Stochastic Dynamics, Brownian Dynamics and Diffusion

Stochastic Dynamics

To this point, we have only discussed molecular dynamics (MD) as a method for simulating biomolecular dynamics. We saw that this method was based on solving the Newtonian equation of motion

$$m\frac{d^2}{dt^2}r_i = -\frac{\partial}{\partial r_i}V(r_1, ..., r_N)$$

where the positions of atom 1 to N are given by r_i, and the potential function $V(r_1, ..., r_N)$ is an appropriate force field that describes the interaction of the atoms within our system. MD simulations are sometimes called *deterministic simulations*, since for the same initial conditions (positions and velocities), the system will follow exactly the same trajectory.

Although this formulation is correct and useful, if we are interested in large systems (many atoms) or long times, it can be too expensive to use. Also, although we are simulating the dynamics of the entire set of atoms, there may be only a select group that we are interested in. This could be part of a biomolecule, such as a binding domain or active site, or it could be the center of mass of the biomolecule itself, such as in the case of transport. Suppose we can identify a set of coordinates $q_1, ..., q_M$ that we are interested in (these do not need to be Cartesian coordinates, but could be some alternative description). We can then write down a *Langevin equation* to describe the system

$$\mu_i\frac{d^2}{dt^2}q_j = -\frac{\partial}{\partial q_j}W(q_1, ..., q_M) - \gamma_i\frac{d}{dt}q_j + \sigma_j\xi_j(t)$$

The l.h.s. of this equation is the "acceleration" of our coordinate q_j. The terms on the r.h.s. represent an effective potential $W(q_1, ..., q_M)$ that describes the interactions of the $q_i's$, a velocity dependent frictional term with coefficient γ_j, and a stochastic or fluctuating force term $\xi_j(t)$ with coupling coefficients σ_j. This stochastic force term has particular properties which we will discuss later, but it is included to capture the thermal motion of the rest of the system on the coordinates that we are interested in.

We can perform simulations by solving this Langevin equation, and the amount of computational time that we save can be significant. This is called *Stochastic Dynamics*. A common method of dividing the system is to just consider the motion of the biomolecule and ignore the solvent (water) dynamics. This can cut the number of atoms in a simulation system by a factor of 2 or more, and may allow the system to explore its conformational space much faster. We will not be performing any stochastic dynamics simulations, but will instead take this simplification one step further.

Einstein Diffusion Equation

Let us consider a system of particles that do not interact with each other. We can write down the general Langevin equation that describes their motion

$$m\ddot{r} = -\gamma\dot{r} + \sigma\xi(t)$$

If we are dealing with biomolecules in water, we have a low Reynold's number and can apply the limit of strong friction

$$|\gamma \dot{r}| \gg |m\ddot{r}|$$

so that our Langevin equation simply becomes

$$\gamma \dot{r} = \sigma \xi(t).$$

To this point we have not discussed the properties of the stochastic term $\xi(t)$, which are

$$\langle \xi_i(t) \rangle = 0$$

$$\langle \xi_i(t_1)\xi_j(t_2) \rangle = \delta_{ij}\delta(t_2 - t_1)$$

Using our skills from stochastic calculus, we find that our simplified Langevin equation corresponds to a Fokker-Planck equation, or in this case the Einstein Diffusion equation

$$\frac{\partial}{\partial t}p(r, t|r_0, t_0) = \frac{\sigma^2}{2\gamma^2}\nabla^2 p(r, t|r_0 t_0)$$

where we have assumed that the coefficients σ and γ are spatially homogeneous. If we were to calculate the mean square displacement of a given particle

$$\langle (r(t) - r(t_0))^2 \rangle = \int d^3r(r(t) - r(t_0))^2 p(r, t|r_0, t_0)$$

we would get (using Greens' theorem)

$$\langle (r(t) - r(t_0))^2 \rangle = 6\frac{\sigma^2}{2\gamma^2}t$$

where we identify the diffusion coefficient as

$$D = \frac{\sigma^2}{2\gamma^2}.$$

Smoluchowski Diffusion Equation

The Einstein diffusion equation described the distribution of a system of non-interacting particles with no external forces. We are more interested in the case of Brownian particles in the presence of a force field $F(r)$, which is described by the equation

