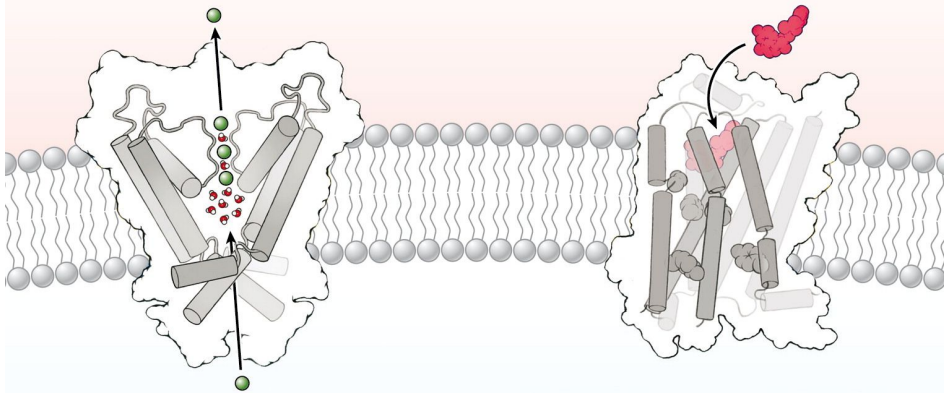


Lecture 10: Molecular dynamics

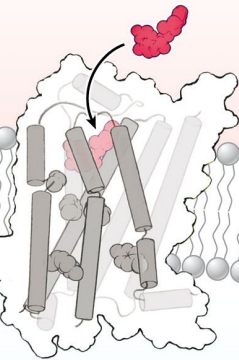
- MD simulation
- Applications

Molecular dynamics (MD) simulations = Computational microscope

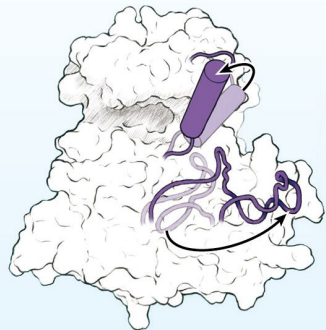
a Transport across membrane



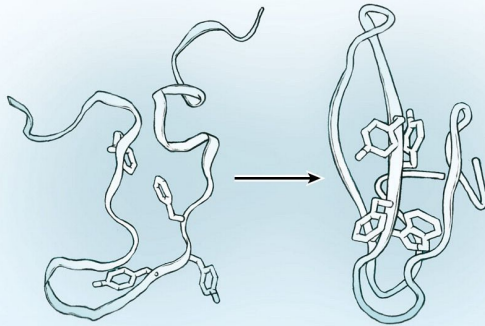
b Ligand binding



c Conformational change



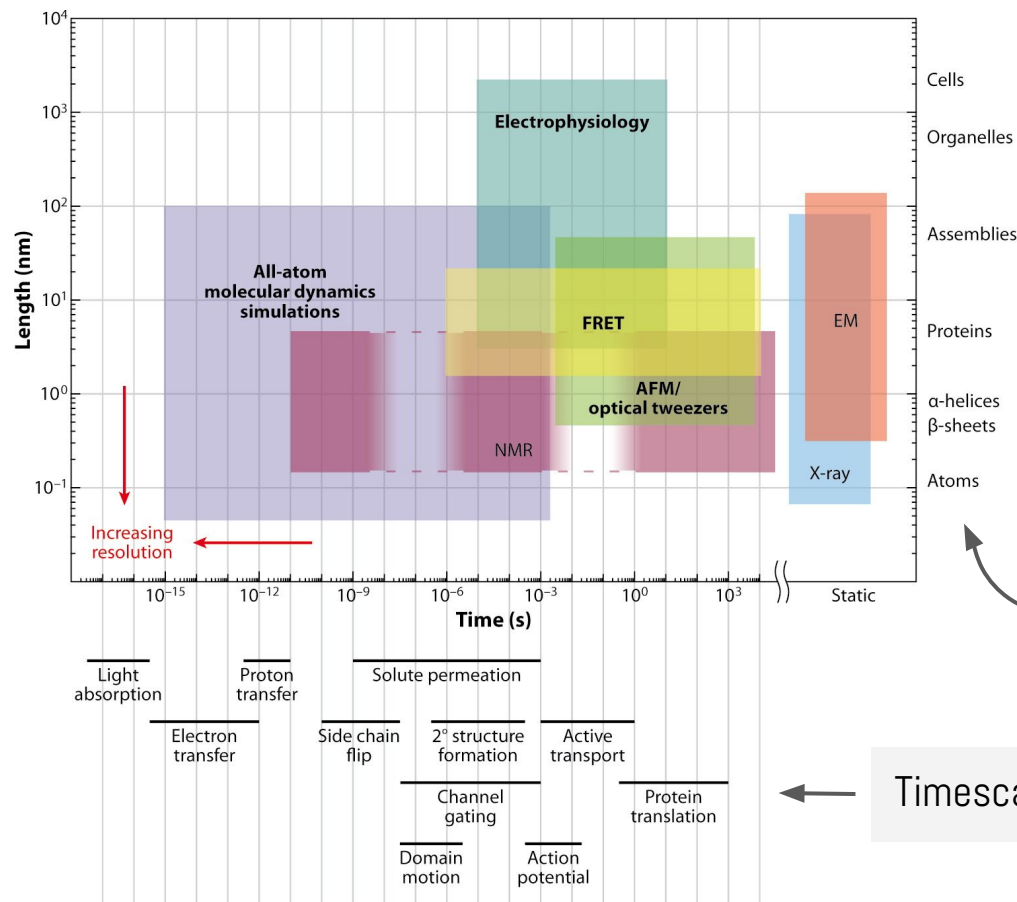
d Protein folding



