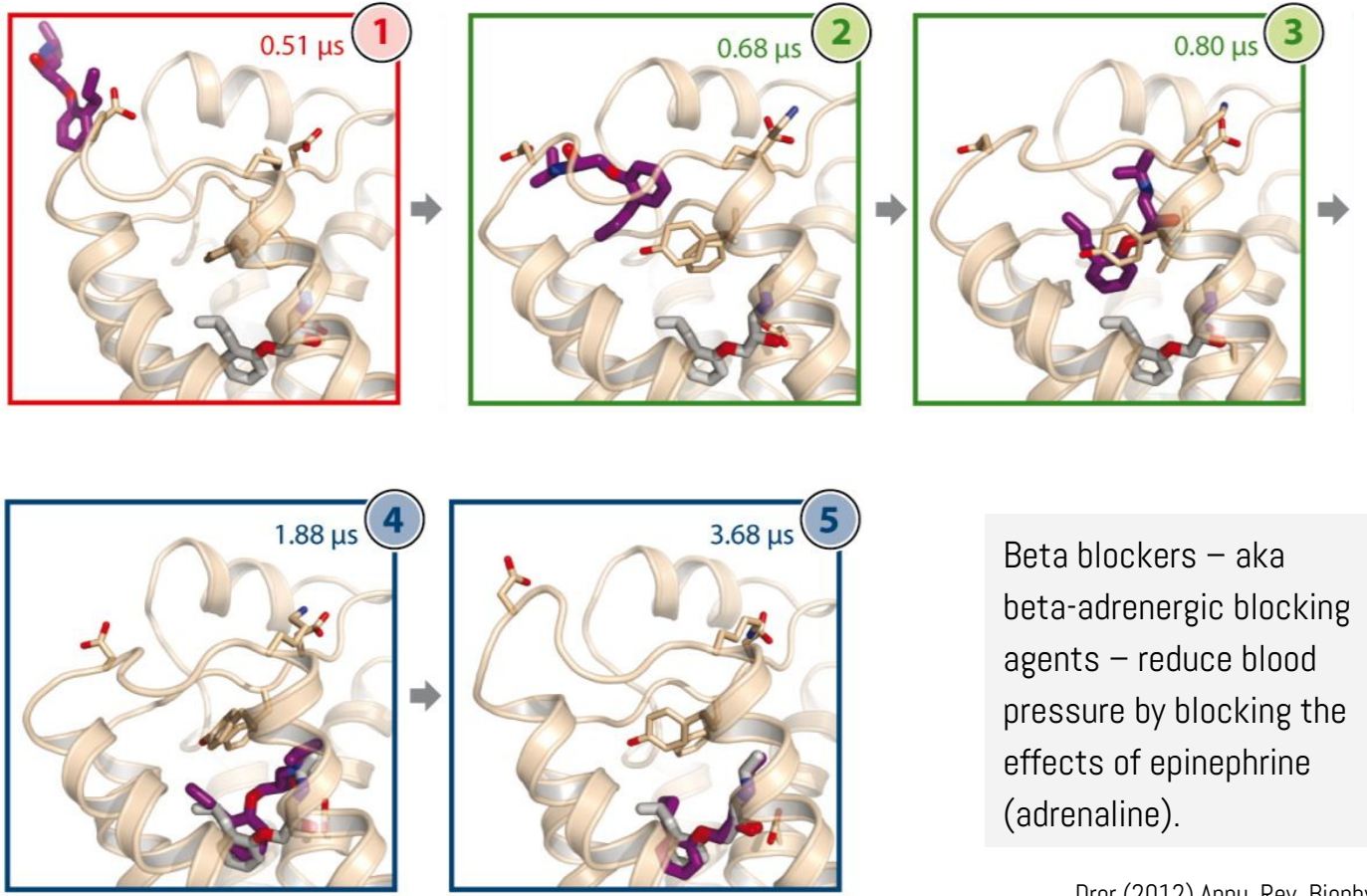
Beta-blockers binding spontaneously to the β2-adrenergic receptor

Metastable Intermediate stages of beta blocker binding.

