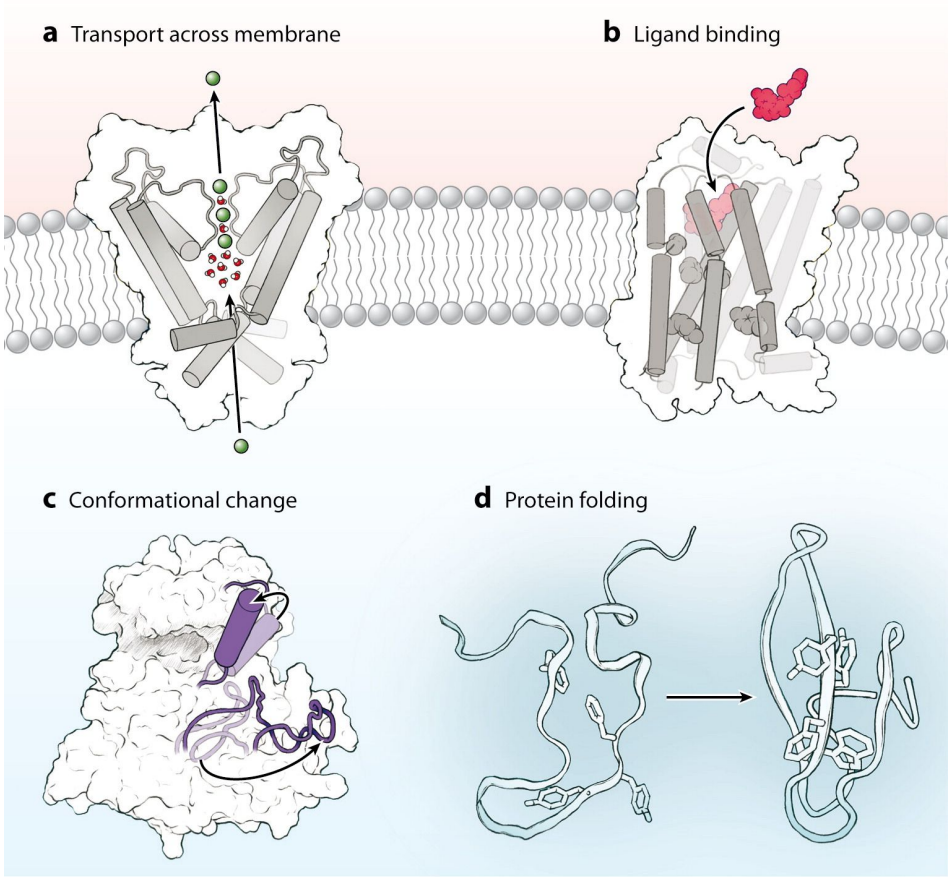
Protein structure

- Amino-acid coevolution
  - Mutual information
  - Maximum entropy modeling
- **Molecular dynamics**

Molecular dynamics (MD) simulations = Computational microscope



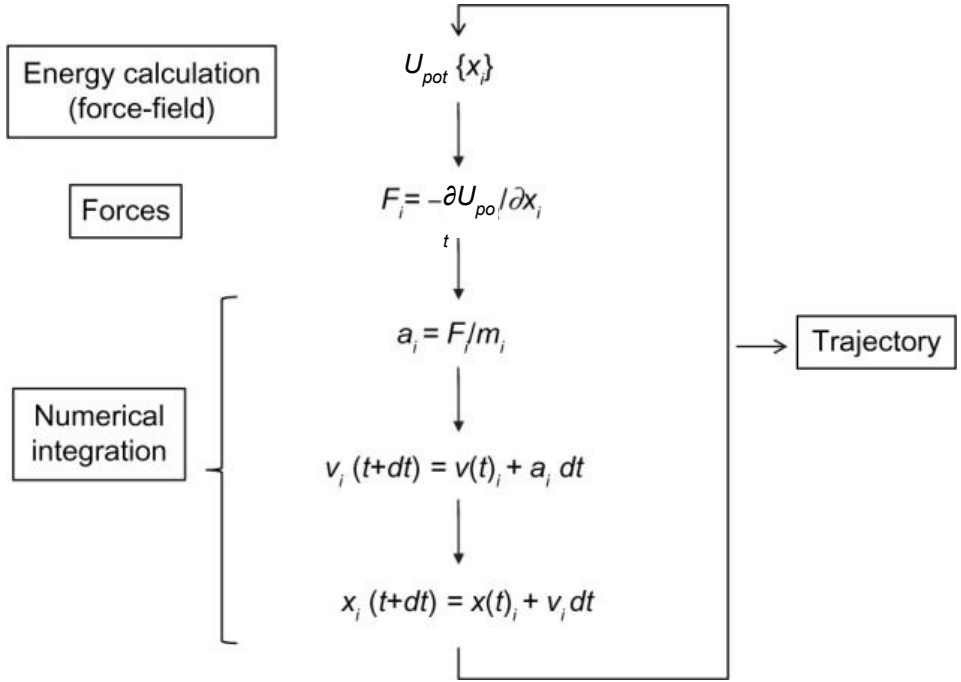
MD simulations reveal the workings of biomolecular systems at a spatial and temporal resolution that is often difficult to access experimentally.

