Molecular Dynamics simulations of Biomolecules

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Computational Biochemistry

Master in Theoretical Chemistry and Computational Modelling

TCCM

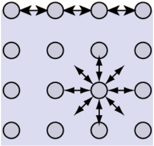
Index

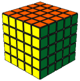
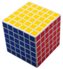
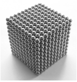
Solvents

- Most of chemical reactions take place in solution
- Good solvent {
  - Inert
  - Able to solve all reactants
  - Adequate ebullition point
  - Easy to separate
- Inert $\neq$ neutral $\Rightarrow$ {
  - Energy fluxes
  - Intermolecular interactions
- TD Quantum-mechanical simulations $\Rightarrow$ computationally forbidden.
- Molecular Dynamics

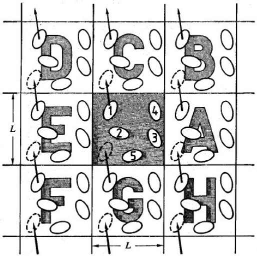
Periodic boundary conditions

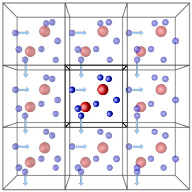
- Cubic box ⇒ Surface effects ⇒ Surface tension



-  $5^3 = 125$ molecules
  - Surface: $25+(25-5)+(25-9)+(25-9)+(25-13)+(25-16)=98$ (78.4 %)
  - Bulk: $125-98=27$ (21.6 %)
-  $6^3 = 216$ molecules
  - Surface: $36+(36-6)+(36-11)+(36-11)+(36-16)+(36-20)=152$ (70.4 %)
  - Bulk: $216-152=64$ (29.6 %)
-  $10^3 = 1000$ mol.
  - Surface: $100+(100-10)+(100-19)+(100-19)+(100-28)+(100-36)=488$ (48.8 %)
  - Bulk: $1000-488=512$ (51.2 %)

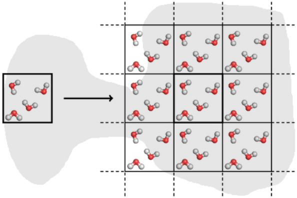
Periodic boundary conditions

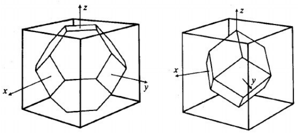




- Central box ⇒ infinite lattice
- Periodic image in each box moves in the same way
- If a molecule leaves a box, one of its images will enter through the opposite face
- The number density in all boxes is constant
- Only $(\boldsymbol{r}_i, \boldsymbol{p}_i)$ of the molecules in the central box are stored

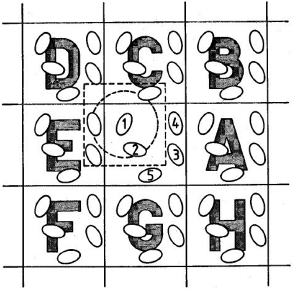
Periodic boundary conditions





- Special conditions {
  - Phase transitions
  - Supercritical fluids
- Test ⇒ increase box size
- Other boxes ⇒ space filling polyhedra
  - Rombic dodecahedron
  - Truncated octahedron

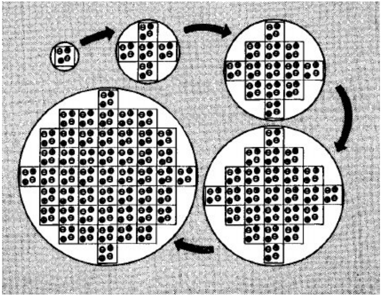
Periodic boundary conditions



- Infinite number of interactions (potential energy and forces)
- Minimun Image Convention ⇒ each molecule interacts with the closest periodic image of the other $N-1$ molecules
- Define a box centered in molecule 1 ⇒ interacts with 2, 3_{E}, 4_{E}, and 5_{C}
- Pairwise-additive interactions ⇒ $\frac{1}{2}N(N-1)$ terms