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.

Spatiotemporal resolution of various techniques



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

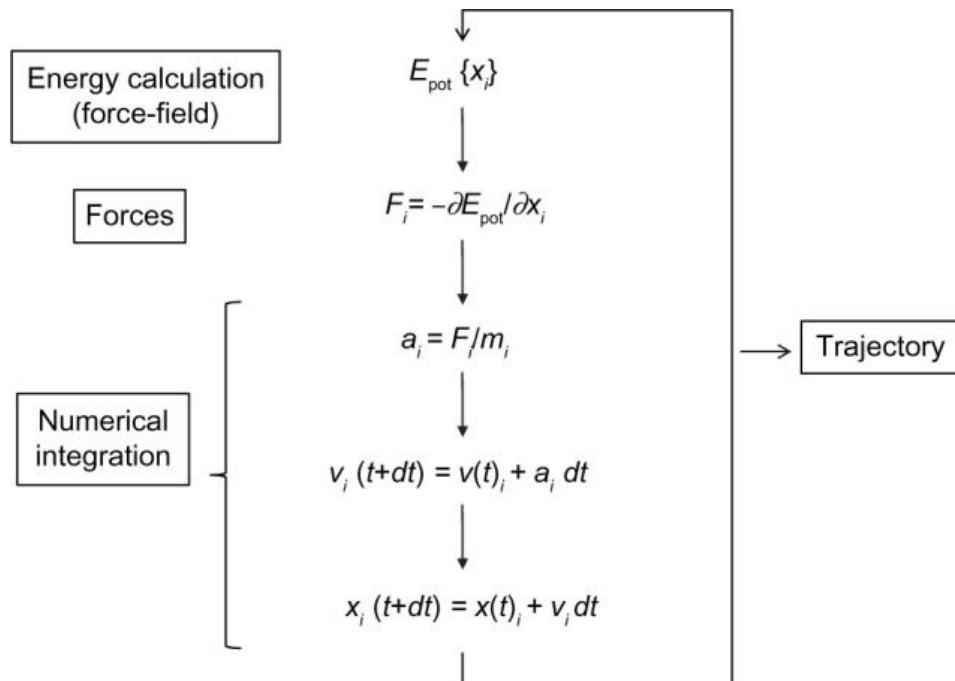
- AFM, atomic force microscopy
- EM, electron microscopy
- FRET, Forster resonance energy transfer
- NMR, nuclear magnetic resonance

Spatial resolution of biological features

Timescales of molecular processes

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.

