

Simulation of Biomolecules

Molecular Dynamics – Part II:

- NPT ensembles: barostats
- Constrained MD
- Langevin Dynamics
- Brownian Dynamics

MD simulations at constant pressure

- Most experiments are performed at constant pressure instead of constant volume
⇒ **isothermal-isobaric ensemble**
- The volume is thus a dynamical variable that changes during the simulation.
- The pressure of a classical N -body system can be calculated using **Clausius virial theorem**,

$$P = \frac{2}{3V} (E_{\text{kin}} - \Xi) \quad (1)$$

with the box volume V , the kinetic energy E_{kin} and the inner virial for pairwise additive interactions

$$\Xi = \frac{1}{2} \sum_{i < j} \mathbf{r}_{ij} \cdot \mathbf{f}(\mathbf{r}_{ij}) \quad (2)$$

$\mathbf{f}(\mathbf{r}_{ij})$ is the force between particles i and j at a distance \mathbf{r}_{ij} .

MD simulations at constant pressure

Derivation of eq. (1): The asymptotic average of the derivative of a bounded function is zero. Intuitively, if you drive around a parking lot (the simulation box) for a long time, your average velocity approaches zero, because as time elapses your net distance traveled does not increase. Formally this can be expressed by noting that, for any constant k and function $r(t)$ bounded such that $|r(t_2) - r(t_1)| < k$ for all t_1 and t_2 , the average of the derivative of r over the range from t_1 to t_2 is

$$\langle \dot{\mathbf{r}} \rangle = \left(\frac{1}{t_2 - t_1} \right) \int_{t_1}^{t_2} \frac{d\mathbf{r}}{dt} dt = \frac{\mathbf{r}(t_2) - \mathbf{r}(t_1)}{t_2 - t_1} \quad (3)$$

The magnitude of the numerator is bounded whereas the time interval $t_2 - t_1$ in the denominator can be increased without limit, so the asymptotic average of $d\mathbf{r}/dt$ as the time interval increases is zero, i.e.,

$$\left| \frac{\mathbf{r}(t_2) - \mathbf{r}(t_1)}{t_2 - t_1} \right| < \frac{k}{t_2 - t_1} \rightarrow 0 \quad (4)$$

If both \mathbf{r} and $d\mathbf{r}/dt$ are bounded functions of t , then so is their product, and it follows from the product rule that

MD simulations at constant pressure

Derivation of eq. (1), continued:

$$\left\langle \frac{d(\mathbf{r} \cdot \dot{\mathbf{r}})}{dt} \right\rangle = \langle \mathbf{r} \cdot \ddot{\mathbf{r}} + |\dot{\mathbf{r}}|^2 \rangle = \langle \mathbf{r} \cdot \ddot{\mathbf{r}} \rangle + \langle |\dot{\mathbf{r}}|^2 \rangle = 0 \quad (5)$$

Now, if \mathbf{r} denotes the spatial position of a particle of mass m , then $m\ddot{\mathbf{r}}$ equals the net force \mathbf{f} on the particle (by Newton's second law), and $m|\dot{\mathbf{r}}|^2$ is twice the kinetic energy E_{kin} of the particle. Thus if we multiply through the above equation by m and consider a set of N particles, we get

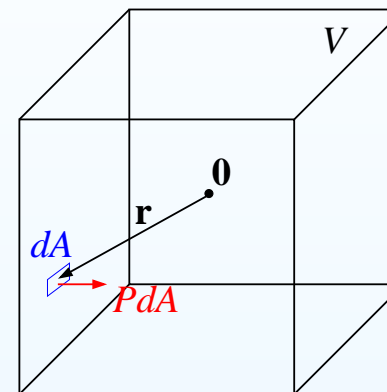
$$\left\langle \sum_{i=1}^N (\mathbf{r}_i \cdot \mathbf{f}_{\text{tot},i}) \right\rangle + 2E_{\text{kin}} = 0 \quad (6)$$

The term $\sum_{i=1}^N \mathbf{r}_i \cdot \mathbf{f}_{\text{tot},i}$ is called the **virial** and can be decomposed into an outer and inner virial denoted as W and Ξ , respectively. W can be calculated assuming that the particles are trapped in a box with volume V and exert a pressure P onto the walls. That means, that a wall element exerts a force $p dA$ onto nearby particles and is directed inside the box.