Long-range interactions

Ewald summation



X. Quian and T. Schlick, Journal of Chemical Physics **116**, 5971 (2002)

$$V = \frac{1}{2}\sum_{\boldsymbol{n}}\sum_{i,j}^{\prime} \frac{q_i\, q_j}{|\boldsymbol{r}_{ij}+\boldsymbol{n}|}$$

$$\boldsymbol{n} = (n_x\, L, n_y\, L, n_z\, L)$$

$$\sum{}' \Rightarrow i = j,\ \boldsymbol{n} = 0$$

$$\mathcal{V}^{zz}(\varepsilon_s = 1) = \tfrac{1}{2}\sum_{i=1}^{N}\sum_{j=1}^{N}\left(\sum_{|\mathbf{n}|=0}^{\infty\,\prime} z_i z_j \frac{\mathrm{erfc}(\kappa|\mathbf{r}_{ij}+\mathbf{n}|)}{|\mathbf{r}_{ij}+\mathbf{n}|} + (1/\pi L^3)\sum_{\mathbf{k}\neq 0} z_i z_j (4\pi^2/k^2)\exp(-k^2/4\kappa^2)\cos(\mathbf{k}\cdot\mathbf{r}_{ij})\right) - (\kappa/\pi^{1/2})\sum_{i=1}^{N} z_i^2 + (2\pi/3L^3)\left|\sum_{i=1}^{N} z_i \mathbf{r}_i\right|^2 .$$

Hamilton's equations

- Newton's second law

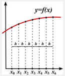
$$\boldsymbol{F}_i = m_i\, \boldsymbol{a}_i = m_i \frac{d^2 \boldsymbol{r}_i}{dt^2} \Rightarrow \text{Second order differential equation}$$

- Hamilton's equations

$$\left.\begin{array}{l} \dot{\boldsymbol{r}}_i = \boldsymbol{p}_i / m_i \\ \dot{\boldsymbol{p}}_i = \boldsymbol{F}_i \end{array}\right\} \Rightarrow \text{Coupled first order differential equations}$$

- Equivalent formulations $\Rightarrow \boldsymbol{F}_i = \dot{\boldsymbol{p}}_i = m_i\, \ddot{r}_i = m_i\, \boldsymbol{a}_i$

- Forces $\Rightarrow \boldsymbol{F}_i = -\nabla^2_{\boldsymbol{r}_i} V = -\left(\frac{\partial V}{\partial x_i}, \frac{\partial V}{\partial y_i}, \frac{\partial V}{\partial z_i}\right)$



Verlet algorithm

$$\boldsymbol{r}(t) = \boldsymbol{r}(t_0) + \underbrace{\dot{\boldsymbol{r}}(t_0)}_{\boldsymbol{v}(t_0)}(t-t_0) + \frac{1}{2}\underbrace{\ddot{\boldsymbol{r}}(t_0)}_{\boldsymbol{a}(t_0)}(t-t_0)^2 + \cancel{O((t-t_0)^3}$$

$$= \boldsymbol{r}(t_0) + \boldsymbol{v}(t_0)(t-t_0) + \frac{1}{2}\boldsymbol{a}(t_0)(t-t_0)^2 \qquad (1)$$

$$\boldsymbol{r}(t\pm\delta) = \boldsymbol{r}(t_0) + \boldsymbol{v}(t_0)(t\pm\delta-t_0) + \frac{1}{2}\boldsymbol{a}(t_0)(t\pm\delta-t_0)^2 \qquad (2)$$

