BEYOND MOLECULAR DYNAMICS

Herman J.C. Berendsen
Biophysical Chemistry, University of Groningen, the Netherlands
Groningen Institute for Biosciences and Biotechnology (GBB)

CSC, Espoo

Lecture nr 4, Thursday, 5 Februari, 2004

Molecular dynamics with atomic details is limited to time scales in the order of 100 ns. Events that are in micro- or millisecond range and beyond, as well as system sizes beyond 100,000 particles, call for methods to simplify the system.

The key is to *reduce the number of degrees of freedom*. The first task is to define *important* degrees of freedom. The 'unimportant' degrees of freedom must be averaged-out in such a way that the thermodynamic and long time-scale properties are preserved.

The reduction of degrees of freedom depends on the problem one wishes to solve. One approach is the use of *superatoms*, lumping several atoms into one interaction unit. The interactions change into *potentials of mean force*, and the omitted degrees of freedom are replaced by *noise* and *friction*. On an even coarser scale one may lump many particles together and describe the behavior in terms of *densities* rather than positions. On a mesoscopic (i.e., nanometer to micrometer) scale, the fluctuations are still important, but on a macroscopic scale they become negligible and the Navier-Stokes equations of continuum fluid dynamics emerge. A modern development is to handle the continuum equations with particles (DPD: dissipative particle dynamics).

REDUCED SYSTEM DYNAMICS

Separate *relevant* d.o.f. $\boldsymbol{r}'$
and *irrelevant* d.o.f. $\boldsymbol{r}''$

Force on $\boldsymbol{r}'$:
part correlated with positions $\boldsymbol{r}'$
part correlated with velocities $\dot{\boldsymbol{r}}'$
rest is 'noise', not correlated with positions or velocities of primed particles.

$$\boldsymbol{F}_i(t) = -\frac{\partial V^{\mathrm{mf}}}{\partial \boldsymbol{r}_i'} + \boldsymbol{F}_i^{\mathrm{friction}} + \boldsymbol{F}_i(t)^{\mathrm{noise}}$$

$\boldsymbol{F}_i^{\mathrm{friction}}(t)$ is a function of $\boldsymbol{v}_j(t-\tau)$.

$\boldsymbol{F}_i(t)^{\mathrm{noise}} = R_i(t)$ with

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

$$\langle v_j(t) R_i(t+\tau) \rangle = 0 \quad (\tau > 0)$$

$R(t)$ is characterized by *stochastic properties*:
- probability distribution $w(R_i)\, dR_i$
- correlation function $\langle R_i(t) R_j(t+\tau) \rangle$

Projection operator technique (Kubo and Mori; Zwanzig) give elegant framework to describe relation between friction and noise

[Van Kampen in *Stochastic Processes in Physics and Chemistry* (1981): "This equation is exact but misses the point. The distribution cannot be determined without solving the original equation...")]

POTENTIAL OF MEAN FORCE-1

Requirement: **Preserve thermodynamics!**

Helmholtz free energy A:

$$A = -k_B T \ln Q$$

$$Q = c \int e^{-\beta V(\boldsymbol{r})}\, d\boldsymbol{r}$$

Define a *reaction coordinate* ξ (may be more than one dimension). Separate integration over the reaction coordinate from the integral in Q:

$$Q = c \int d\xi \int d\boldsymbol{r} e^{-\beta V(\boldsymbol{r})} \delta(\xi(\boldsymbol{r}) - \xi)$$

Define potential of mean force $V^{\mathrm{mf}}(\xi)$ as

$$V^{\mathrm{mf}}(\xi) = -k_B T \ln \left[c \int d\boldsymbol{r} e^{-\beta V(\boldsymbol{r})} \delta(\xi(\boldsymbol{r}) - \xi) \right],$$

so that

$$Q = \int e^{-\beta V^{\mathrm{mf}}(\xi)}\, d\xi$$

and

$$A = -k_B T \ln \left[\int e^{-\beta V^{\mathrm{mf}}(\xi)}\, d\xi \right]$$

Note that the potential of mean force is an integral over multidimensional hyperspace. It is generally not possible to evaluate such integrals from simulations. As we shall see, it will be possible to evaluate derivatives of V^{mf} from ensemble averages. Therefore we shall be able to compute V^{mf} by integration over multiple simulation results, up to an unknown additive constant.

POTENTIAL OF MEAN FORCE-2

To simplify, look at cartesian coordinates. $\xi = \boldsymbol{r}'$. So $\boldsymbol{r}'$ are the *important* coordinates, and $\boldsymbol{r}''$ are the *unimportant* coordinates. How can we determine the PMF from simulations?