MD simulations at constant pressure

Derivation of eq. (1), continued:

\mathbf{r} denotes the vector from the origin to the wall element dA , which exerts a force $P\mathbf{n}dA$ (with \mathbf{n} as the vector normal to the surface element dA) on the **nearby** particles i , thus $\mathbf{r}_i \rightarrow \mathbf{r}$.



The contribution of dA to the outer virial can thus be written as

$$\sum_{i=1}^N \mathbf{r}_i \cdot \mathbf{f}_{P,i} = \mathbf{r} \cdot \sum_{i=1}^N \mathbf{f}_{P,i} = -P \mathbf{r} \cdot \mathbf{n} dA \quad (7)$$

By integration over the whole surface and using the divergence theorem we then obtain

$$W = -P \int_{\partial V} \mathbf{r} \cdot \mathbf{n} dA = -P \int_V \text{div } \mathbf{r} dV = -3PV \quad (8)$$

where we have used that the divergence of a vector field \mathbf{F} is $\text{div } \mathbf{F} = \sum_{i=1}^n \partial F_i / \partial x_i$ from which $\text{div } \mathbf{r} = 3$ immediately follows.

MD simulations at constant pressure

Derivation of eq. (1), continued:

Combining eqs. (6) and (8) gives

$$\Xi - 3PV + 2E_{\text{kin}} = 0 \quad \Rightarrow \quad P = \frac{2}{3V} \left(E_{\text{kin}} + \frac{1}{2} \sum_{i=1}^N \mathbf{r}_i \cdot \mathbf{f}_i \right) \quad (9)$$

For pairwise interactions, Ξ is more conveniently expressed in a form which is explicitly independent of the origin of coordinates, yet dependent on interatomic distances. This is done by expressing \mathbf{f}_i as the sum of forces \mathbf{f}_{ij} on atom i due to atom j :

$$\sum_i \mathbf{r}_i \cdot \mathbf{f}_i = \sum_i \sum_{j \neq i} \mathbf{r}_i \cdot \mathbf{f}_{ij} = \frac{1}{2} \sum_i \sum_{j \neq i} \mathbf{r}_i \cdot \mathbf{f}_{ij} + \mathbf{r}_j \cdot \mathbf{f}_{ji}$$

The second equality follows because the indices i and j are equivalent. Newton's third law $\mathbf{f}_{ji} = -\mathbf{f}_{ij}$ is used to switch indices:

$$\sum_i \sum_{j \neq i} \mathbf{r}_i \cdot \mathbf{f}_i = \frac{1}{2} \sum_i \sum_{j \neq i} (\mathbf{r}_i - \mathbf{r}_j) \cdot \mathbf{f}_{ij} = \frac{1}{2} \sum_i \sum_{j \neq i} \mathbf{r}_{ij} \cdot \mathbf{f}_{ij} = \sum_i \sum_{j > i} \mathbf{r}_{ij} \cdot \mathbf{f}_{ij} \quad (10)$$

Combining eqs. (10) and (9) gives the expression for the pressure in eq. (1).

MD simulations at constant pressure

- The above derivation is not really valid for infinite periodic systems since there are no container walls and no external forces. Nonetheless, the result is the same!
- The pressure is actually **not a scalar** (as supposed above) but a **second order tensor**:

$$\mathbf{P} = \begin{pmatrix} P_{xx} & P_{xy} & P_{xz} \\ P_{yx} & P_{yy} & P_{yz} \\ P_{zx} & P_{zy} & P_{zz} \end{pmatrix} \quad (11)$$

where, e.g., the tensor element P_{xy} is the force in y direction acting on the surface element with its vector normal in x direction.

- Only in isotropic systems, i.e., $P = P_{xx} = P_{yy} = P_{zz}$, can the pressure be expressed as a scalar:

$$P = \text{Tr}(\mathbf{P})/3$$

which is in this case known as the hydrostatic pressure.

MD simulations at constant pressure

Barostats:

- Correcting the pressure in a simulation can be achieved through a change in the inner virial Ξ by scaling the inter particle distances. This is the common procedure in all barostats described below.
- The ideas in pressure coupling methods are very similar to those in temperature coupling methods.
- Barostats with constant box shape
 - Berendsen barostat
 - Andersen barostat (Nosé-Hoover, Martyna-Tuckerman-Klein, Nosé-Hoover Langevin piston barostats)
- Barostats for changing box shape
 - Parrinello-Rahman barostat

Berendsen barostat

- The Berendsen barostat is very similar to the Berendsen thermostat.
- With the Berendsen barostat the system is made to obey the equation of motion at the beginning of each time step

$$\frac{dP(t)}{dt} = \frac{P_{\text{md}} - P(t)}{\tau_P}$$

where $P(t)$ is the instantaneous pressure, P_{md} is the desired pressure, and τ_P is the barostat relaxation time constant.