Force field and the energy function

The potential energy of N interacting atoms $U(\mathbf{r}_1, \dots, \mathbf{r}_N)$ 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:

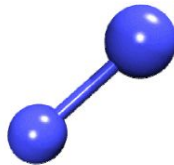
$$\mathbf{F}_i = -\nabla_{\mathbf{r}_i} U(\mathbf{r}_1, \dots, \mathbf{r}_N) = -\left(\frac{\partial U}{\partial x_i}, \frac{\partial U}{\partial y_i}, \frac{\partial U}{\partial z_i}\right)$$

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

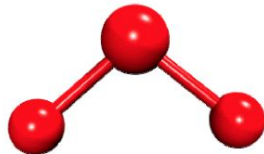
Verlet algorithm:

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

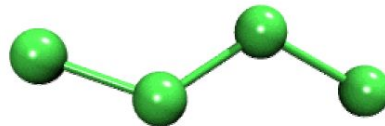
Bond



Angle



Dihedral



Improper



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

$$\begin{aligned}
 U(\vec{R}) = & \underbrace{\sum_{bonds} k_i^{bond} (r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle} (\theta_i - \theta_0)^2}_{U_{angle}} + \\
 & \underbrace{\sum_{dihedrals} k_i^{dihe} [1 + \cos(n_i \phi_i + \delta_i)]}_{U_{dihedral}} + \\
 & \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}
 \end{aligned}$$

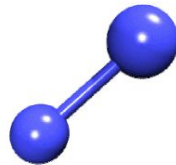
U_{bond} : oscillations about the equilibrium bond length

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

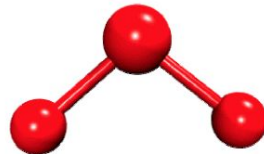
$U_{dihedral}$: torsional rotation of 4 atoms about a central bond

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

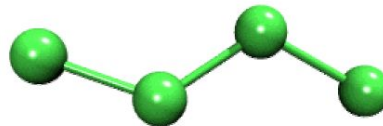
Bond



Angle



Dihedral



Improper



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.

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A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

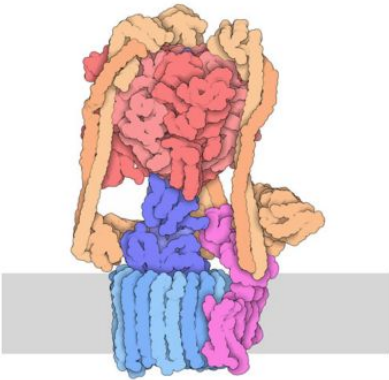
As a member of the wwPDB, the RCSB PDB curates and annotates PDB data.

The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

New Video: What is a Protein?



March Molecule of the Month

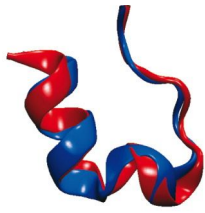


Vacuolar ATPase

Simulations of structurally diverse proteins



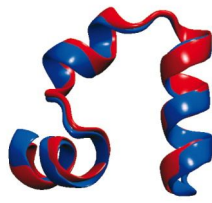
Chignolin



Trp-cage



BBA



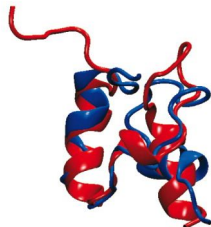
Villin



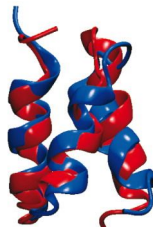
WW domain



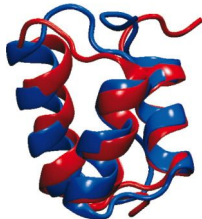
NTL9



BBL



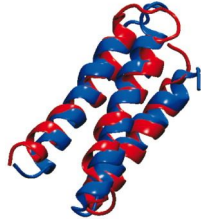
Protein B



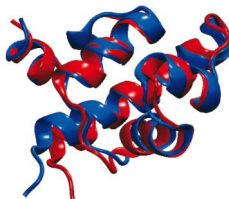
Homeodomain



Protein G



α3D



λ repressor

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 μ s – allowing observation of at least 10 folding & 10 unfolding events for each protein.