1: Ligand moves from bulk solvent…

2, 3: … into the extracellular vestibule, and finally…

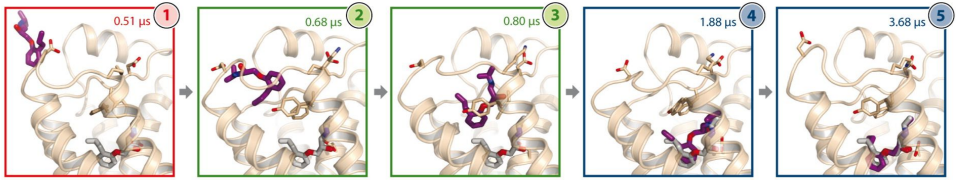
4, 5: … into the binding pocket.

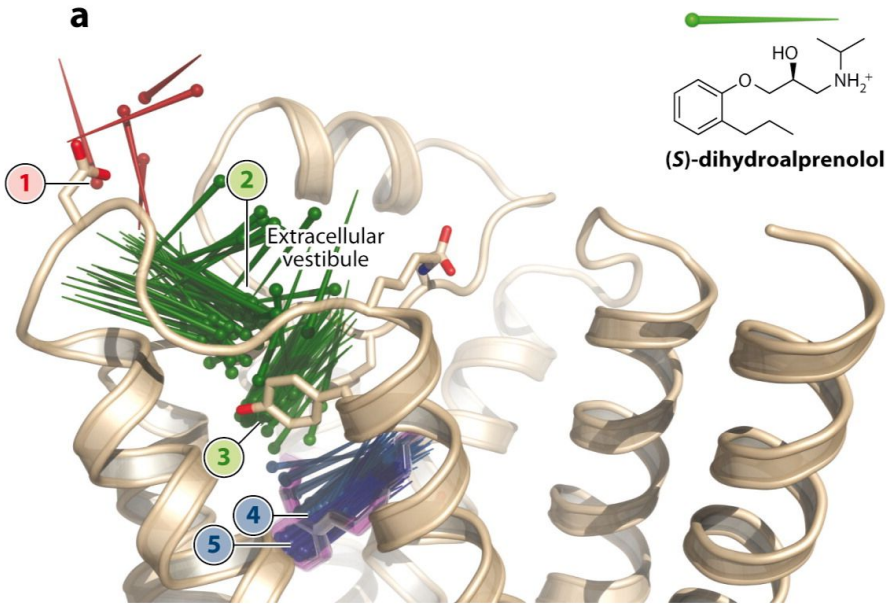


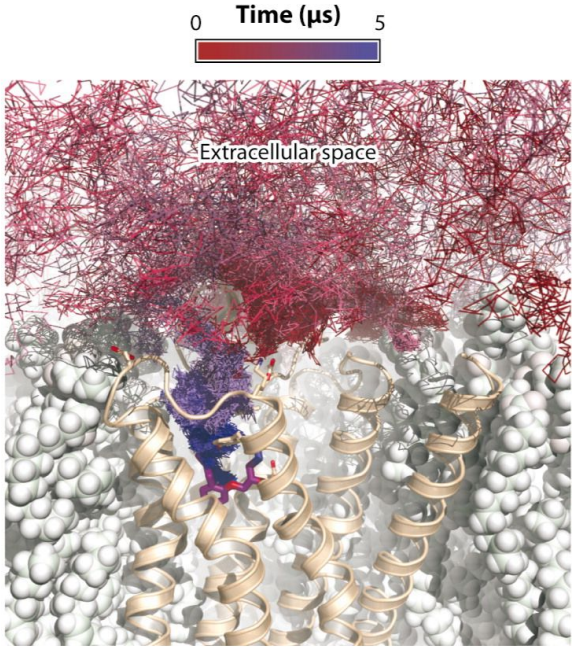
Beta blockers – aka beta-adrenergic blocking agents – reduce blood pressure by blocking the effects of epinephrine (adrenaline).