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

Dror (2012) Annu. Rev. Biophys.

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).

U_{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 $r_i(t + \Delta t)$ at time $t + \Delta t$ in terms of the already known positions at time t.

Verlet algorithm:

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

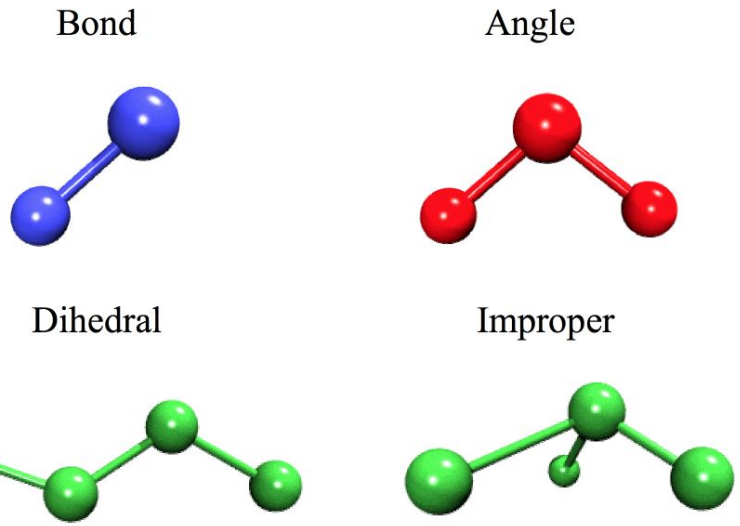
Force field: energy function used to compute the forces acting on atoms (due to interatomic interactions) during an MD simulation.

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

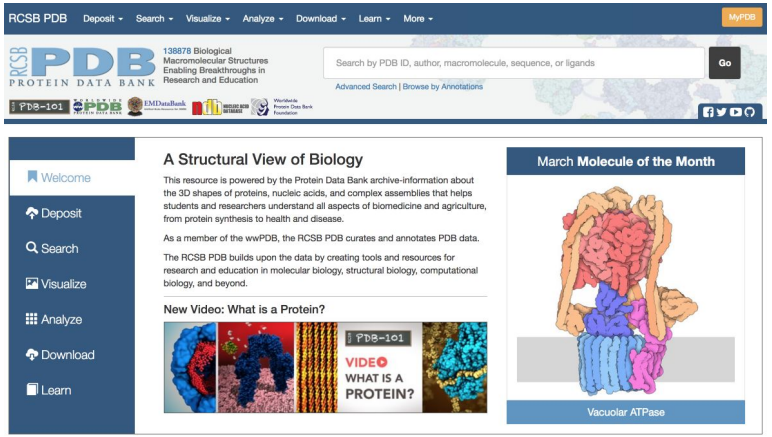
$U_{dihedral}$: torsional rotation of 4 atoms about a central bond