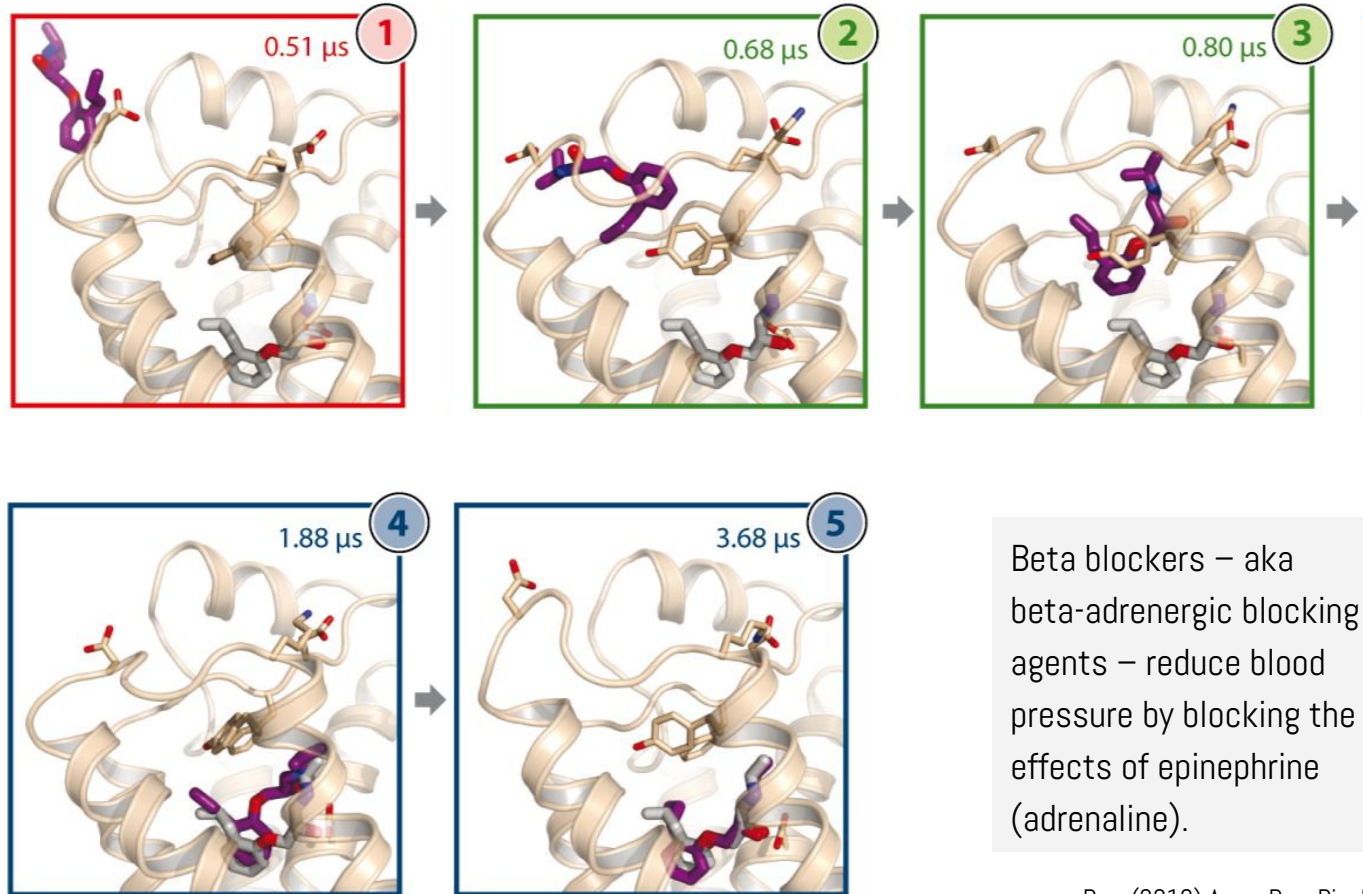
Beta-blockers binding spontaneously to the $\beta 2$ -adrenergic receptor

Metastable Intermediate stages of beta blocker binding.

1: Ligand moves from bulk solvent...