Dror (2012) Annu. Rev. Biophys.

Beta-blockers binding spontaneously to the β2-adrenergic receptor



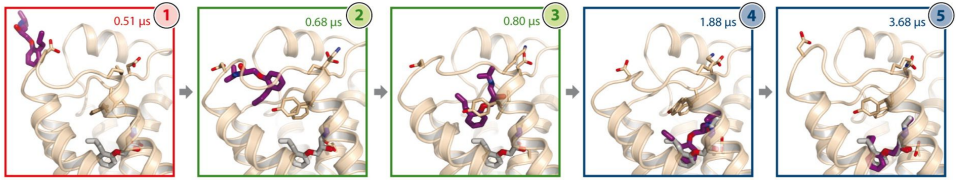


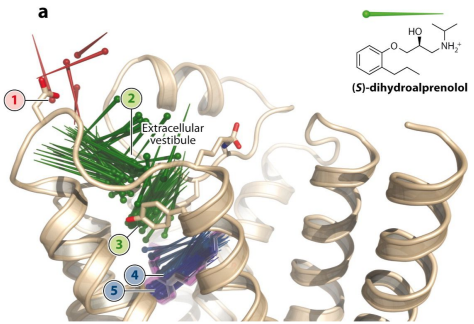


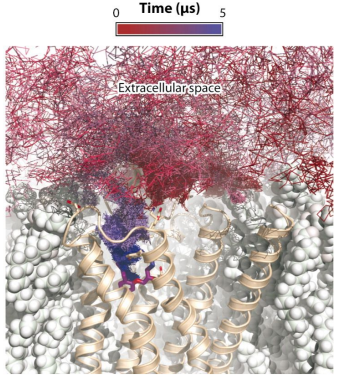
Pins: successive positions

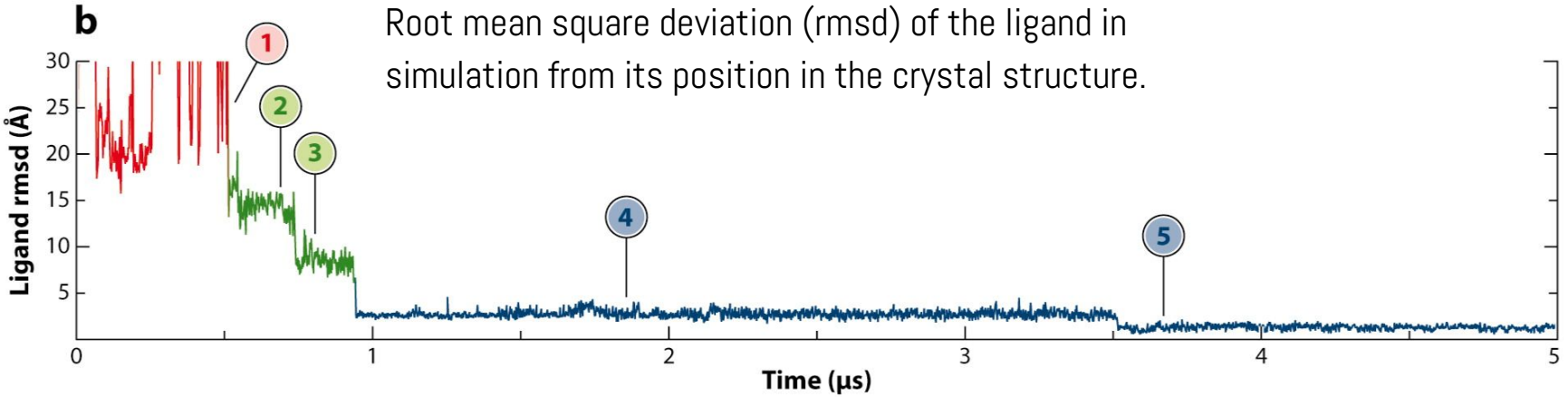
Dror (2012) Annu. Rev. Biophys.