- This leads to cell size variations, where at each step the MD cell volume is scaled by a factor η , and the coordinates and cell vectors by $\eta^{1/3}$:

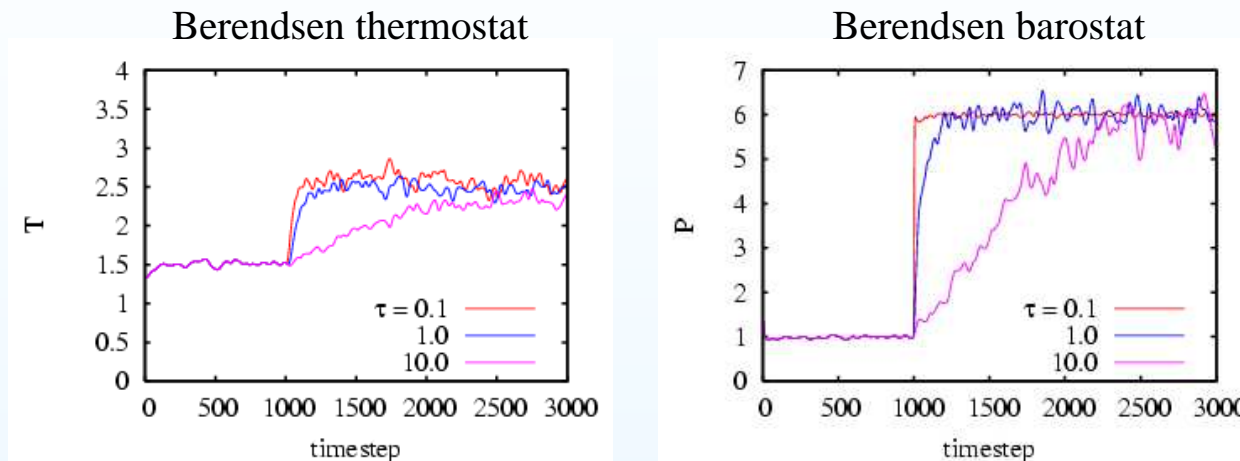
$$\eta(t) = 1 - \frac{\Delta t}{\tau_P} \gamma (P_{\text{md}} - P(t))$$

where γ is the isothermal compressibility of the system.

Berendsen barostat

- **Isotropic scaling:** the same η for x , y and z direction
Anisotropic scaling: different scaling factors for different dimensions (cell shape can change between , e.g., box and cube)
- γ is usually a specified constant which takes to be the isothermal compressibility of liquid water. The exact value is not critical to the algorithm as it relies on the ratio γ/τ_P .
- τ_P is a specified time constant for pressure fluctuations, usually supplied by the user.
- For the strength of the coupling between the system and the "pressure bath", the same applies as for τ in the Berendsen thermostat: The larger τ_P , the weaker the coupling:

Berendsen barostat



- The Berendsen barostat and the thermostat are independent and fully separable.

The same publication for the Berendsen thermostat and barostat:
Berendsen et al, J. Chem. Phys. 81, 3684 (1984)

Andersen barostat

- Unlike the Berendsen barostat is the Andersen barostat not similar in idea to the thermostat of the same name.
- The Andersen barostat is an extended system method (compare with the Nosé-Hoover thermostat), which involves coupling the system to an external variable V , the volume of the simulation box.
- This coupling mimics the action of a piston on a real system.
- The piston has a 'mass' Q (which actually has the units of $(\text{mass})(\text{length})^{-4}$) and is associated with a kinetic and potential energy:

$$E_{V,\text{kin}} = \frac{1}{2}Q\dot{V}^2 \quad E_{V,\text{pot}} = P_{\text{md}}V \quad (12)$$

i.e., V is the coordinate of the piston and $P_{\text{md}}V$ is the potential energy resulting from an external pressure P_{md} acting on the piston.