$$\begin{aligned}
(1),(2) \Rightarrow \boldsymbol{r}(t+\delta)+\boldsymbol{r}(t-\delta)-2\,\boldsymbol{r}(t) &= \cancel{\boldsymbol{r}(t_0)}+\cancel{\boldsymbol{v}(t_0)(t+\delta-t_0)}+\tfrac{1}{2}\boldsymbol{a}(t_0)(t+\delta-t_0)^2 \\
&+\cancel{\boldsymbol{r}(t_0)}+\cancel{\boldsymbol{v}(t_0)(t-\delta-t_0)}+\tfrac{1}{2}\boldsymbol{a}(t_0)(t-\delta-t_0)^2 \\
&-\cancel{2\,\boldsymbol{r}(t_0)}-\cancel{2\,\boldsymbol{v}(t_0)(t-t_0)}-\boldsymbol{a}(t_0)\,(t-t_0)^2 \\
&=\tfrac{1}{2}\,\boldsymbol{a}(t_0)\Big(\cancel{(t-t_0)^2}+\delta^2+\cancel{2\,(t-t_0)\,\delta}\Big) \\
&+\tfrac{1}{2}\,\boldsymbol{a}(t_0)\Big(\cancel{(t-t_0)^2}+\delta^2-\cancel{2\,(t-t_0)\,\delta}\Big) \\
&-\cancel{\boldsymbol{a}(t_0)\,(t-t_0)^2}=\boldsymbol{a}(t_0)\,\delta^2
\end{aligned}$$

Verlet algorithm

$$\mathbf{r}(t+\delta) = 2\,\mathbf{r}(t) - \mathbf{r}(t-\delta) + \mathbf{a}(t_0)\,\delta^2$$

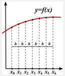
$$\boxed{\mathbf{r}(t_0+\delta) = 2\,\mathbf{r}(t_0) - \mathbf{r}(t_0-\delta) + \mathbf{a}(t_0)\,\delta^2} \Leftarrow \text{Verlet}$$

$$(1) \Rightarrow \dot{\mathbf{r}}(t) = \mathbf{v}(t) = \mathbf{v}(t_0) + \mathbf{a}(t_0)\,(t-t_0) \qquad (3)$$

$$\begin{aligned}
\mathbf{r}(t+\delta)-\mathbf{r}(t-\delta) &= \cancel{\mathbf{r}(t_0)} + \mathbf{v}(t_0)\,(\cancel{t}+\delta-\cancel{t_0}) + \tfrac{1}{2}\,\mathbf{a}(t_0)\,(t+\delta-t_0)^2 \\
&- \cancel{\mathbf{r}(t_0)} - \mathbf{v}(t_0)\,(\cancel{t}-\delta-\cancel{t_0}) - \tfrac{1}{2}\,\mathbf{a}(t_0)\,(t-\delta-t_0)^2 \\
&= 2\,\mathbf{v}(t_0)\,\delta + \tfrac{1}{2}\,\mathbf{a}(t_0)\left(\cancel{(t-t_0)^2} + \cancel{\delta^2} + 2\,(t-t_0)\,\delta - \cancel{(t-t_0)^2} - \cancel{\delta^2} + 2\,(t-t_0)\,\delta\right) \\
&= 2\,\mathbf{v}(t_0)\,\delta + 2\,\mathbf{a}(t_0)\,(t-t_0)\,\delta = 2\,\mathbf{v}(t)\,\delta
\end{aligned}$$

$$\mathbf{v}(t) = \frac{\mathbf{r}(t+\delta)-\mathbf{r}(t-\delta)}{2\,\delta}$$

$$\boxed{\mathbf{v}(t_0) = \frac{\mathbf{r}(t_0+\delta)-\mathbf{r}(t_0-\delta)}{2\,\delta}} \Leftarrow \text{Verlet}$$



Leap-grog algorithm

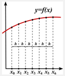
$$(3) \text{ with } t \to t_0 + \tfrac{\delta}{2} \Rightarrow \boldsymbol{v}(t_0 + \tfrac{\delta}{2}) = \boldsymbol{v}(t_0) + \boldsymbol{a}(t_0)\,(t_0 + \tfrac{\delta}{2} - t_0) = \boldsymbol{v}(t_0) + \tfrac{1}{2}\,\boldsymbol{a}(t_0)\,\delta \qquad (4)$$

