Brownian motion: a hierarchy of dynamical theories

I. Include all classical degrees of freedom

timescale: 10^{-15} s

collisions: ~ 10

system state: $(\mathbf{q}, \mathbf{p})$ = posit. / momenta of *N* gas molecules + bead

distribution: $\mathcal{P}(\mathbf{q}, \mathbf{p}, t)$ = prob. density of finding $(\mathbf{q}, \mathbf{p})$ at time *t*

normalization: $\int d^{3(N+1)}q \int d^{3(N+1)}p \, \mathcal{P}(\mathbf{q}, \mathbf{p}, t) = 1$ for all *t*

initialization: $\mathcal{P}(\mathbf{q}, \mathbf{p}, 0) = \delta(\mathbf{q} - \mathbf{q}_0)\delta(\mathbf{p} - \mathbf{p}_0)$

evolution: Liouville equation corresponding to total Hamiltonian $\mathcal{H}$

$$\frac{\partial \mathcal{P}}{\partial t} = -\sum_{i=1}^{3(N+1)} \left[\frac{\partial \mathcal{H}}{\partial p_i} \frac{\partial \mathcal{P}}{\partial q_i} - \frac{\partial \mathcal{H}}{\partial q_i} \frac{\partial \mathcal{P}}{\partial p_i} \right] \equiv -\{\mathcal{P}, \mathcal{H}\}$$

ext. parameters: none

The dynamics are completely deterministic: if $\mathcal{P}(\mathbf{q}, \mathbf{p}, t)$ is a delta function, it will continue being a delta function at later times.

Brownian motion: a hierarchy of dynamical theories

II. Include only bead position / velocity

timescale: 10^{-9} s

collisions: $\sim 10^7$

system state: $(x, v_x) = \hat{x}$ components of bead position / velocity

distribution: $\mathcal{P}(x, v_x, t)$ = prob. density of finding (x, v_x) at time t

normalization: $\int dx \int dv_x \, \mathcal{P}(x, v_x, t) = 1$ for all t

initialization: $\mathcal{P}(x, v_x, 0) = \delta(x - x_0)\delta(v_x - v_{x0})$

evolution: multi-dim. Fokker-Planck (a.k.a. Kramers) equation

$$\frac{\partial \mathcal{P}}{\partial t} = -\frac{\partial}{\partial x}(v_x \mathcal{P}) + \frac{\partial}{\partial v_x}\left(\frac{v_x}{\tau}\mathcal{P}\right) + \frac{D}{\tau^2}\frac{\partial^2 \mathcal{P}}{\partial v_x^2}$$

ext. parameters: $\tau \equiv \frac{M}{\gamma}, D \equiv \frac{k_B T}{\gamma}$

The dynamics are probabilistic: missing gas degrees of freedom mean a delta function $\mathcal{P}$ spreads out to a distribution at later times

Brownian motion: a hierarchy of dynamical theories

III. Include only bead position

timescale: 10^{-3} s

collisions: $\sim 10^{13}$

system state: $x = \hat{\mathrm{x}}$ component of bead position

distribution: $\mathcal{P}(x, t)$ = prob. density of finding x at time t

normalization: $\int dx\, \mathcal{P}(x, t) = 1$ for all t

initialization: $\mathcal{P}(x, 0) = \delta(x - x_0)$

evolution: diffusion equation (special case of Fokker-Planck)

$$\frac{\partial \mathcal{P}}{\partial t} = D \frac{\partial^2 \mathcal{P}}{\partial x^2}$$

ext. parameters: $D \equiv \frac{k_B T}{\gamma}$

The dynamics are probabilistic: missing gas/bead degrees of freedom mean a delta function $\mathcal{P}$ spreads out to a distribution at later times

Turtles all the way down

Each theory in the hierarchy is a single "turtle", built on top of some more fundamental description at smaller scales. But the detailed nature of the bottom turtle is mostly irrelevant. The few relevant aspects are encoded in a small set of external parameters.

For equilibrium physics, renormalization group theory allows us to formally build a stack of turtles, keeping track of the relevant parameters at each scale.

The central argument of the course

Far from equilibrium, we do not have such a formalism. But upper turtles (coarse-grained dynamical theories) share universal characteristics, which we will derive from two basic assumptions:

- ► Markovian time evolution
- ► detailed balance (microscopic time reversibility)

We will explore these ideas through a unified framework based on discrete master equations, which are more general and mathematically easier than continuum theories like Fokker-Planck.

The central argument of the course

In the absence of external driving, a system will necessarily:

- approach equilibrium
- minimize free energy
- generate entropy (2nd law of thermodynamics)

Even in a driven system universal relations like the Jarzynski equality or Crooks fluctuation theorem hold.