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

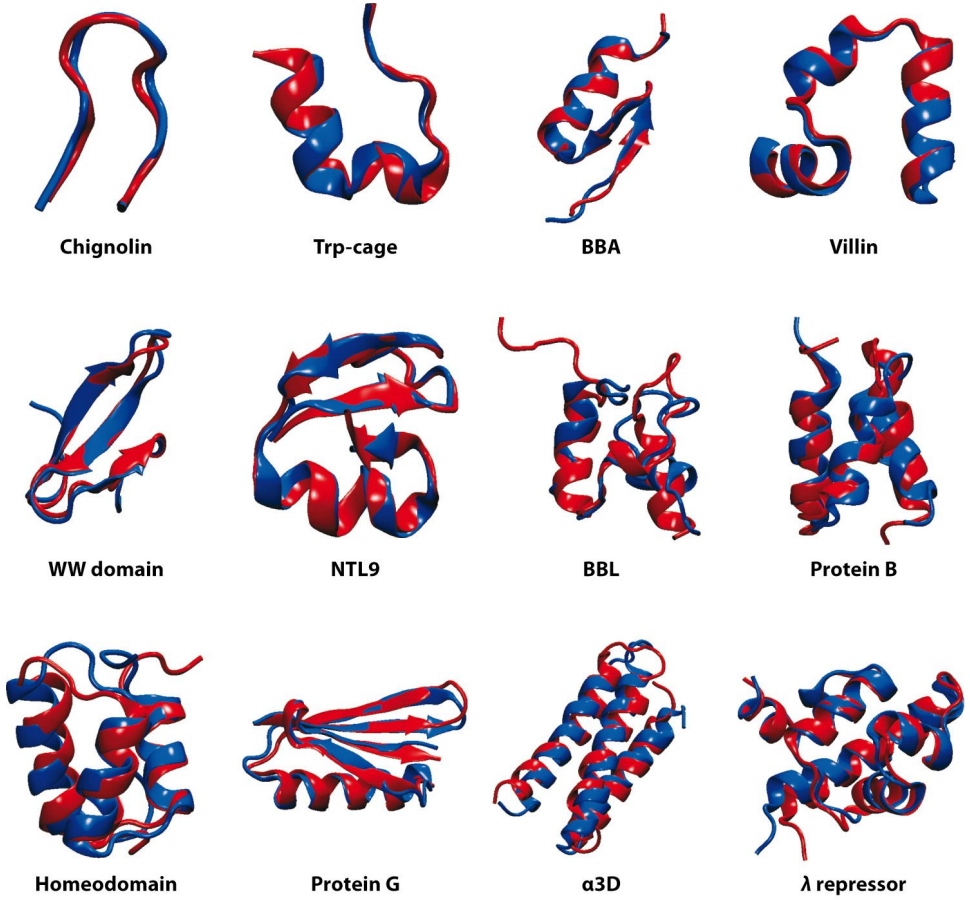
Force field: energy function used to compute the forces acting on atoms (due to interatomic interactions) during an MD simulation.

Steps in a typical MD simulation

1. **Preparing 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**: Evaluate observables (macroscopic level properties); Or relate to single molecule experiments.



Simulations of structurally diverse proteins



Simulations with a single force field.

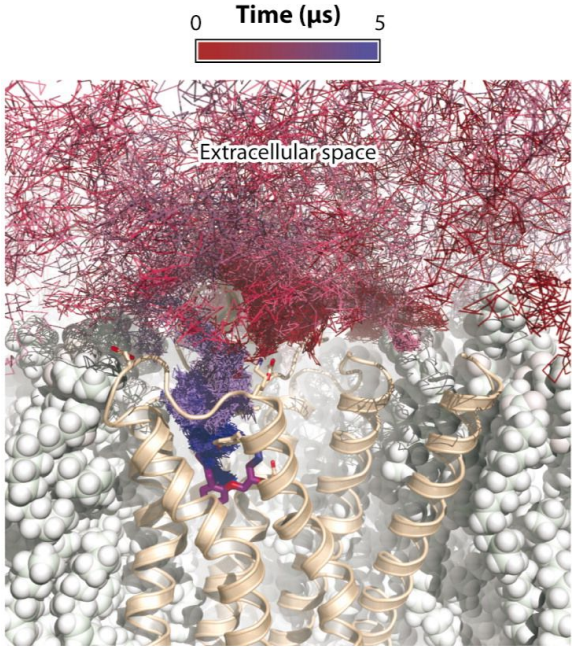
- 12 structurally diverse proteins fold spontaneously to a structure (blue) closely resembling that determined experimentally (red).
- Simulation snapshots chosen automatically based on a **clustering analysis** that did not exploit knowledge of the experimental structure.
- Total simulation time per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

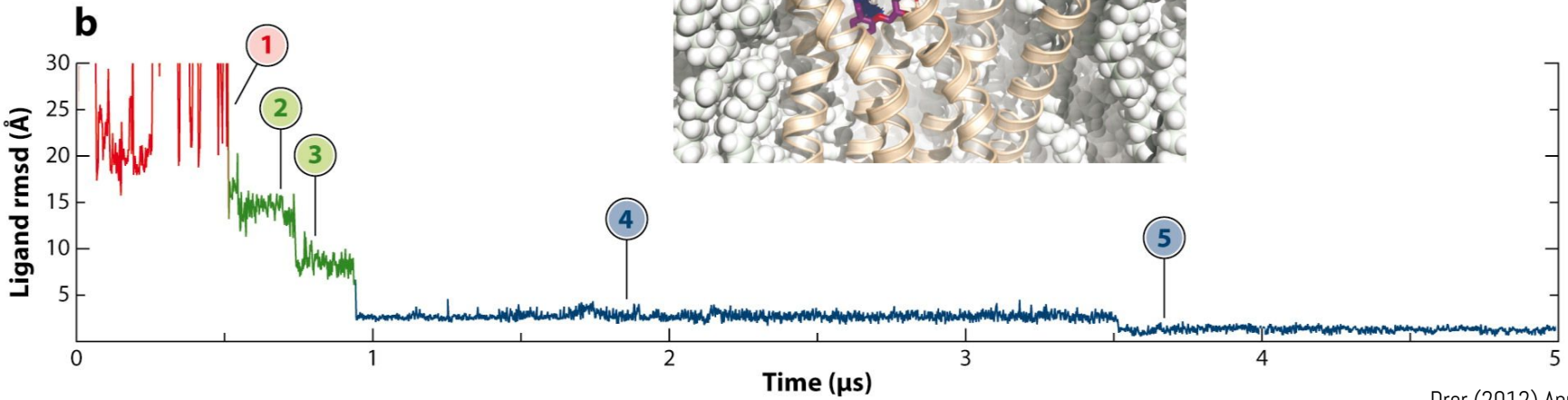
Dror (2012) Annu. Rev. Biophys.