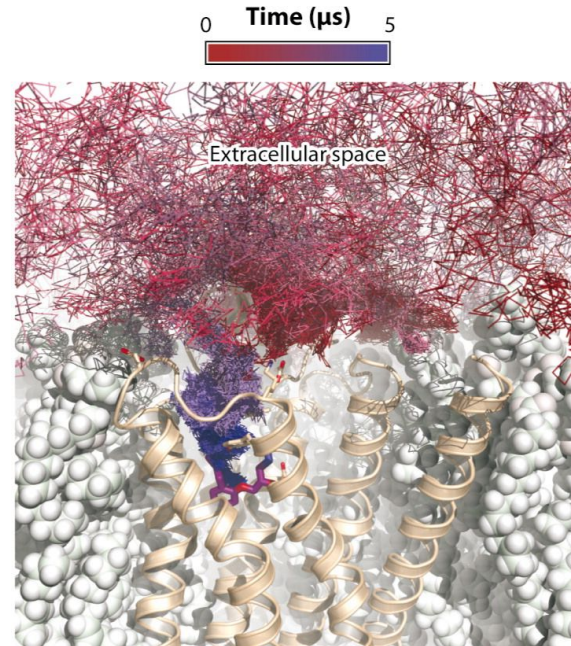
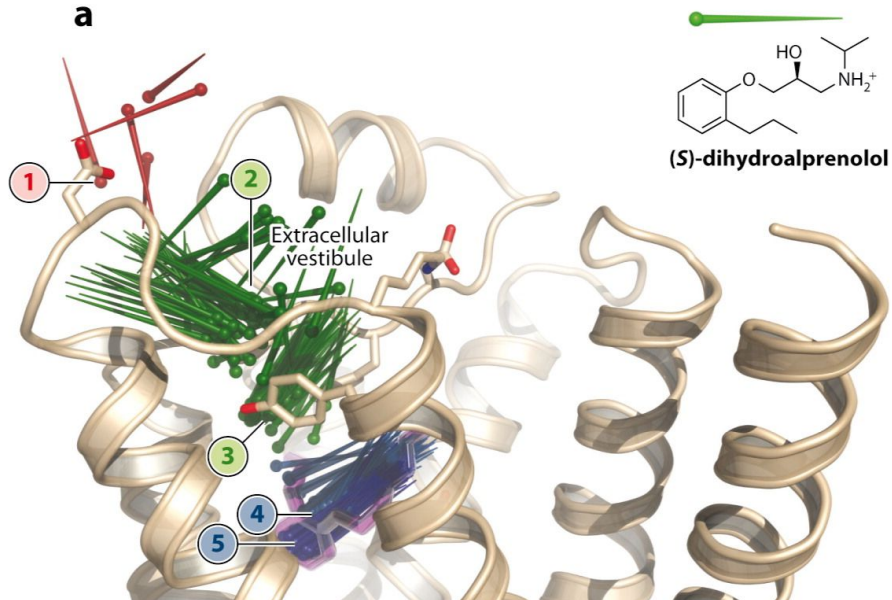
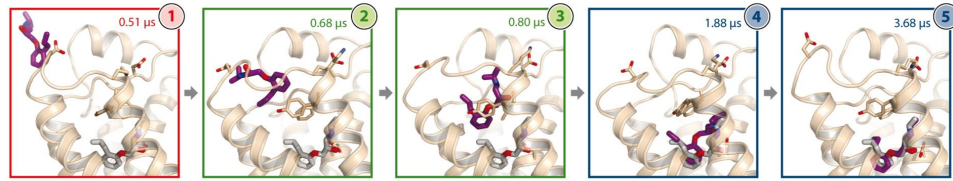
2, 3: ... into the extracellular vestibule, and finally...

4, 5: ... into the binding pocket.