Beta-blockers binding spontaneously to the β2-adrenergic receptor





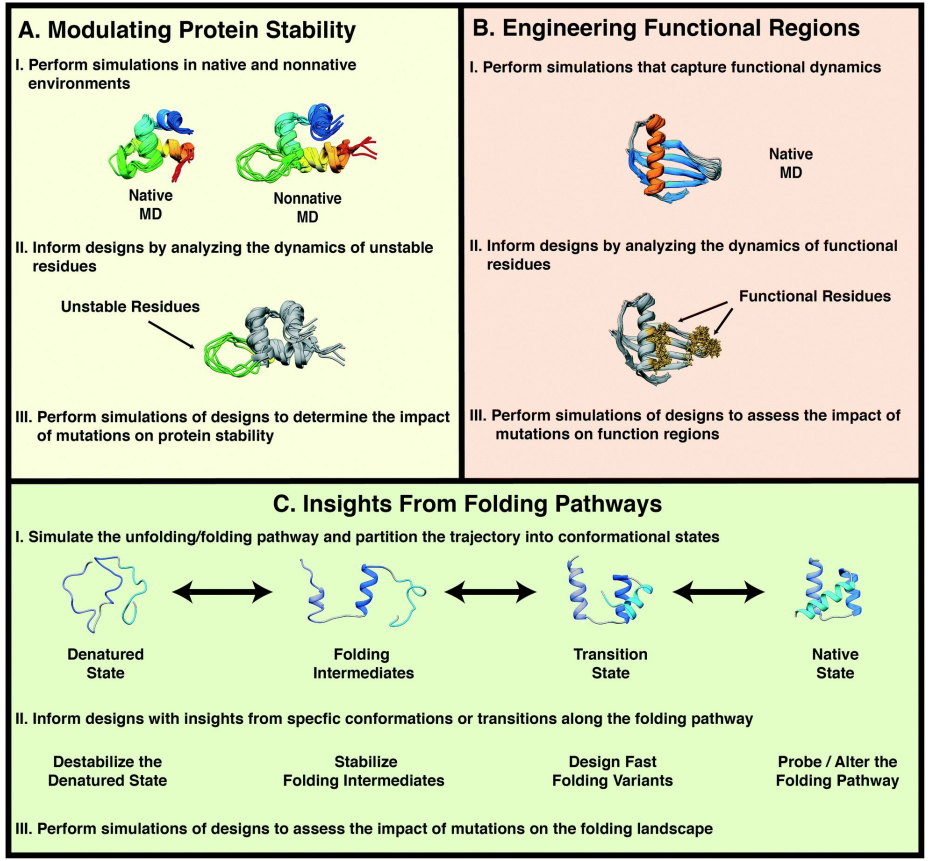




Root mean square deviation (rmsd) of the ligand in simulation from its position in the crystal structure.