Beta-blockers binding spontaneously to the β2-adrenergic receptor

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

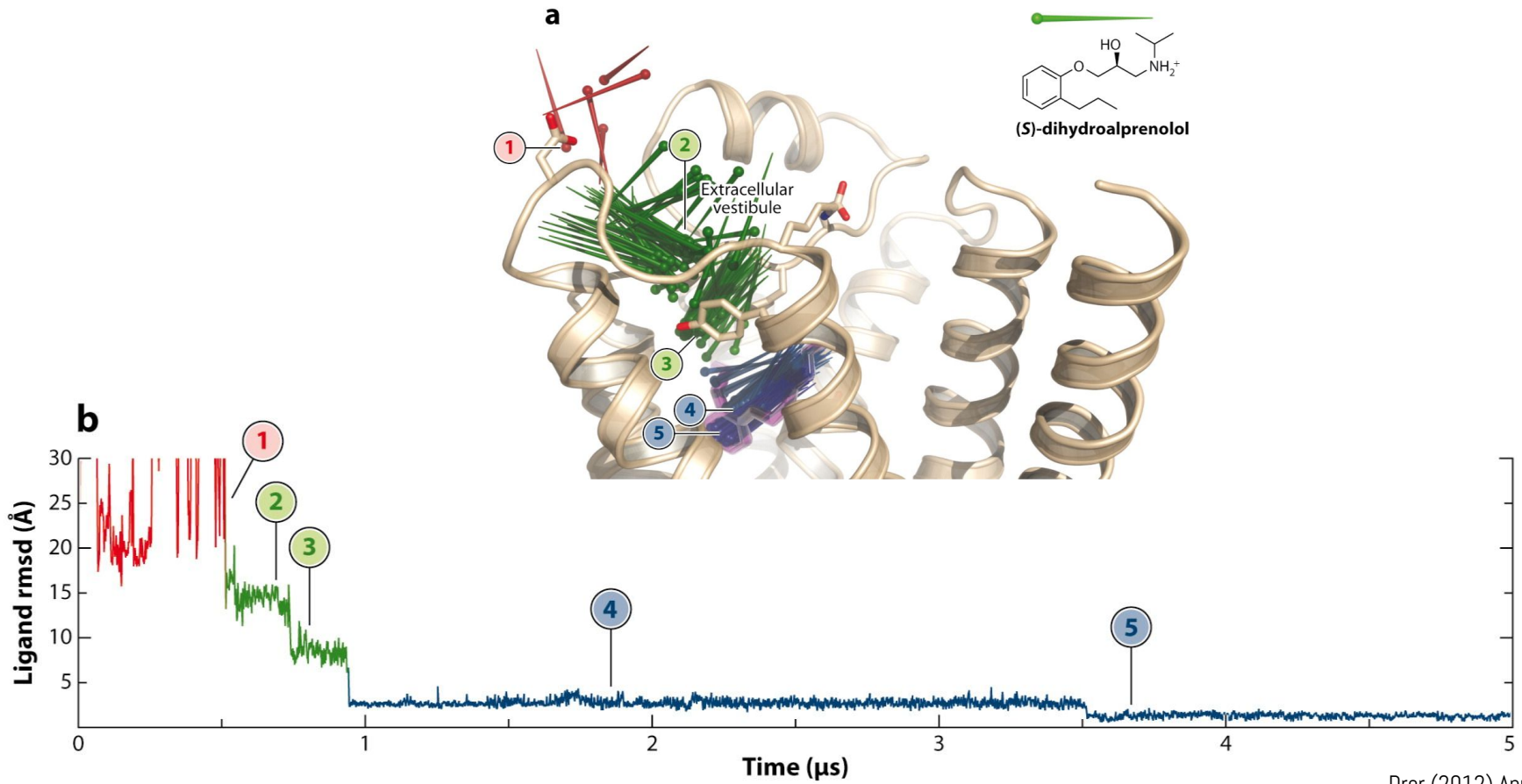
Root mean square deviation (rmsd) of the ligand in simulation from its position in the crystal structure.