$$m\ddot{r} = -\gamma \dot{r} + F(r) + \sigma \xi(t).$$

If we again apply the limit of strong friction we get

$$\gamma \dot{r} = F(r) + \sigma \xi(t)$$

which corresponds to a Fokker-Planck equation of the form

$$\frac{\partial}{\partial t}p(r, t|r_0, t_0) = \left(\nabla^2 \frac{\sigma^2}{2\gamma^2} - \nabla \cdot \frac{F(r)}{\gamma} \right) p(r, t|r_0, t_0)$$

which we can write as the *Smoluchowski Diffusion equation*

$$\frac{\partial}{\partial t} p(r, t | r_0, t_0) = \nabla \cdot \left(\nabla D - \frac{F(r)}{\gamma} \right) p(r, t | r_0, t_0).$$

If we integrate this equation of a volume V, we will get the number of particles within this volume

$$N = \int_V d^3 r \, p(r, t | r_0, t_0).$$

Taking the partial time derivative of each side and using the Smoluchowski diffusion equation we find

$$\partial_t N = \int_V d^3 r \, \nabla \cdot \left(\nabla D - \frac{F(r)}{\gamma} \right) p(r, t | r_0, t_0).$$

Applying Gauss' theorem gives us

$$\partial_t N = \int_{\partial V} da \cdot \left(\nabla D - \frac{F(r)}{\gamma} \right) p(r, t | r_0, t_0).$$

Since particle are not being created or destroyed within this volume, this integral must must represent the particle flux over the boundary ∂V

$$j(r) = \left(\nabla D - \frac{F(r)}{\gamma} \right) p(r, t | r_0, t_0).$$

If the force term is time independent (as we have written it), and if it can be related to a scalar potential (i.e. $F(r) = -\nabla V(r)$), we can expect that the probability distribution $p(r, t)$ must be the Boltzmann distribution $\exp[-V(r)/kT]$. Also, if the flux or current vanishes at the boundary (the number of particles is constant), we see that

$$\left(\nabla D - \frac{F(r)}{\gamma} \right) e^{-\beta V(r)} = 0$$

where we have introduced $\beta = 1/kT$. If we apply the derivative term we get

$$e^{-\beta V(r)} \left(D \beta F(r) + \nabla D - \frac{F(r)}{\gamma} \right) = 0$$

which implies

$$\nabla D = F(r) \left(\frac{1}{\gamma} - D\beta \right).$$

This is the *Fluctuation-Dissipation theorem*. If the diffusion constant is spatially homogeneous, and using the fact that $D = \sigma^2 / 2\gamma^2$, we get

$$\sigma^2 = 2kT\gamma.$$

This equation implies that the amplitude of the fluctuation forces σ are balanced by the frictional coefficient γ in a temperature dependent fashion.

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Ermak-McCammon Equation

Let's return to our Langevin equation for a system of particle in a force field

$$m\ddot{r} = -\gamma\dot{r} + F(r) + \sigma\xi(t).$$

Instead of applying the limit of strong friction, we can average this equation over a time Δt that is much longer than the momentum relaxation time

$$\Delta t \gg \frac{mD}{kT}.$$

In this average, the acceleration term does not contribute $< m\ddot{r} >_{\Delta t} = 0$, and the other terms take on time averaged forms

$$\langle \gamma\dot{r} \rangle = \gamma\frac{\Delta x}{\Delta t}$$

$$\langle F(r) \rangle = F$$

$$\langle \xi(t) \rangle = \frac{1}{\sqrt{\Delta t}}\tilde{\xi}$$

which gives us

$$\gamma\frac{\Delta x}{\Delta t} = F + \frac{\sigma}{\sqrt{t}}\tilde{\xi}.$$

If we rearrange this to solve to Δx, we get

$$\Delta x = \frac{\Delta t}{\gamma}F + \frac{\sigma\sqrt{\Delta t}}{\gamma}\tilde{\xi}$$

and using the fact that $1/\gamma = D/kT$ and $\sigma/\gamma = \sqrt{2D}$, we find

$$\Delta x = \frac{D\Delta t}{kT}F + \sqrt{2D\Delta t}\tilde{\xi}$$

or equivalently

$$\Delta x = \frac{D\Delta t}{kT}F + S$$

where the stochastic term S has the properties

$$\langle S \rangle = 0 \qquad\qquad \langle S^2 \rangle = 2D\Delta t.$$

This is the *Ermak-McCammon equation* and it will become the basis for our Brownian dynamics simulations.