$$\begin{aligned} (2) \text{ with } t \to t_0 \Rightarrow \boldsymbol{r}(t_0+\delta) &= \boldsymbol{r}(t_0) + \boldsymbol{v}(t_0)\,\delta + \tfrac{1}{2}\,\boldsymbol{a}(t_0)\,\delta^2 \\ &= \boldsymbol{r}(t_0) + \delta\left(\boldsymbol{v}(t_0) + \tfrac{1}{2}\,\boldsymbol{a}(t_0)\,\delta\right) \\ &\underset{(4)}{=} \boldsymbol{r}(t_0) + \boldsymbol{v}(t_0 + \tfrac{\delta}{2})\,\delta \end{aligned}$$

$$\boxed{\boldsymbol{r}(t_0+\delta) = \boldsymbol{r}(t_0) + \boldsymbol{v}(t_0 + \tfrac{\delta}{2})\,\delta} \Leftarrow \text{Leap-frog}$$

$$\left.\begin{aligned} (4) \Rightarrow \boldsymbol{v}(t_0+\tfrac{\delta}{2}) &= \boldsymbol{v}(t_0) + \tfrac{1}{2}\,\boldsymbol{a}(t_0)\,\delta \\ (4) \text{ with } \delta \to -\delta \Rightarrow \boldsymbol{v}(t_0-\tfrac{\delta}{2}) &= \boldsymbol{v}(t_0) - \tfrac{1}{2}\,\boldsymbol{a}(t_0)\,\delta \end{aligned}\right\} \boldsymbol{v}(t_0+\tfrac{\delta}{2}) - \boldsymbol{v}(t_0-\tfrac{\delta}{2}) = \boldsymbol{a}(t_0)\,\delta$$

$$\boxed{\boldsymbol{v}(t_0+\tfrac{\delta}{2}) = \boldsymbol{v}(t_0-\tfrac{\delta}{2}) + \boldsymbol{a}(t_0)\,\delta} \Leftarrow \text{Leap-frog}$$



Other algorithms

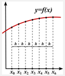
$$
\begin{aligned}
\boldsymbol{r}(t_0+\delta) &= \boldsymbol{r}(t_0) + \boldsymbol{v}(t_0)\,\delta + \tfrac{1}{2}\,\boldsymbol{a}(t_0)\,\delta^2 \\
\boldsymbol{v}(t_0+\tfrac{\delta}{2}) &= \boldsymbol{v}(t_0) + \tfrac{1}{2}\boldsymbol{a}(t_0)\,\delta \\
\boldsymbol{v}(t_0+\delta) &= \boldsymbol{v}(t_0+\tfrac{\delta}{2}) + \tfrac{1}{2}\boldsymbol{a}(t_0+\delta)\,\delta
\end{aligned}
$$

$\Leftarrow$ Velocity Verlet

$$
\begin{aligned}
\boldsymbol{r}(t_0+\delta) &= \boldsymbol{r}(t) + \boldsymbol{v}(t_0)\,\delta + \tfrac{2}{3}\,\boldsymbol{a}(t_0)\,\delta^2 - \tfrac{1}{6}\,\boldsymbol{a}(t_0-\delta)\,\delta^2 \\
\boldsymbol{v}(t_0+\delta) &= \boldsymbol{v}(t_0) + \tfrac{1}{3}\,\boldsymbol{a}(t_0+\delta)\,\delta + \tfrac{5}{6}\,\boldsymbol{a}(t_0)\,\delta - \tfrac{1}{6}\,\boldsymbol{a}(t_0-\delta)\,\delta
\end{aligned}
$$

$\Leftarrow$ Beeman

Verlet, Leap-frog, velocity Verlet, Beeman,... $\Rightarrow$ Similar global errors