Andersen barostat

- The coordinates of the molecules are given in terms of scaled variables, s_i :

$$\mathbf{r}_i = V^{1/3} \mathbf{s}_i \quad \mathbf{v}_i = V^{1/3} \dot{\mathbf{s}}_i \quad (13)$$

- The equations of motion are then obtained as

$$\ddot{\mathbf{s}}_i = \frac{\mathbf{f}_i}{m_i V^{1/3}} - \frac{2}{3} \frac{\dot{\mathbf{s}}_i \dot{V}}{V} \quad \ddot{V} = \frac{P(t) - P_{\text{md}}}{Q} \quad (14)$$

where the forces \mathbf{f}_i and the instantaneous pressure $P(t)$ are calculated using the unscaled coordinates and momenta of the molecules.

- The Hamiltonian of the system,

$$H = E_{\text{kin}}(\mathbf{R}) + E_{\text{pot}}(\mathbf{R}) + E_{V,\text{kin}} + E_{V,\text{pot}}$$

is conserved, being equal to the enthalpy of the system plus an additional term of $(1/2)k_{\text{B}}T$ associated with the volume fluctuation (the piston).

Andersen barostat

- Thus the equations of motion (14) produce trajectories which sample the **isobaric-isoenthalpic ensemble**. The combination with one of the constant-temperature methods allows NPT simulations.
- The parameter Q , the 'piston mass', is a user supplied parameter.
- A low 'mass' will result in rapid box size oscillations, which are not damped very efficiently by the motions of the molecules.
- A large 'mass' will give rise to a slow adjustment of the volume, i.e., the pressure, and infinite mass restores normal MD. (compare with the mass Q in the Nosé-Hoover thermostat).
- The Nosé-Hoover barostat and the Martyna-Tuckerman-Klein barostat are both based on the Andersen barostat.

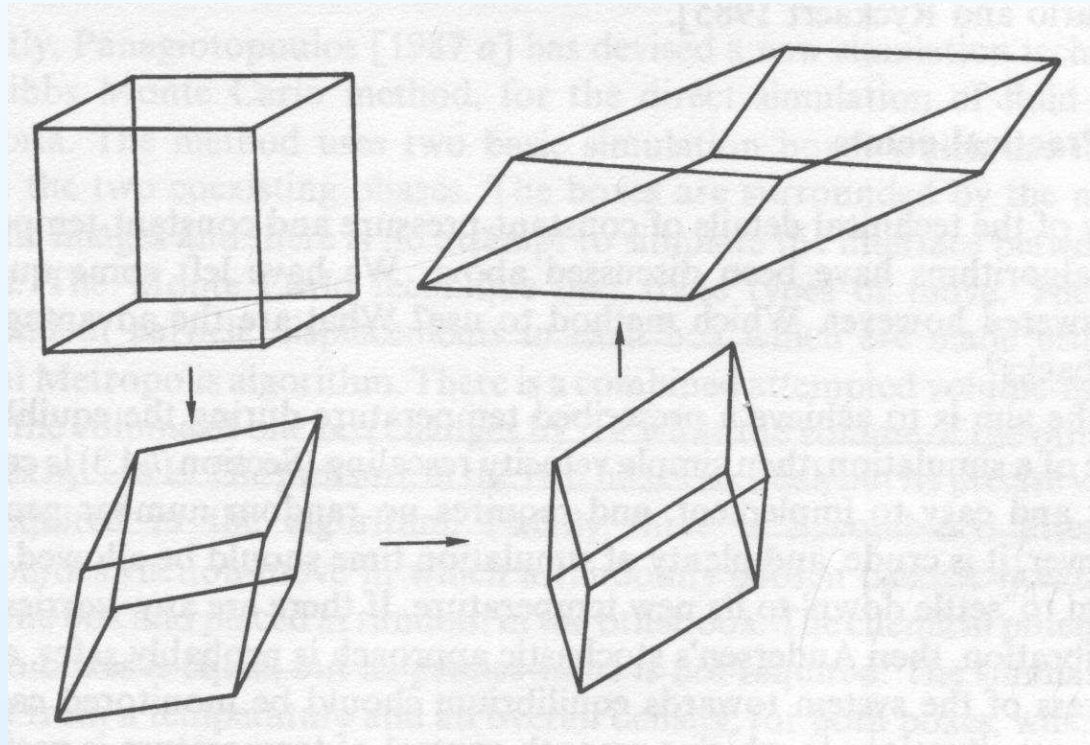
H. C. Andersen. *Molecular dynamics at constant pressure and/ or temperature*. J. Chem. Phys. 72 (1980), 2384