Dror (2012) Annu. Rev. Biophys.

Beta-blockers binding spontaneously to the β2-adrenergic receptor



Dror (2012) Annu. Rev. Biophys.

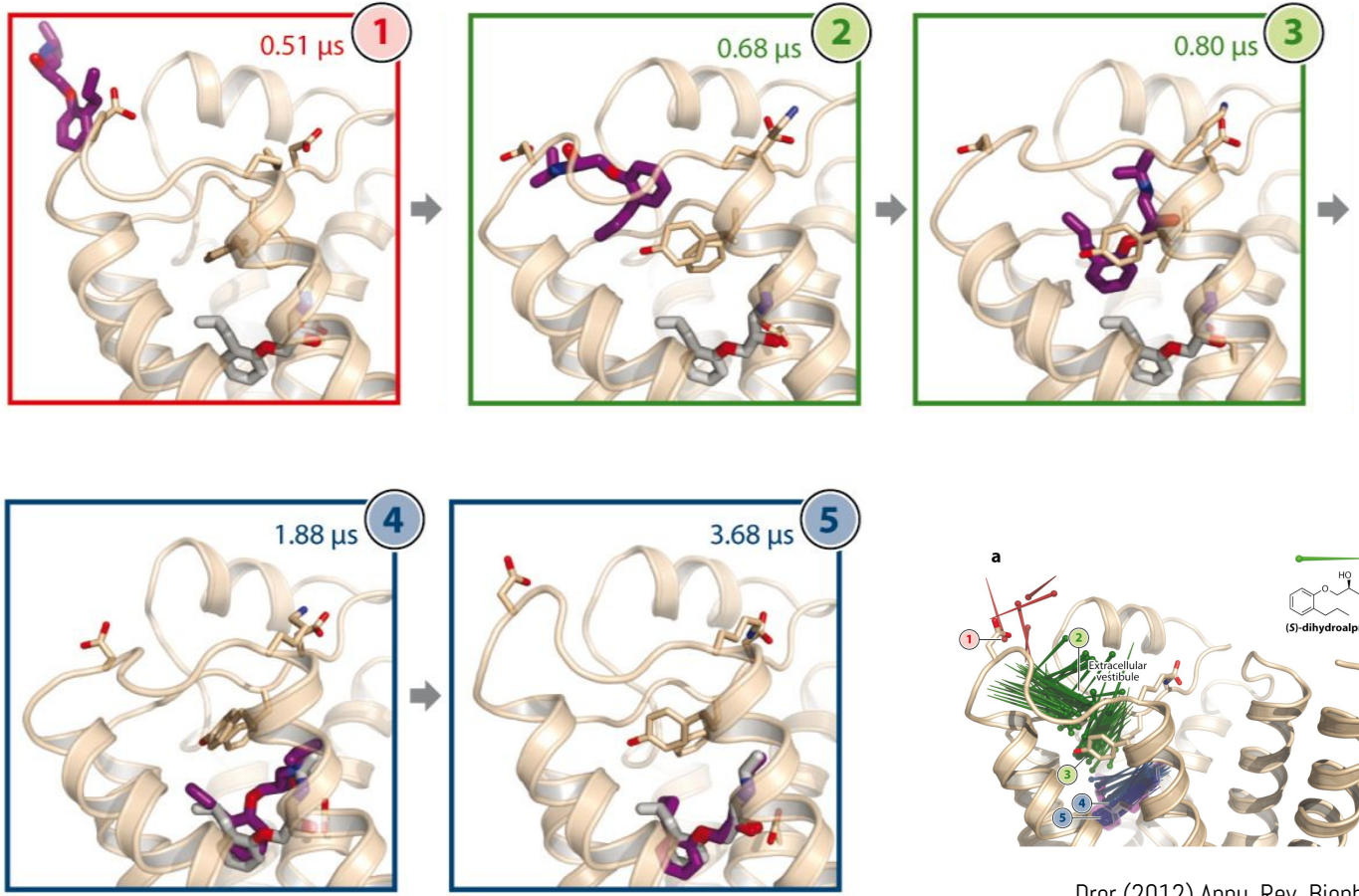
Beta-blockers binding spontaneously to the β2-adrenergic receptor

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.