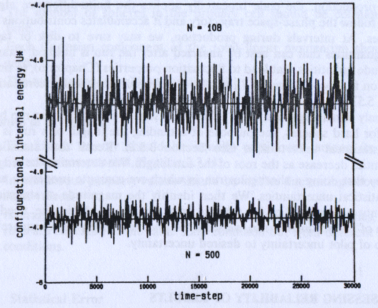


References

- L. Verlet. *Computer "experiments" on classical fluids. I. Thermodynamical properties of Lennard-Jones molecules.* Phys. Rev. **159**, 98-103 (1967).
- W.C. Swope, H.C. Andersen, P.H. Berens and K.R. Wilson. *Computer simulation method for the calculation of equilibrium constants for the formation of physical clusters of molecules: Application to small water clusters.* J. Chem. Phys. **76**, 637-649 (1982).
- W.H. Press, S.A: Teukolsly, W.T. Vetterling and B.P. Flanney. *Numerical recipes in Fortran 77.* Cambridge University Press. 1992. Chapter 16.7.

NVE ensemble

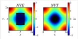
- *NVE* ensemble $\Rightarrow \begin{cases} N/V \;\rightarrow\; \text{density} \\ E \text{ constant} \rightarrow \text{ Hamilton's equations} \end{cases}$



$$E = \frac{p^2}{2\,m} + V(\boldsymbol{r})$$

$$\dot{E} = \frac{\cancel{2}\,\boldsymbol{p}\cdot\dot{\boldsymbol{p}}}{\cancel{2}\,m} + \dot{V}(\boldsymbol{r}) = \frac{\boldsymbol{p}\cdot\dot{\boldsymbol{p}}}{m} + \nabla_{\boldsymbol{r}} V \cdot \dot{\boldsymbol{r}}$$

$$= \frac{\boldsymbol{p}}{m}\cdot\left(\dot{\boldsymbol{p}} + \nabla_{\boldsymbol{r}} V\right) = 0 \;\Rightarrow\; \dot{\boldsymbol{p}} = -\nabla_{\boldsymbol{r}} V$$



NVT ensemble

- Equilibrium $\Rightarrow$ degree of freedoom $\Rightarrow$ $\frac{1}{2}\, k_{\mathrm{B}}\, T$

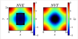
- Temperature $\Rightarrow K = \sum_{i=1}^{N} \frac{1}{2}\, m_i\, \mathbf{v}_i^2 = 3N \left(\frac{1}{2}\, k_{\mathrm{B}}\, T\right) \Rightarrow T = \frac{2\,K}{3N\,k_{\mathrm{B}}}$

- Scaling

$$\left.\begin{array}{r} K = \sum_{i=1}^{N} \frac{1}{2}\, m_i\, \mathbf{v}_i^2 = 3N \left(\frac{1}{2}\, k_{\mathrm{B}}\, T\right) \\ \sum_{i=1}^{N} \frac{1}{2}\, m_i\, \mathbf{v}_i'^2 = 3N \left(\frac{1}{2}\, k_{\mathrm{B}}\, T_f\right) \end{array}\right\} \frac{\sum_i m_i\, \mathbf{v}_i^2}{\sum_i m_i\, \mathbf{v}_i'^2} = \frac{T}{T_f} \rightarrow \sum_i m_i\, \mathbf{v}_i^2 = \sum_i m_i\, \mathbf{v}_i'^2\, \frac{T}{T_f}$$

$$\mathbf{v}_i^2 = \mathbf{v}_i'^2\, \frac{T}{T_f}$$

$$\mathbf{v}_i' = \frac{T_f}{T}\, \mathbf{v}_i$$



NVT ensemble

- Coupling to a external bath [Berendsen 1984]

$$\boldsymbol{v}_i' = \lambda\, \boldsymbol{v}_i \;\rightarrow\; \lambda = \sqrt{1 + \frac{\Delta t}{\tau}\left(\frac{T_f}{T} - 1\right)}$$

- Other thermostats (Nose-Hoover,. . .)
- Equilibration (*NVT*) - Production (*NVE*)
- Other emsembles (*NPT*,. . .)

