# Molecular simulations of biomolecules
## Remote Lecture #2
### minimization and dynamics
### basic connections to thermodynamics

CCB 550, Spring 2020

# Molecular dynamics algorithms

Start with Newton's equations:

$$a = d^2x/dt^2 = F/m = (\partial V/\partial x)/m$$

Then

$$
\begin{aligned}
x(t+h) &= x(t) + v(t)h + \frac{1}{2}a(t)h^2 + \frac{1}{6}\frac{d^3x}{dt^3}h^3 + O(h^4) \\
x(t-h) &= x(t) + -v(t)h + \frac{1}{2}a(t)h^2 - \frac{1}{6}\frac{d^3x}{dt^3}h^3 + O(h^4) \\
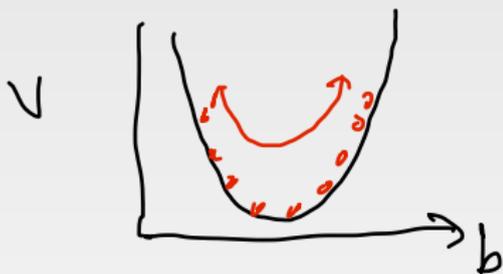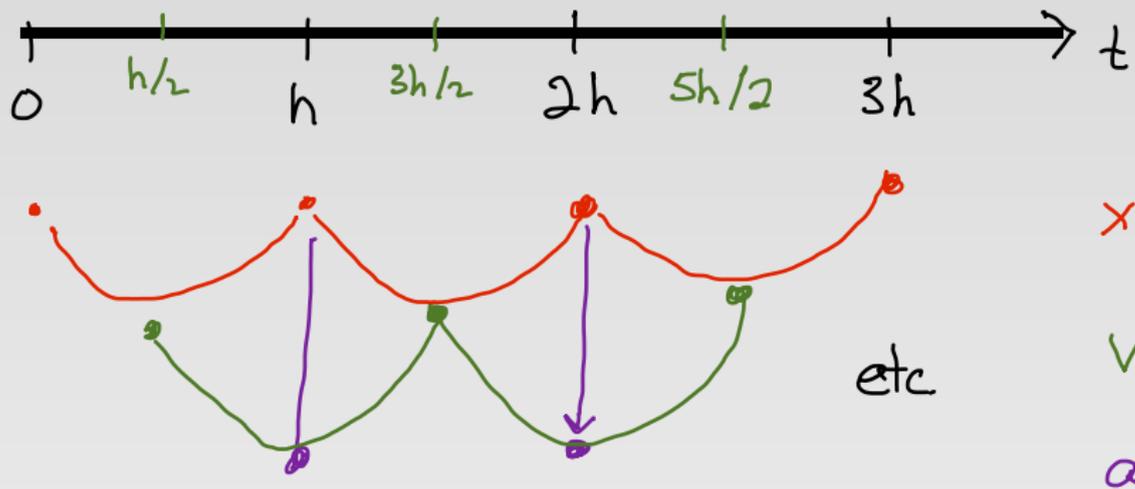x(t+h) &= 2x(t) - x(t-h) + a(t)h^2 + O(h^4) \quad\quad (1) \\
x(t+h) - x(t) &= x(t) - x(t-h) + a(t)h^2 + O(h^4) \\
v(t+\tfrac{1}{2}h) &= v(t-\tfrac{1}{2}h) + a(t)h + O(h^3) \quad\quad (2) \\
x(t+h) &= x(t) + v(t+\tfrac{1}{2}h)h + O(h^4) \quad\quad (3)
\end{aligned}
$$

Eq. (1) is the original Verlet propagation algorithm; Eqs. 2 and 3 are the "leap-frog" version of that.

# Looking at the leap-frog algorithm

## Regulating temperature

"Temperature" is a measure of the mean kinetic energy. The instantaneous $T(t)$ is related to the current kinetic energy:

$$KE = \frac{1}{2} \sum_i^{N_{dof}} m_i [v_i(t)]^2 = N_{dof} \frac{k_B T(t)}{2}$$

(cf. classical rule of thumb: "$k_B T/2$ of energy for every squared degree of freedom in the Hamiltonian")

Suppose the temperature is not what you want. At each step, you could scale the velocities by:

$$\lambda = \left[ 1 + \frac{h}{2\tau} \left( \frac{T_0}{T(t)} - 1 \right) \right]^{1/2}$$

This is the "Berendsen" or "weak-coupling" formula, that has a minimal disruption on Newton's equations of motion. But it does not guarantee a canonical distribution of positions and velocities. See Morishita, *J. Chem. Phys.* 113:2976, 2000; and Mudi and Chakravarty, *Mol. Phys.* 102:681, 2004. To fix things, see Bussi *et al.*, *J. Chem. Phys.* 126:014101, 2007.