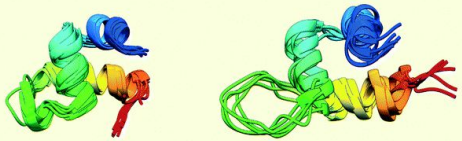


Dror (2012) Annu. Rev. Biophys.

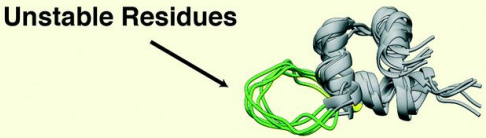
MD simulations for protein design

A. Modulating Protein Stability

I. Perform simulations in native and nonnative environments



II. Inform designs by analyzing the dynamics of unstable residues

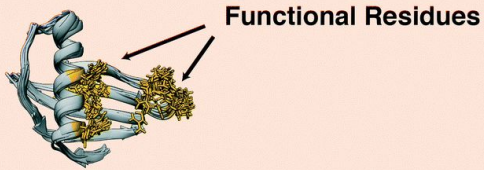


III. Perform simulations of designs to determine the impact of mutations on protein stability

B. Engineering Functional Regions

I. Perform simulations that capture functional dynamics

II. Inform designs by analyzing the dynamics of functional residues



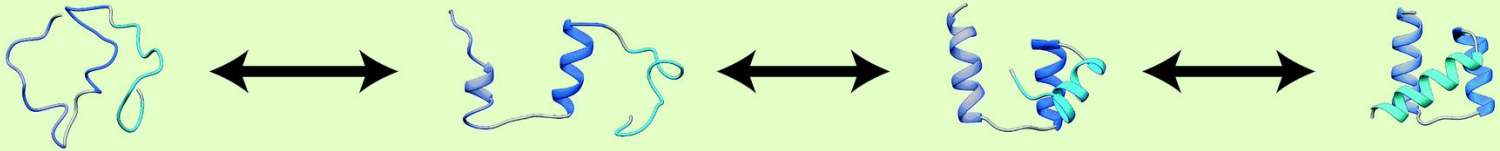
III. Perform simulations of designs to assess the impact of mutations on function regions

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

MD simulations for protein design

C. Insights From Folding Pathways

I. Simulate the unfolding/folding pathway and partition the trajectory into conformational states



Denatured State	Folding Intermediates	Transition State	Native State

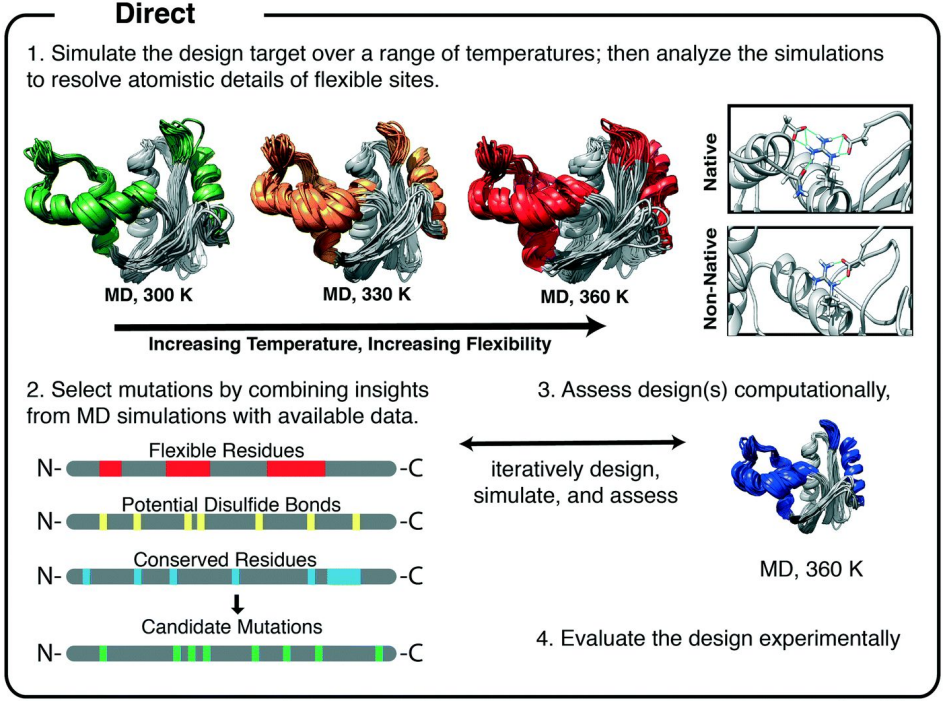
II. Inform designs with insights from specfic conformations or transitions along the folding pathway