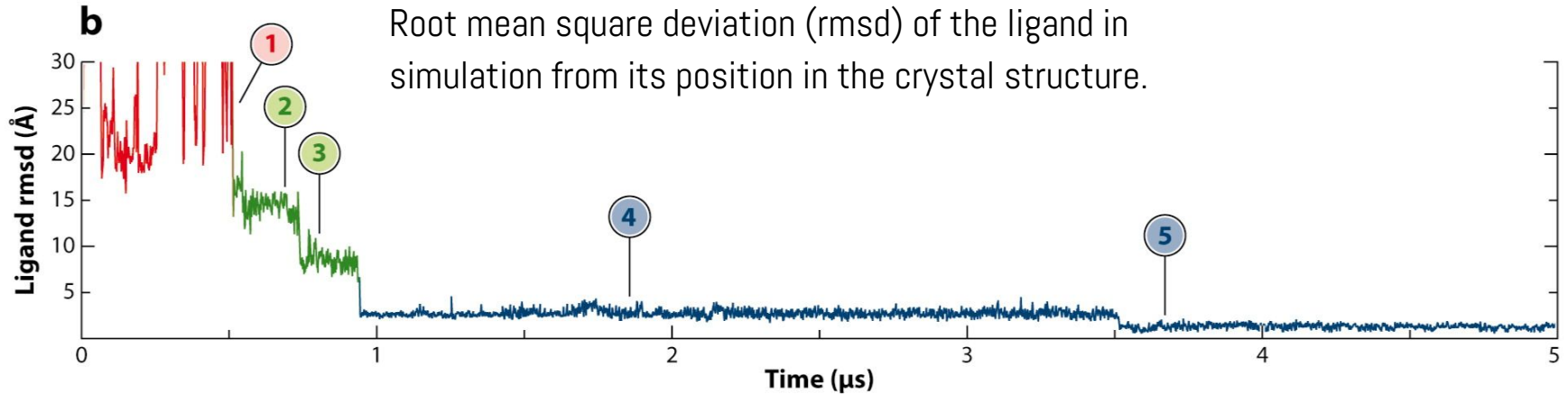
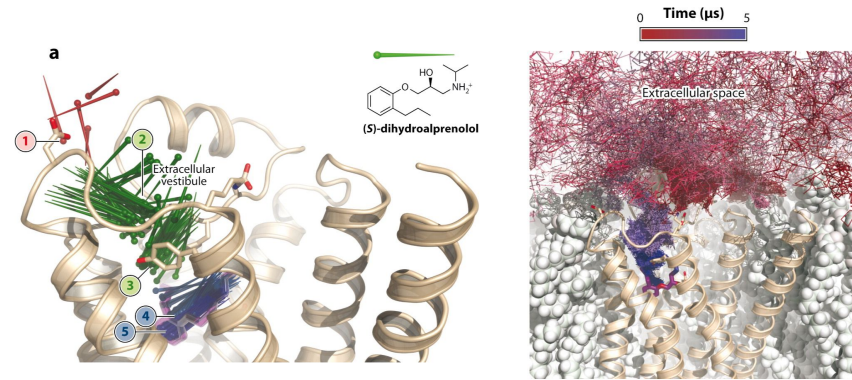
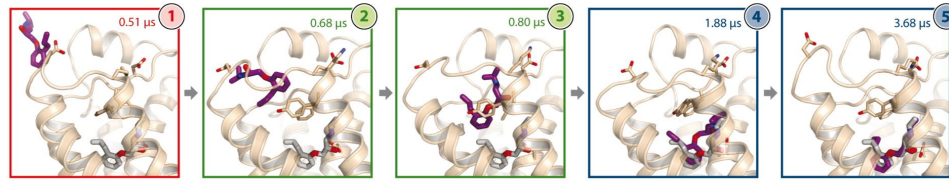
Beta blockers – aka beta-adrenergic blocking agents – reduce blood pressure by blocking the effects of epinephrine (adrenaline).

