

1 Molecular dynamics algorithm

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

Eq. (1) is the original Verlet propagation algorithm; Eqs. 2 and 3 are the “leap-frog” version of that. Remember that $a = d^2x/dt^2 = F/m = (\partial U/\partial x)/m$.

2 Thermodynamic integration

Now suppose that U (and hence Q and A) are parameterized by $\lambda : U \rightarrow U(\lambda)$. Then, since $A = -kT \ln Q$:

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

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

$$\Delta A = A(1) - A(0) = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_{\lambda} d\lambda
 \tag{4}$$

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

3 Thermodynamic cycles for ligand binding