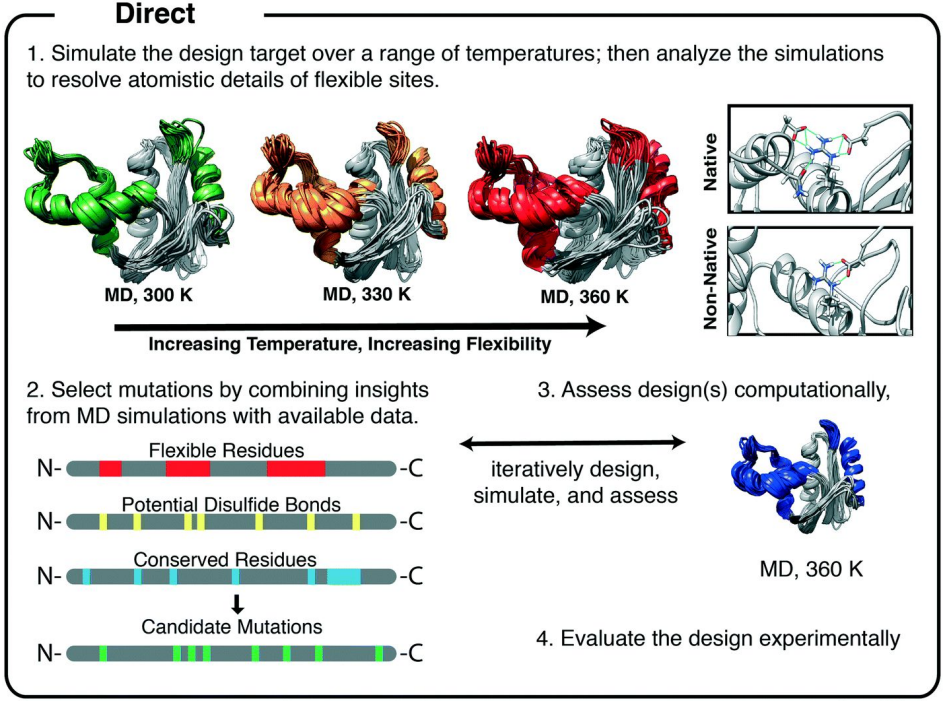
Dror (2012) Annu. Rev. Biophys.