Beta-blockers binding spontaneously to the $\beta 2$ -adrenergic receptor

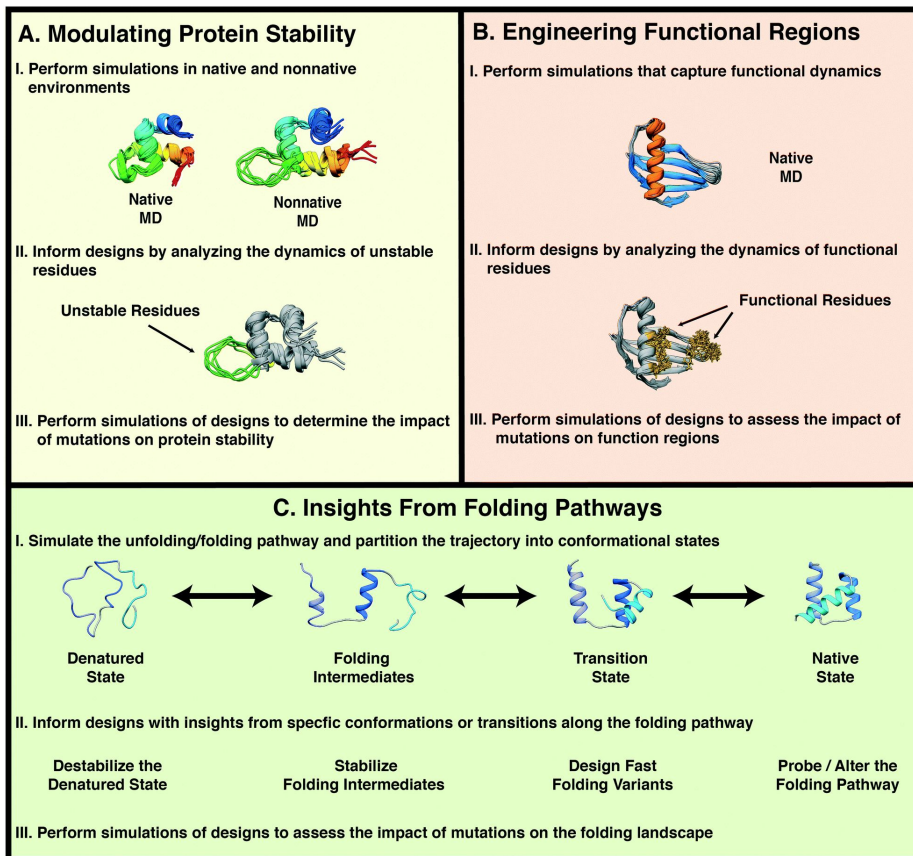


Pins:
successive
positions

Beta-blockers binding spontaneously to the β 2-adrenergic receptor



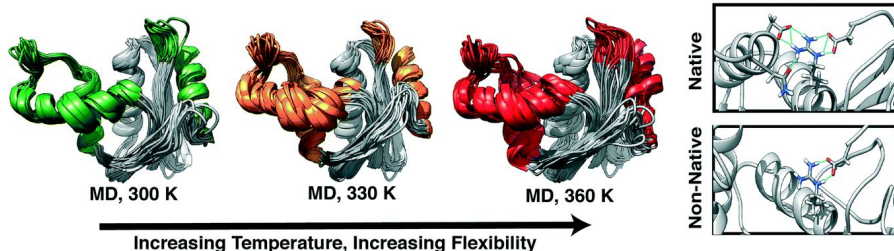
MD simulations for protein design



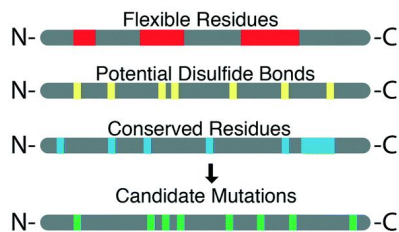
MD simulations for protein design

Direct

1. Simulate the design target over a range of temperatures; then analyze the simulations to resolve atomistic details of flexible sites.