W. G. Hoover. *Constant pressure equations of motion*. Phys. Rev. A 31 (1986), 1695

G. J. Martyna, D. J. Tobias and M. L. Klein. *Constant pressure molecular-dynamics algorithms* J. Chem. Phys. 101 (1994), 4177

Parrinello-Rahman barostat

- Extension of the constant-pressure method of Andersen by Parrinello and Rahman to allow for the simulation box to change shape as well as size.
- Not of great use in liquid-state simulations but particularly helpful in the study of solids, since it allows for phase changes in the simulation:



Parrinello-Rahman barostat

- The cell can have an arbitrary shape, which can be described by the three vectors \mathbf{a} , \mathbf{b} , \mathbf{c} representing the sides of the cell. The vectors can be of different lengths.
- The volume is given by

$$V = \det \mathbf{H} = \mathbf{a} \cdot (\mathbf{b} \times \mathbf{c}) \quad (15)$$

where $\mathbf{H} = \{\mathbf{a}, \mathbf{b}, \mathbf{c}\}$ is a 3×3 matrix.

- The scaled coordinates are now introduced through

$$\mathbf{r}_i = \mathbf{H} \mathbf{s}_i \quad \text{compare with eq. (13)} \quad (16)$$

- The potential and kinetic energies associated with the fluctuating volume [compare with eq. (14)] are

$$E_{\text{pot},V} = PV \quad E_{\text{kin},V} = \frac{1}{2} Q \text{Tr}(\dot{\mathbf{H}}^T \dot{\mathbf{H}}) \quad (17)$$

where T stands for transpose and Q is again the cell ‘mass’ (see Andersen thermostat).

Parrinello-Rahman barostat

- The equations of motion are then obtained as

$$\ddot{\mathbf{s}}_i = \frac{\mathbf{H}^{-1}\mathbf{f}_i}{m} - \mathbf{G}^{-1}\dot{\mathbf{G}}\dot{\mathbf{s}} \quad \ddot{\mathbf{H}} = \frac{(\mathbf{P} - \mathbf{1}P_{\text{md}})V(\mathbf{H}^{-1})^T}{Q} \quad (18)$$

where $\mathbf{G} = \mathbf{H}^T\mathbf{H}$ is a metric tensor and the pressure tensor (11) was used.

- The similarity between eqs. (18) and the equations of motion for the Andersen thermostat (14) are obvious.

M. Parrinello and A. Rahman:

(i) Phys. Rev. Lett. 45 (1980) 1196

(ii) J. Appl. Phys. 52 (1981) 7182

(iii) J. Chem. Phys. 76 (1982) 2662

Which thermostat and barostat to use?

- Do not use any trivial quenching scaling methods. They suppress fluctuations, and do not provide the correct statistical ensembles.
- Berendsen T and P control are simple to implement and use. In addition, they can steadily drive the system state far from equilibrium toward equilibrated state. This is very handy at the start of the simulation, where significant fluctuations may take place.
- However, if you need to produce the correct statistical ensemble, you will need to use other methods. Nosé-Hoover thermostat with Rahman-Parrinello barostat is a possible option there.
- It also depends on which thermostats and barostats are implemented in the MD package currently used, for instance,
 - NAMD: Langevin thermostat, Nosé-Hoover Langevin piston barostat
 - GROMACS: Berendsen and Nosé-Hoover thermostats, Berendsen barostat
 - AMBER: Berendsen thermostat and barostat

Constrained Molecular Dynamics

- To improve the efficiency of MD simulations one can fix the lengths of the covalent bonds, i.e., decreasing the number of degrees of freedom.
- From the physical point of view, this approach introduces additional constraint forces that act on the atoms along their bonds in accordance with Newton's third law.
- Hence the bond between atoms i and j gives rise to a pair of forces: the force $\mathbf{g}_{ij} = \lambda_{ij}(\mathbf{r}_j - \mathbf{r}_i)$ acting on atom i and the force $\mathbf{g}_{ji} = \lambda_{ji}(\mathbf{r}_i - \mathbf{r}_j)$ acting on atom j , with equal coefficients λ_{ji} and λ_{ij} .
- The modified equations of motion, in combination with the conditions $|\mathbf{r}_j(\Delta t) - \mathbf{r}_i(\Delta t)| = |\mathbf{r}_j(0) - \mathbf{r}_i(0)|$, determines a system of non-linear equations with respect to the coefficients λ_{ij} .
- This system can be solved numerically by standard methods, such as the SHAKE, RATTLE or LINCS algorithms.