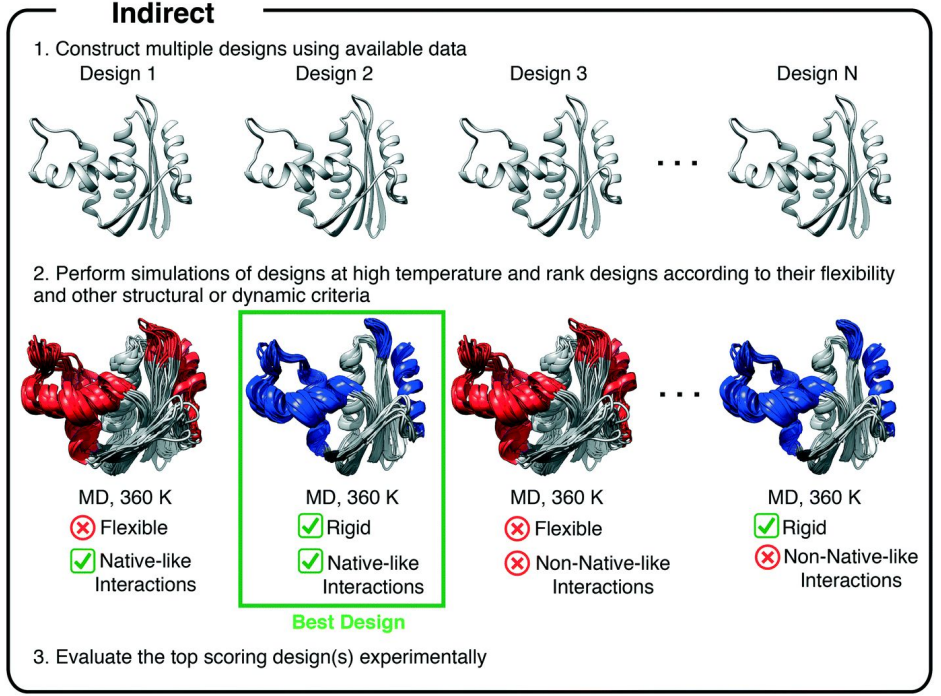
MD simulations for protein design



Childers & Daggett (2017) Mol. Syst. Des. Eng.,

MD simulations for protein design





Childers & Daggett (2017) Mol. Syst. Des. Eng.,

Virtual screening: docking & MD simulations

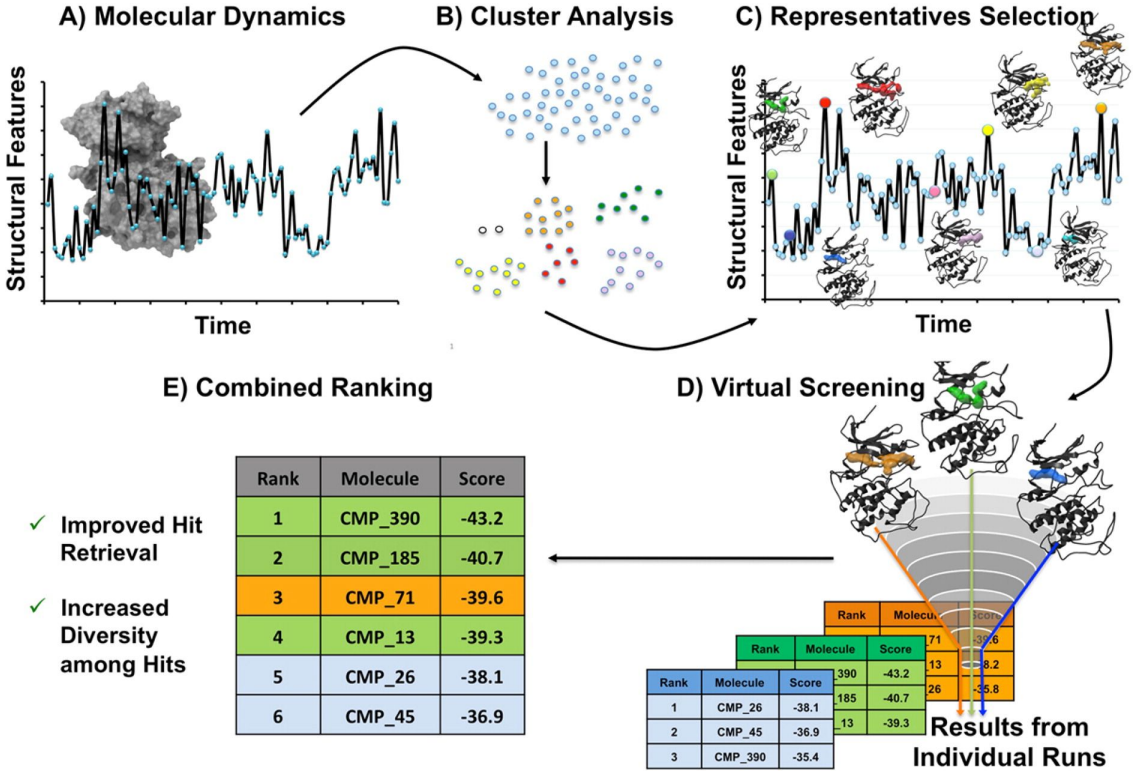
(A) An MD trajectory is used to explore the receptor conformational space.

(B) From the trajectory, several snapshots are extracted and redundancy is eliminated by means of cluster analysis.

(C) From each cluster, a representative structure (e.g., medoid) is selected.

(D) Virtual ligand screening is independently carried out at each representative conformation.

(E) Activity predictions returned by independent runs are combined together in a global ranking.



De Vivo (2016) J. Med. Chem.

Distributed computing & Crowdsourcing

Folding@home: folding.stanford.edu

- Distributed computing project for MD simulations (e.g., protein folding, computational drug design).
- Uses the idle resources of personal computers owned by volunteers from all over the world.

Foldit: fold.it

- An online game that poses complex puzzles about how proteins fold.
- Helped solve the structure of a protein-sniping enzyme critical for reproduction of the AIDS virus within 3 weeks; Identified targets for drugs to neutralize it.