Consider the stochastic, Langevin equation:

$$\mathbf{a} = d\mathbf{v}/dt = -\zeta\mathbf{v} + \mathbf{A}(t) + \mathbf{F}(t)/m \qquad (4)$$

By Stokes' law, the friction coefficient is related to the vicsocity of the environment: $\zeta = 6\pi a\eta/m$. At long times, we want this system to go to equilibrium at a temperature $T$, which is a Maxwell-Boltzmann distribution (for the case where $\mathbf{F} \equiv 0$:

$$W(\mathbf{v}, t; \mathbf{v}_0) \sim \exp\left[-m\mathbf{v}^2/2k_B T\right]$$

for every value of $\mathbf{v}_0$. This places restraints on the properties of the stochastic force $\mathbf{A}(t)$. It can be shown that

$$\zeta = (\beta/m) < A^2 > \qquad (5)$$

where we have assumed that $< A > = 0$ and
$< A(0).A(t) > = < A^2 > \delta(t)$. To implement this integrator, at each step we add $-\zeta\mathbf{v} + \mathbf{A}(t)$ to the acceleration in the Verlet scheme, where $A(t)$ is chosen randomly from a Gaussian distribution with width given by Eq. 5. This will generate a true canonical (Boltzmann) distribution.

# Why run MD simulations?

1. **Search conformational space; optimize poor starting structures**
   - set the target temperature to zero; the run MD
   - set a high target temperature; run MD to sample widely in configurations space; take snapshots and optimize each

2. **Study time-dependence of motions**
   - compare to vibrational, NMR, other time-dependent techniques. Doesn't directly work for time scales beyond 1 $\mu$s
   - Artificially trigger some change (e.g. break a bond), and follow the time-dependent response

3. **Find structures consistent with experimental restraints**
   - All NMR "structures" and most Xray and cryoEM structure refinements use this technique
   - Can also be used for sparse restraints, where one wants to find the ensemble of structures consistent with the data

4. **Make connections to thermodyanmics**
   - This takes advantage of the fact that MD snapshots sample configurations from a Boltzmann ensemble (next slide)
   - Giant caveat: MD for complex systems never fully samples configuration space, and is generally heavily weighted toward configurations that are near to the starting point

In earlier lectures we discussed the idea that all of thermodynamics can be computed from knowing the partition function Q:

$$Q = \sum_{states\, i} \exp(-\beta E_i) \simeq \int e^{-\beta V(\mathbf{x})} d\mathbf{x} \qquad (6)$$

*quantum*      *classical*

For gas-phase quantum calculations, we could adopt the RRHO (rigid rotor-harmonic osciallator) approximation, and compute Q by summing over all of the quantized energy states of the system.

But what if we have many, many atoms, or are in a liquid, and cannot write down the energies needed to compute Q? We will assume that we can extract samples from the Boltzmann distribution: this fundamentally implies that we can evaluate averages of mechanical properties, that is, of variables that are functions just of the structures we sample.

$$\langle f(\mathbf{x}) \rangle \equiv \int f(\mathbf{x}) e^{-\beta V(\mathbf{x})} d\mathbf{x} / \int e^{-\beta V(\mathbf{x})} d\mathbf{x} \simeq (1/N) \sum_{i}^{N} f(\mathbf{x}_i) \qquad (7)$$

This says that the themodynamic average (on the left, over a Boltzmann distribution) is just the arithmetic average (on the right) of snapshots taken from an MD simulation.

# Thermodynamic integration

Suppose that the potential energy, V (and hence Q and A), are parameterized by $\lambda : V \to V(\lambda)$. Then, since $A = -kT \ln Q$:

$$\frac{\partial A(\lambda)}{\partial \lambda} = -kT \int \frac{\partial}{\partial \lambda} e^{-\beta V(\lambda)} dq / Q = \frac{1}{Q} \int \left( \frac{\partial V}{\partial \lambda} \right) e^{-\beta V(\lambda)} dq = \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} \tag{8}$$

The total change in A on going from $\lambda = 0$ to $\lambda = 1$ is:

*thermodynamics, includes S*

$$\Delta A = A(1) - A(0) = \int_0^1 \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} d\lambda \tag{9}$$

*mechanical property, estimate via MD*

This is called thermodynamic integration, and is a fundamental connection between macroscopic free enegies, and microscopic simulations. The integral over $\lambda$ can be done by quadrature, and the Boltzmann averages $\langle \partial V / \partial \lambda \rangle_{\lambda}$ can be carried out by molecular dynamics or Monte Carlo procedures.

# Linear mixing

Consider the special case of *linear mixing*, where

$$V(\lambda) = (1-\lambda)V_0 + \lambda V_1$$

Then $\partial V / \partial \lambda = V_1 - V_0 \equiv \Delta V$ (often called the *energy gap*), and

$$\boxed{\Delta A = \int_0^1 \langle \Delta V \rangle_\lambda \, d\lambda} \tag{10}$$

The simplest numerical approximation to the $\lambda$ integral is just to evaluate the integrand at the midpoint, so that $\Delta A = \langle \Delta V \rangle_{1/2}$. This says that the free energy difference is approximately equal to the average potential energy difference, evaluated for a (hypothetical) state half-way between $\lambda = 0$ and $\lambda = 1$. Another approximate formula uses only the endpoints:

$$\Delta A \simeq \frac{1}{2} \langle \Delta V \rangle_0 + \frac{1}{2} \langle \Delta V \rangle_1 \tag{11}$$

And more elaborate formulas (*e.g.* from Gaussian integration) are feasible (and often used). See Hummer & Szabo, *J. Chem. Phys.* **105,** 2004 (1996) for a fuller discussion.