Langevin Dynamics

- We have seen that one way to construct a thermostat is to introduce random forces and to compensate for their overheating effect using phenomenological ‘friction’ terms.
- Here we consider the Langevin equation, which is often used in combination with implicit solvent models:

$$\ddot{\mathbf{r}}_i = \mathbf{f}_i/m_i - \gamma \dot{\mathbf{r}}_i + \mathbf{A}_i(t)/m_i, \quad (19)$$

where the force $\mathbf{A}_i(t)$ is a random function of time that fluctuates very rapidly in comparison with the time step Δt and the characteristic time $1/\gamma$. It does not depend on the positions and velocities.

- For any time interval of interest, $\Delta\tau$, the forces $\mathbf{A}_i(t)$ and $\mathbf{A}_i(t + \Delta\tau)$ are assumed to be not correlated in space and time:

$$\langle \mathbf{A}_i(t) \rangle = 0 \quad (20)$$

$$\langle A_{i,\alpha}(t_1) A_{i,\alpha}(t_2) \rangle = 2m_i \gamma_i k_B T \delta(t_1 - t_2); \quad \alpha = x, y, z. \quad (21)$$

Langevin Dynamics

- The physical origin of the random force $\mathbf{A}_i(t)$ is the collisions of atom i with the molecules of solvent.
- In a collision occurring at the time τ , the atom gains an additional random velocity $d\mathbf{v}(\tau) = \mathbf{A}(\tau)d\tau/m$, where $d\tau$ is the collision duration (the index i is omitted). After this event the velocity decays exponentially as

$$d\mathbf{v}(\tau) e^{-\gamma(t-\tau)}. \quad (22)$$

- The corresponding displacement of the atom at the time t is

$$d\mathbf{v}(\tau) \int_{\tau}^t e^{-\gamma(t'-\tau)} dt' = \frac{d\mathbf{v}(\tau)}{\gamma} (1 - e^{-\gamma(t-\tau)}). \quad (23)$$

- Assuming that t corresponds to the end of the time step Δt , and integrating Eq. (23) over the collision time τ between 0 to Δt , we obtain the net random displacement of the atom during the time step:

Langevin Dynamics

$$\mathbf{r}_{\text{coll}}(\Delta t) = \int_0^{\Delta t} \frac{\mathbf{A}(\tau) d\tau}{m\gamma} (1 - e^{-\gamma(\Delta t - \tau)}). \quad (24)$$

- The net random gain in velocity at the end of the step can be found by integration of expression (22):

$$\mathbf{v}_{\text{coll}}(\Delta t) = \int_0^{\Delta t} \frac{\mathbf{A}(\tau) d\tau}{m} e^{-\gamma(\Delta t - \tau)}. \quad (25)$$

- Both $\mathbf{v}_{\text{coll}}(\Delta t)$ and $\mathbf{r}_{\text{coll}}(\Delta t)$ are normally distributed and do not depend on the state of the system.
- Since the random displacement is independent of the deterministic motion of the system, the former term can simply be added to the latter.

Langevin Dynamics

The integration algorithm then becomes:

$$\mathbf{r}(\Delta t) = \mathbf{r}(0) + \frac{\dot{\mathbf{r}}(0)}{\gamma} (1 - e^{-\gamma\Delta t}) + \frac{\mathbf{f}(0)}{m\gamma^2} [\gamma\Delta t - (1 - e^{-\gamma\Delta t})] + \mathbf{r}_{\text{coll}}(\Delta t) \quad (26)$$

$$\dot{\mathbf{r}}(\Delta t) = \dot{\mathbf{r}}(0) e^{-\gamma\Delta t} + \frac{1}{m\gamma} [\mathbf{f}(0) e^{-\frac{1}{2}\gamma\Delta t} + \mathbf{f}(\Delta t)] (1 - e^{-\frac{1}{2}\gamma\Delta t}) + \mathbf{v}_{\text{coll}}(\Delta t) \quad (27)$$