A hierarchy in practice: six ways of looking at protein
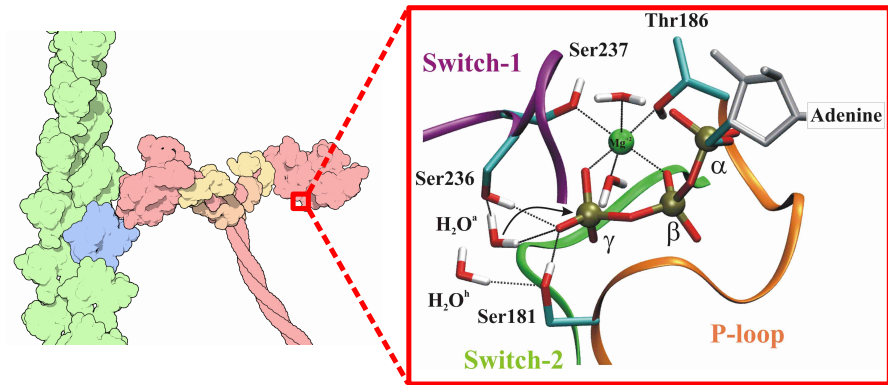
I. Hybrid quantum/classical simulations: keep electronic orbitals only on subset of atoms, represent the others by positions/velocities of nuclei. [2013 Nobel Prize in chemistry]

Timescales: $10^{-15} - 10^{-10}$ s

Hybrid quantum/classical simulation of ATP hydrolysis

See movie ATP_hydrolysis.mpg on course website.

Molecular dynamics: all-atom
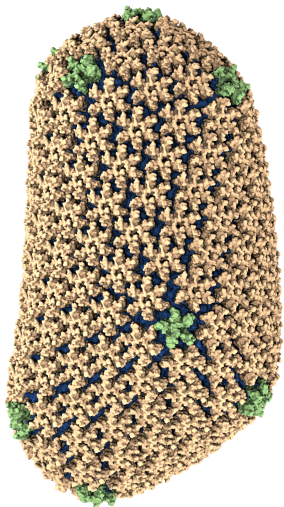
See movie hiv.mov on course website.

II. Classical molecular dynamics:
simulate positions/velocities of all atomic
nuclei subject to effective force fields.

Record: 64×10^6 atom HIV capsid for 100 ns [Zhao et al., Nature (2013)]

Timescales: $10^{-12} - 10^{-6}$ s, up to 10^{-3} s for small proteins
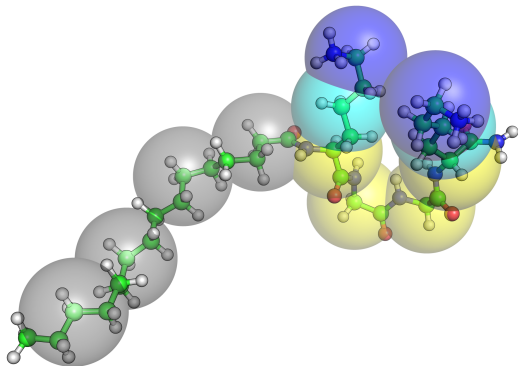
Molecular dynamics: implicit solvent
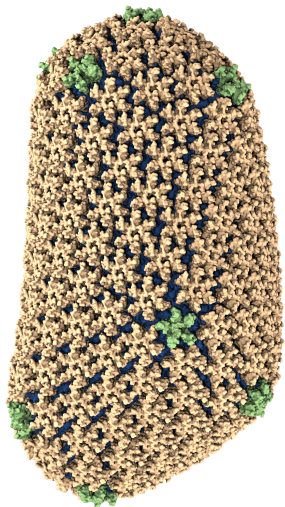
See movie hiv.mov on course website.

III. Implicit-solvent molecular dynamics: replace water molecules by effective potential (10-100x speed-up).

Timescales: $10^{-12} - 10^{-6}$ s, up to 10^{-3} s for small proteins
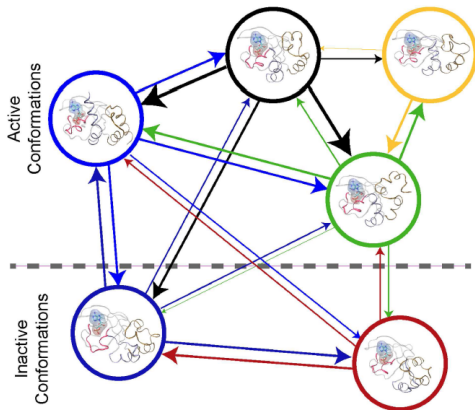
Coarse-grained protein models

IV. Coarse-grained (Brownian) dynamics: replace groups of atoms by beads subject to random forces.

Image courtesy of: http://membrane.urmc.rochester.edu/horn
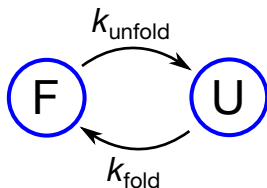
Timescales: $10^{-9} - 10^{-3}$ s

Kinetic networks

V. Kinetic network models: group similar protein conformations into "states". Assign transition probability rates between the states.

Image courtesy of: Boras *et. al.*, Front. Physiol. (2015)

Timescales: $10^{-3} - 10^2$ s

Two-state model

VI. Two-state model: kinetic network with all folded conformations grouped into one state, and all unfolded conformations into another.

Timescales: $10^{-3} - 10^2$ s