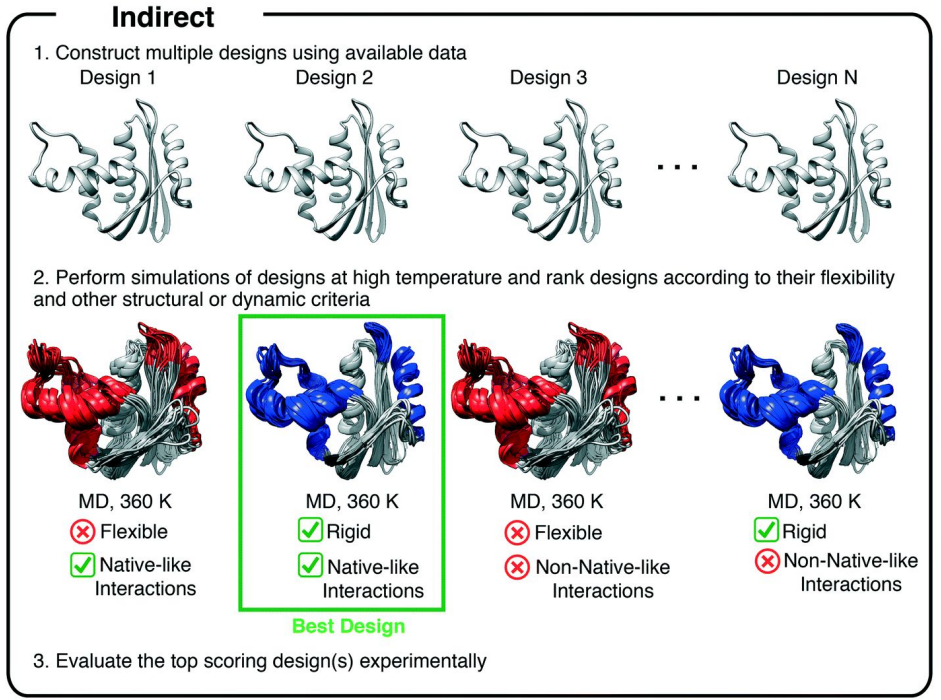
Destabilize the Denatured State	Stabilize Folding Intermediates	Design Fast Folding Variants	Probe / Alter the Folding Pathway