The random values $\mathbf{r}_{\text{coll}}(\Delta t)$ and $\mathbf{v}_{\text{coll}}(\Delta t)$ can be generated in the following way: Let χ_1 and χ_2 be independent random numbers with a normal distribution of unit variance. Then

$$r_{\text{coll}} = \chi_1 \sqrt{\langle r_{\text{coll}}^2 \rangle} \quad (28)$$

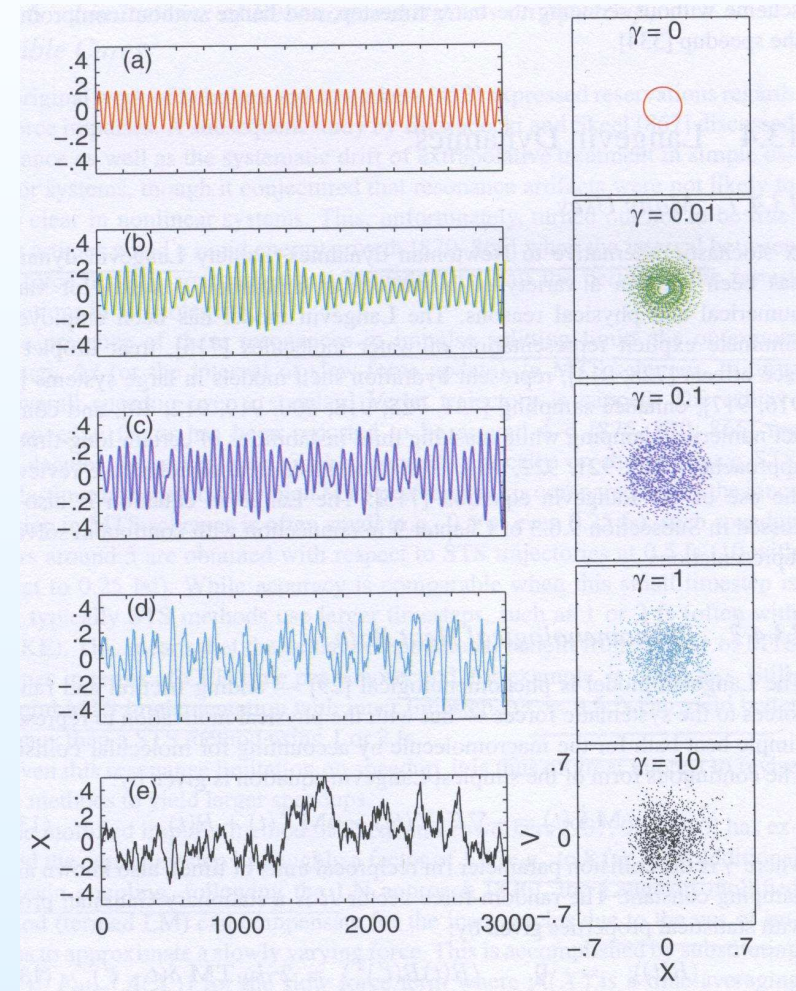
$$v_{\text{coll}} = \chi_1 \sqrt{\langle r_{\text{coll}} v_{\text{coll}} \rangle^2 / \langle r_{\text{coll}}^2 \rangle} + \chi_2 \sqrt{\langle v_{\text{coll}}^2 \rangle - \langle r_{\text{coll}} v_{\text{coll}} \rangle^2 / \langle r_{\text{coll}}^2 \rangle} \quad (29)$$

where $\langle r_{\text{coll}} \rangle$, $\langle v_{\text{coll}} \rangle$ and $\langle r_{\text{coll}} v_{\text{coll}} \rangle$ do not depend on the current state of the system, hence, need only be calculated only once at the beginning of a simulation run (for each particle in the system).

Langevin Dynamics

The effect of γ :

- The magnitude of γ determines the relative strength of the *inertial* forces with respect to the random (*external*) forces.
- As γ increases, one goes from the inertial to the diffusive (Brownian) regime.
- For the harmonic oscillator (right figure) the harmonic motion and closed, circular trajectories in phase space, characteristic at zero viscosity, change as the random forces increase.



Langevin Dynamics

- A physical value for γ can be chosen according to Stokes' law for a hydrodynamic particle of radius a :

$$\gamma = 6\pi\eta a/m \quad (30)$$

where m is the particle's mass and η is the solvent viscosity.

- From this equation the estimated value for water at room temperature is $\gamma = 54.9 \text{ ps}^{-1}$.
- In Langevin simulations with implicit solvent values between 5 and 20 ps^{-1} are usually used.