Let us perform a simulation in which $\boldsymbol{r}'$ is constrained, while $\boldsymbol{r}'$ is free to move.

$$V^{\mathrm{mf}}(\boldsymbol{r}') = -k_B T \ln \left[c \int e^{-\beta V(\boldsymbol{r}', \boldsymbol{r}'')} \, d\boldsymbol{r}'' \right]$$

$$\begin{aligned} \frac{\partial V^{\mathrm{mf}}(\boldsymbol{r}')}{\partial \boldsymbol{r}'_i} &= \frac{\int \frac{\partial V(\boldsymbol{r}', \boldsymbol{r}'')}{\partial \boldsymbol{r}'_i} e^{-\beta V(\boldsymbol{r}', \boldsymbol{r}'')} \, d\boldsymbol{r}''}{\int e^{-\beta V(\boldsymbol{r}' \boldsymbol{r}'')} \, d\boldsymbol{r}''} \\ &= \left\langle \frac{\partial V(\boldsymbol{r}', \boldsymbol{r}'')}{\partial \boldsymbol{r}'_i} \right\rangle_{''} \\ &= \langle \boldsymbol{F}_i^c \rangle. \end{aligned}$$

Derivative of potential of mean force is the ensemble-averaged constraint force (cartesian).

The constraint force follows from the coordinate resetting in constraint dynamics.

(This is still true in more complex 'reaction coordinates', but there are small metric tensor corrections)

DIFFUSION COEFFICIENT

How to determine the diffusion constant from constrained simulations?

Determine fluctuation of constraint force $\Delta F^c(t) = F^c(t) - \langle F^c \rangle$.

Fluctuation-dissipation theorem:

$$\langle \Delta F^c(0) \Delta F^c(t) \rangle = k_B T \zeta(t)$$

$$\zeta = \int_0^\infty \zeta(t)\, dt$$

$$D = \frac{k_B T}{\zeta}$$

Hence

$$D = \frac{(k_B T)^2}{\int_0^\infty \langle \Delta F^c(0) \Delta F^c(t) \rangle \, dt}$$

LANGEVIN DYNAMICS-1

General form of friction force: approximated by linear response in time, linear in velocities:

$$\boldsymbol{F}_i^{\rm fr}(t) = m_i \sum_j \int_0^t \gamma_{ij}(\tau)\boldsymbol{v}_j(t-\tau)\,d\tau$$

This gives (in cartesian coordinates) the *generalized Langevin equation*:

$$m_i \frac{d\boldsymbol{v}_i}{dt} = -\frac{\partial V^{\rm mf}}{\partial \boldsymbol{r}_i} - m_i \sum_j \int_0^t \gamma_{ij}(\tau)\boldsymbol{v}_j(t-\tau)\,d\tau + \boldsymbol{R}_i(t)$$

If a *constrained dynamics* is carried out with $\boldsymbol{r}'$ constant (hence $\boldsymbol{v}' = 0$), then the 'measured' force on i approximates a representation of $\boldsymbol{R}_i(t)$. So one can determine an approximation to the noise correlation function

$$C_{ij}^R(\tau) = \langle R_i(t) R_j(t+\tau)\rangle$$

.

(assumption: motion of $\boldsymbol{r}''$ that determines $R(t)$ is *fast* compared to the motion of $\boldsymbol{r}'$)

There is a relation between friction and noise.

LANGEVIN DYNAMICS-2

Relation between friction and noise

Average total energy should be conserved
(averaged over time scale large compared to noise correlation time)

- *Systematic force* is conservative (change in kinetic energy cancels change in V^{mf})
- *Frictional force* is dissipative: decreases kinetic energy
- *Stochastic force* has in first order no effect since $\langle v_j(t) R_i(t+\tau)\rangle = 0$. In second order it increases the kinetic energy.

The cooling by friction should cancel the heating by noise (fluctuation-dissipation theorem). This leads to

$$\langle R(0)R(t)\rangle = k_B T m \gamma(t)$$

LANGEVIN APPROXIMATIONS

(write $m_i\gamma_{ij} = \zeta_{ij}$)

Generalized Langevin

$$m_i\dot{v}_i(t) = -\frac{\partial V^{\rm mf}}{\partial x_i} - \sum_j \int_0^t \zeta_{ij}(\tau)v_j(t-\tau)\,d\tau + R_i(t)$$

with

$$\langle R_i(0)R_j(t)\rangle = k_BT\zeta_{ji}(t)$$

includes *coupling* (space) and *memory* (time).