2. Select mutations by combining insights from MD simulations with available data.



3. Assess design(s) computationally,

iteratively design,
simulate, and assess

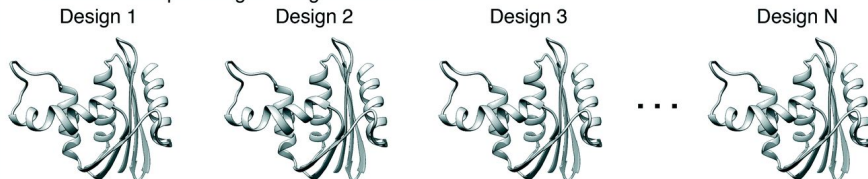


MD, 360 K

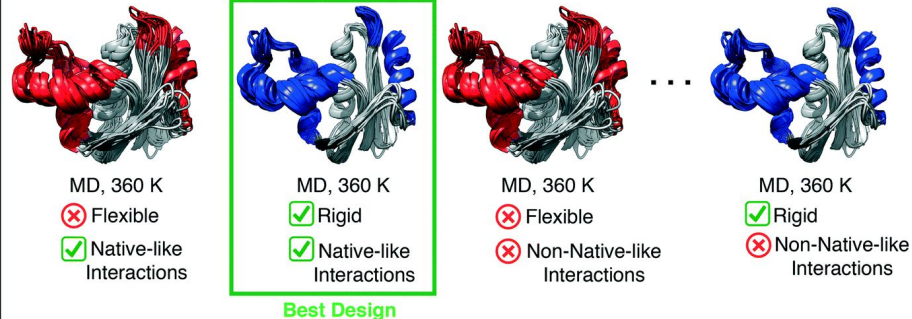
4. Evaluate the design experimentally

Indirect

1. Construct multiple designs using available data



2. Perform simulations of designs at high temperature and rank designs according to their flexibility and other structural or dynamic criteria



3. Evaluate the top scoring design(s) experimentally

Virtual screening: docking & MD simulations

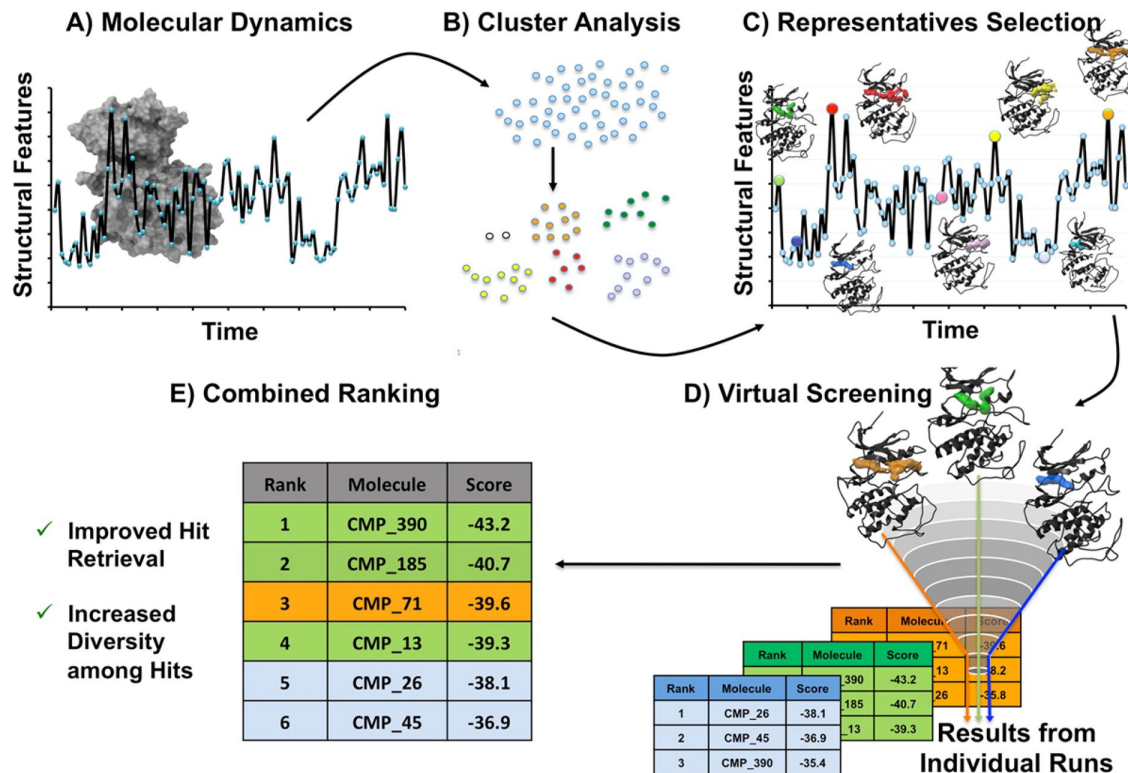
(A) An MD trajectory is used to explore the receptor conformational space.

(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.



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.