Brownian Dynamics

- The mathematical theory of Brownian motion is rich and subtle.
- Important contributors to the theory include Einstein and Planck.
- The term *Brownian* is credited to the botanist Robert Brown, who in 1827 observed that fine particles — like pollen grains, dust, and soot — immersed in a fluid undergo a continuous irregular motion due to collisions of the particles with the solvent molecules.
- The effective force on such particles originates from friction, as governed by Stokes' law (30), and a fluctuating random force.
- Here, Brownian Dynamics (BD) will be presented as an extension to the Langevin model. Only a short introduction to BD will be given.

Brownian Dynamics

- The Langevin equation (19) can be extended to include **hydrodynamic coupling** by using a friction tensor Γ to describe the frictional interactions between particles. Γ replaces the single parameter γ in (19):

$$m_i \ddot{\mathbf{r}}_i = \mathbf{f}_i - \sum_j \mathbf{Z}_{ij} \dot{\mathbf{r}}_j + \mathbf{A}_i(t) \quad (31)$$

where $\mathbf{Z}_{ij} = m_i \Gamma_{ij}$

- If the systematic force (i.e. the internal force of the system) does not change much on the time scale of the velocity correlation function [remember: the velocity decays exponentially after a collision according to eq. (22)], the average acceleration becomes small and can be neglected (**non-inertial dynamics**):

$$0 \approx \mathbf{f}_i - \sum_j \mathbf{Z}_{ij} \dot{\mathbf{r}}_j + \mathbf{A}_i(t) \quad (32)$$

Brownian Dynamics

Hence, the velocities $\dot{\mathbf{r}}_j(t)$ can be solved from matrix equation:

$$\dot{\mathbf{r}}(t) = \mathbf{Z}^{-1} \mathbf{f}(t) + \mathbf{Z}^{-1} \mathbf{A}(t) \quad (33)$$

This can be rewritten in *Brownian dynamics* form:

$$\dot{\mathbf{r}}(t) = \frac{\mathbf{D}}{k_{\text{B}}T} \mathbf{f}(t) + \mathbf{A}'(t) \quad (34)$$

where \mathbf{D} is the **diffusion tensor**: $\mathbf{D} = k_{\text{B}}T\mathbf{Z}^{-1}$

The mean and co-variance of the random forces $\mathbf{A}'(t) = \mathbf{Z}^{-1} \mathbf{A}(t)$ are

$$\langle A'_{i,a}(t) \rangle = 0 \quad \langle A'_{i,a}(t) A'_{j,a}(t + \Delta t) \rangle = 2\mathbf{D}_{ij} \delta(\Delta t) \quad (35)$$

i.e., the random forces are coupled in space (through \mathbf{D}), but without memory.

Brownian Dynamics

- Without hydrodynamic coupling, i.e., no off-diagonal elements in \mathbf{D} , the equations of motion simplify, leading to following numerical solution:

$$\mathbf{r}_i(\Delta t) = \mathbf{r}_i(0) + (D_i \mathbf{f}_i(0)/k_B T) \Delta t + \mathbf{A}'_i(\Delta t), \quad (36)$$

with

$$\langle A'_{i,a}(\Delta t) \rangle = 0 \quad \langle A'^2_{i,a}(\Delta t) \rangle = 2D_i \Delta t \quad (37)$$

- Eq. (36) shows that the solvent effects are sufficiently large to make inertial forces negligible so that the motion is overall Brownian and random in character.
- BD is a very useful tool, especially for coarse-grained modelling, because, in this case, the condition $\gamma_i \Delta t \gg 1$ can be easily satisfied (high friction limit). If the (pseudo)atoms are represented by spheres of radius a_i , then the diffusion coefficient is defined by the Stokes formula (30):
 $D_i/k_B T = 1/6\pi\eta a_i$, i.e., small diffusion \iff high friction.

Comparison of sampling techniques

| Method | Underlying equation | Trajectories | Solvent | Realistic dynamics | Typical time step | |
|--------|---------------------|-------------------|--------------------|--------------------|-------------------|-----------------|
| MD | ND | Newton equation | deterministic | explicit | possible | $\sim 1 - 2$ fs |
| | LD | Langevin equation | stochastic | explicit, implicit | possible | ~ 3 fs |
| BD | diffusion equation | stochastic | implicit | possible | ~ 30 fs | |
| MC | detailed balance | stochastic | typically implicit | not possible | not defined | |

ND: Newtonian Dynamics

LD: Langevin Dynamics

BD: Brownian Dynamics

MC: Monte Carlo (next lecture, 06 October 2010, 9:00-11:00 !!!)