III. Perform simulations of designs to assess the impact of mutations on the folding landscape

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

MD simulations for protein design

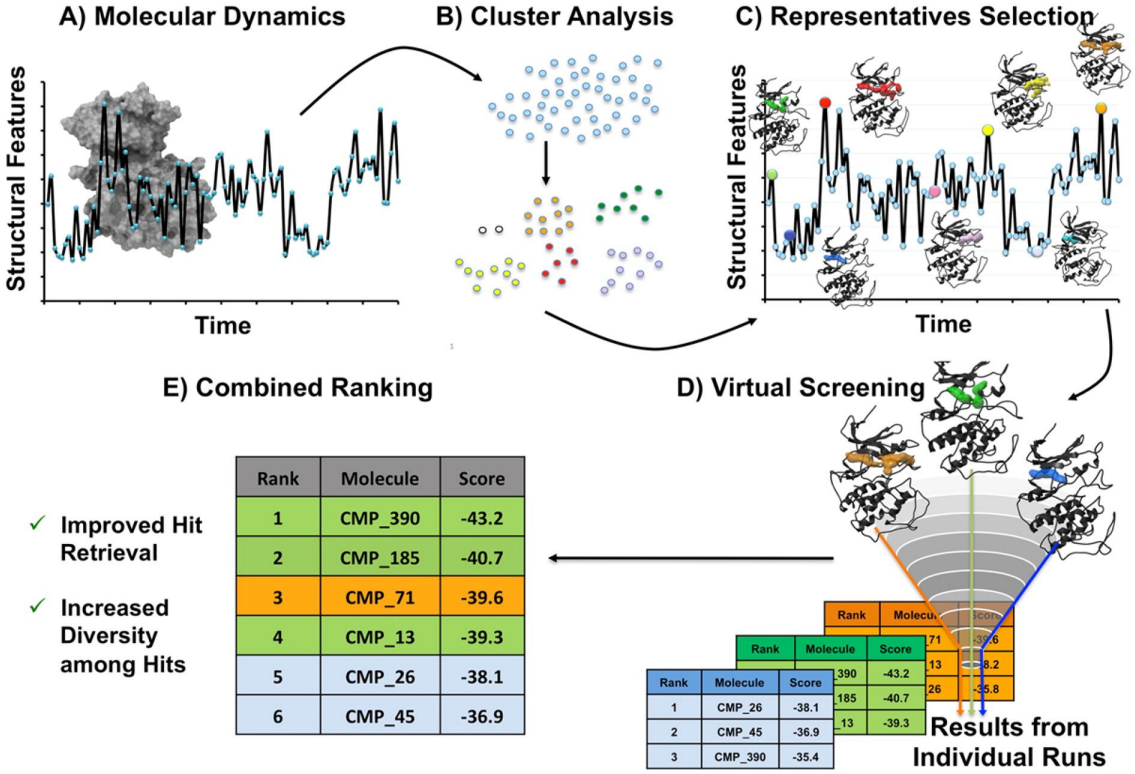




Childers & Daggett (2017) Mol. Syst. Des. Eng.,

Virtual screening: docking & MD simulations

A. Use MD trajectory to explore the receptor conformational space.
B. Extract several snapshots from the trajectory; clustering to eliminate redundancy.
C. From each cluster, select a representative structure (e.g., medoid).
D. Carry out virtual ligand screening independently at each representative conformation.
E. Return activity predictions by independent runs and combine together in a global ranking.



De Vivo (2016) J. Med. Chem.

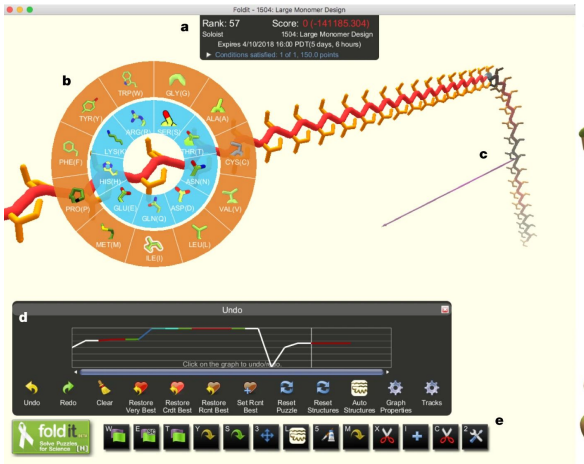
Distributed computing & Crowdsourcing

Folding@home: foldingathome.org

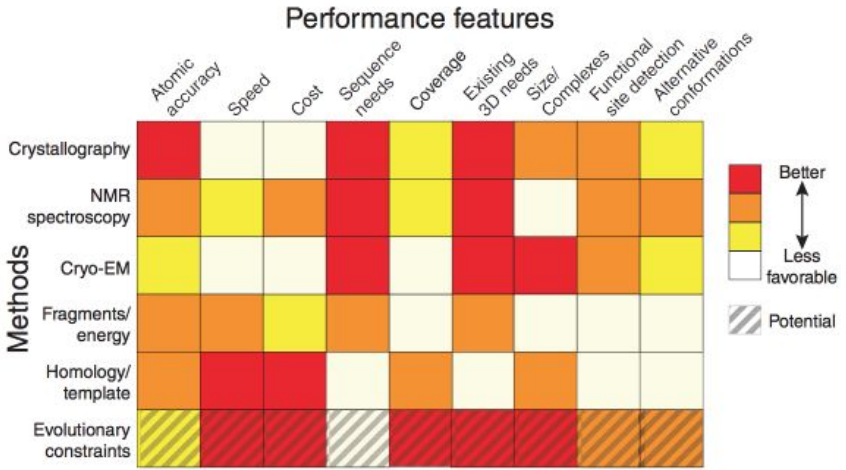
- Distributed computing project for MD simulations (e.g., protein folding, computational drug design).
- Uses the idle resources of personal computers owned by volunteers from all over the world.
- https://foldingathome.org/2020/02/27/foldinghome-takes-up-the-fight-against-covid-19-2019-ncov/

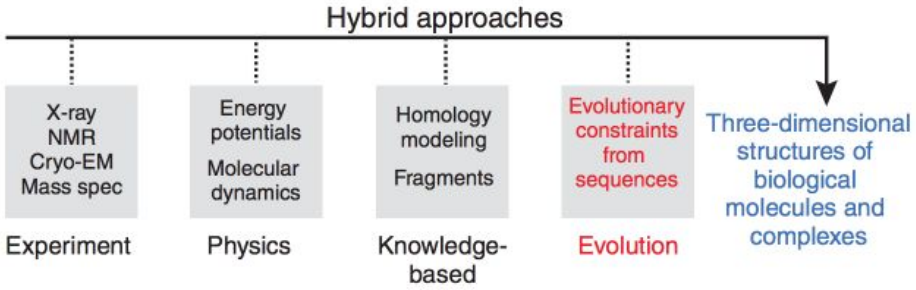
Foldit: fold.it

- 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.



Hybrid approaches for determining protein 3D structure





Marks (2012) Nat. Biotech.