Simple Langevin with hydrodynamic coupling

$$m_i\dot{v}_i(t) = -\frac{\partial V^{\rm mf}}{\partial x_i} - \sum_j \zeta_{ij}v_j(t) + R_i(t)$$

with

$$\langle R_i(0)R_j(t)\rangle = 2k_BT\zeta_{ji}\delta(t)$$

includes *coupling* (space), but no memory.

Simple Langevin

$$m_i\dot{v}_i(t) = -\frac{\partial V^{\rm mf}}{\partial x_i} - \zeta_i v_i(t) + R_i(t)$$

with

$$\langle R_i(0)R_j(t)\rangle = 2k_BT\zeta_i\delta(t)\delta_{ij}$$

includes neither coupling nor memory.

BROWNIAN DYNAMICS-1

If systematic force does not change much on the time scale of the velocity correlation function, we can average over a time $\Delta t > \tau_c$. The average acceleration becomes small and can be neglected (**non-inertial dynamics**):

$$0 \approx \overline{F}_i(x) - \sum_j \zeta_{ij} \overline{v}_j(t) + \overline{R}_i$$

with

$$\overline{R}_i = \int_t^{t+\Delta t} R(t')\, dt'$$

$$\langle R_i(0) R_j(t) \rangle = 2 k_B T \zeta_{ji} \delta(t)$$

Be aware that the average acceleration is not zero if there is a cooperative motion with large mass

Hence $\overline{v}_j(t)$ can be solved from matrix equation

$$\zeta \overline{\mathbf{v}} = \overline{\mathbf{F}} + \overline{\mathbf{R}}(t)$$

Solve in time steps Δt

Random force $\overline{R}_i$ with

$$\langle \overline{R}_i \rangle = 0$$

$$\langle \overline{R}_i \overline{R}_j \rangle = 2 k_B T \zeta_{ji} \Delta t$$

$\overline{R}_i$ and $\overline{R}_j$ are correlated random numbers, chosen from bivariate gaussian distributions.

BROWNIAN DYNAMICS-2

Without hydrodynamic coupling:

$$\overline{v}_i = \frac{\overline{F}_i}{\zeta_i} + r_i$$

r_i is random number chosen from (gaussian) distribution with variance $2k_BT\Delta t/\zeta_i$.

$$x_i(t + \Delta t) = x_i(t) + v_i\Delta t$$

Velocity can be eliminated. Write $D = k_BT/\zeta$ (diffusion constant) yields **Brownian dynamics**

$$x(t + \Delta t) = x(t) + \frac{D}{k_BT}F(t)\Delta t + r(t)$$

$$\langle r \rangle = 0$$

$$\langle r^2 \rangle = 2D\Delta t$$

F must assumed to be constant during Δt. The longer Δt, the smaller the noise.

For slow processes in macroscopic times the noise goes to zero.

REDUCED PARTICLE DYNAMICS

Superatom approach

Lump a number of atoms together into one particle (e.g. 10 monomers of a homopolymer). Design force field for those superatoms including bonding and nonbonding terms. For polymer:

- soft harmonic spring between particles, representing Gaussian distribution of superatom-distance distributions
- harmonic angular term in chain, representing stiffness
- Lennard-Jones type interactions between particles
- solvent: LJ particle

Derive parameters from

- experimental data (density, heat of vaporization, solubility, surface tension, ...,
- atomic simulations of small system (radius of gyration, end-to-end distance distribution, radial distribution functions, ...

Perform normal Molecular Dynamics. Adding friction and noise has influence on dynamics, but is not needed for equilibrium properties.

Example: Nielsen *et al.*, J. Chem. Phys. **119** (2003) 2043.

DPD

We can also describe the space and time-dependent *densities* as the important variables (e.g. described on a grid of points), and consider all detailed degrees of freedom as unimportant. This leads first to *mesoscopic dynamics* (still including noise), and for even coarser averaging to the macroscopic *Navier-Stokes equation*.

The Navier-Stokes equation is normally solved on a grid of points.

Dissipative Particle Dynamics attempts to solve the Navier-Stokes equations using an ensemble of special particles.

Originally proposed by Hoogerbrugge and Koelman, Europhys. Lett. **19** (1992) 155.

Improved by Español, Warren, Flekkoy, Coveney.

See article by Español in SIMU Newsletter Issue 4, Chapter III, `http://simu.ulb.ac.be/newsletters/N4III.pdf`