Conservation principles

- Mass $\Rightarrow M = \sum_i m_i$
- Energy $\Rightarrow E = \sum_i \frac{\boldsymbol{p}_i^2}{2\, m_i} + V(\boldsymbol{r}_i)$
- Linear momentun $\Rightarrow \sum_i \boldsymbol{p}_i = 0$
- Angular momentun $\Rightarrow \sum_i \boldsymbol{r}_i \times \boldsymbol{p}_i = 0$

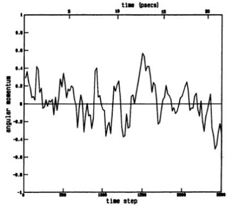


FIGURE 2.15 Fluctuations in the y-component of the angular momentum $\mathscr{Q}_y(t) = \Sigma_i^N(z_i \dot{x}_i - \dot{z}_i x_i)$, computed during a molecular dynamics simulation of 108 Lennard-Jones atoms at $\rho\sigma^3 = 0.7$, $kT/\varepsilon = 1$. Units are σ for position and $(m/\varepsilon)^{1/2}$ for velocity. Values are plotted at intervals of 20 integration time-steps; using potential parameters for argon, 20 time-steps = 0.172 psec.

Maxwell-Boltzmann distribution

- Velocity distribution

$$\rho(v_x) = \sqrt{\frac{m}{2\pi k_\mathrm{B} T}}\, e^{-\frac{1}{2} m v_x^2 / k_\mathrm{B} T} \Leftarrow \int_{-\infty}^{\infty} \rho(v_x)\, dv_x = 1$$

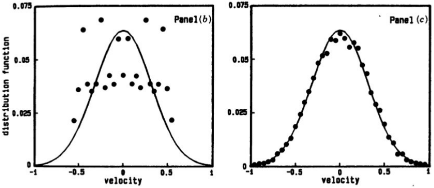


FIGURE 3.9 Approach to equilibrium for the 256-hard-sphere simulation described in Figure 3.7. (*a*) Same as Figure 3.8(*a*). (*b*) The velocity distribution $f(v_x)\,dv_x$ averaged over the first 5000 collisions of the run (points) compared to the Maxwell distribution (line) at the same kinetic energy. (*c*) The velocity distribution $f(v_x)\,dv_x$ averaged over collisions 6000–11,000 of the run (points) compared to the Maxwell distribution (line).

Static properties

- Time average

$$\langle A \rangle = \lim_{\tau \to \infty} \frac{1}{\tau} \int_0^{\tau} A(t)\, dt \approx \frac{1}{M} \sum_{k=1}^{M} A(t_k)$$

- Fluctuations

$$\delta A = A - \langle A \rangle$$

$$\begin{aligned} \langle (\delta A)^2 \rangle &= \langle (A - \langle A \rangle)^2 \rangle \\ &= \langle A^2 - 2\, A \,\langle A \rangle + \langle A \rangle^2 \rangle \\ &= \langle A^2 \rangle - \langle A \rangle^2 \end{aligned}$$

Static properties

- Pressure

$$P = \rho k_{\mathrm{B}} T + \frac{\langle W \rangle}{V}$$

$$W = \frac{1}{3} \sum_{i}^{N} \boldsymbol{r}_i \cdot \boldsymbol{F}_i \rightarrow \text{internal virial}$$

- Heat capacity $\Rightarrow C_V = \left(\frac{\partial E}{\partial T}\right)_V \rightarrow \; C_V^* = \left(1 - \frac{2}{3NT^{*2}} \langle (\delta K^*)^2 \rangle\right)^{-1}$
- Adiabatic compresibility $\Rightarrow \kappa = -\frac{1}{V}\left(\frac{\partial V}{\partial P}\right)_S$

$$\kappa^* = \left(7P^* - \frac{16}{3}\rho^* T^* - 8\rho^* U^* - \frac{N}{\rho^*} T^* \langle (\delta P^*)^2 \rangle\right)^{-1}$$

- Thermal pressure coefficient $\Rightarrow \gamma = \left(\frac{\partial P}{\partial T}\right)_V$

$$\gamma^* = \frac{2}{3} C_V^* \left(\rho * - \frac{1}{T^{*2}} \langle \delta K^* \delta P^* \rangle\right)$$

Static properties

- Radial distribution function $g(r)$

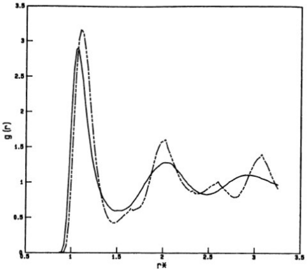


FIGURE 6.22 The radial distribution function $g(r)$ may often be used to distinguish a fluid state (continuous line) from a metastable solidlike state (broken line). These curves are from simulations that used the Lennard-Jones potential with 256 atoms at a density of $\rho\sigma^3 = 0.9$. The fluid state was at $kT/\varepsilon = 1.087$, while the metastable state was at $kT/\varepsilon = 0.80$. See Figure 5.7 for the location of these states on the Lennard-Jones phase diagram.

$$g(r) = \frac{\rho(r)}{\rho}$$

$$r \in (R, R+\delta) \rightarrow V = \frac{4}{3}\pi\left((R+\delta)^3 - R^3\right)$$

$$\rho(R) = \frac{n(R)}{V}$$

Dynamic properties

- Time correlation functions

$$\left\langle A(t_0)\, B(t_0+t)\right\rangle = \left\langle A(0)\, B(t)\right\rangle = \lim_{\tau\to\infty} \frac{1}{\tau} \int_0^{\tau} A(t_0)\, B(t_0+t)\, dt_0$$

$$\simeq \frac{1}{M} \sum_{k=1}^{M} A(t_k)\, B(t_k+t)$$

- Limits $\left\langle A(0)\, B(t)\right\rangle$

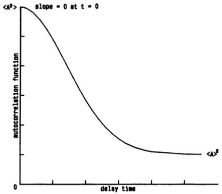


FIGURE 7.2 An autocorrelation function $\langle A(0)A(t)\rangle$ is initially equal to $\langle A^2\rangle$, but as the delay time grows, it decays, initially with zero slope, to $\langle A\rangle^2$.

$$t=0 \Rightarrow \left\langle A\, B\right\rangle \simeq \frac{1}{M} \sum_{k=1}^{M} A(t_k)\, B(t_k)$$

$$t\to\infty \Rightarrow \left\langle A\right\rangle \left\langle B\right\rangle \text{ (uncorrelated)}$$

Dynamic properties

- Transport coefficients

$$\text{Flux} = -\text{coefficient} \times \text{gradient}$$

$$\text{Fick's law} \Rightarrow N\dot{x} = -D\frac{\partial N}{\partial x} \begin{cases} N(x,t) \rightarrow \text{number atoms/unit volumen} \\ \dot{x}(x,t) \rightarrow \text{local velocity} \end{cases}$$

TABLE 7.1 Generalized Einstein and Green–Kubo Formulas for Self-Diffusion Coefficient, Shear, and Longitudinal Viscosity

$$K = \lim_{t\to\infty} \langle [A(t) - A(0)]^2 \rangle / 2t = \int_0^\infty d\tau \langle \dot{A}(\tau)\dot{A}(0)\rangle$$

K	$A(t)$	$\dot{A}(t)$
Self-diffusion coefficient D	$x_i(t)$	$\dot{x}_i(t)$
Shear viscosity ηVkT	$m\sum_i^N \dot{x}_i(t) y_i(t)$	$m\sum_i^N \dot{x}_i(t)\dot{y}_i(t) + \sum_{i<j}^N y_{ij}(t) F_{ijx}(t)$
Longitudinal viscosity[a] $(\frac{4}{3}\eta + \zeta)VkT$	$m\sum_i^N \dot{x}_i(t) x_i(t)$	$m\sum_i^N \dot{x}_i(t)\dot{x}_i(t) + \sum_{i<j}^N x_{ij}(t) F_{ijx}(t) - PV$

[a] ζ is the bulk viscosity.