

# Computational biophysics

## Protein's geometry

Centre of mass  $\vec{R}_{cm} = \frac{\sum_{i=1}^N m_i \vec{r}_i}{\sum_{i=1}^N m_i}$

Radius of gyration  $r_g = \sqrt{\frac{\sum_{i=1}^N m_i (\vec{r}_i - \vec{R}_{cm})^2}{\sum_{i=1}^N m_i}}$

$RMSD(t) = \sqrt{\frac{1}{N} \sum_{i=1}^N (\vec{r}_i(t) - \vec{r}_i(0))^2}$

$RMSF_i = \sqrt{\langle \Delta r_i^2 \rangle} = \sqrt{\frac{1}{M} \sum_{f=1}^M (\vec{r}_{i,f} - \langle \vec{r}_i \rangle)^2}$

$B_i = \frac{8\pi^2}{3} RMSF_i^2$

## Semi-empirical force fields

### Bond stretching

Harmonic  $U(r_{AB}) = \frac{1}{2} k_{AB} (r_{AB} - r_{AB,eq})^2$

Anarmonic  $U(r_{AB}) = \frac{1}{2} \left[ k_{AB} + k_{AB}^{(3)} (r_{AB} - r_{AB,eq}) \right] (r_{AB} - r_{AB,eq})^2$

Quartic correction  $U(r_{AB}) = \frac{1}{2} \left[ k_{AB} + k_{AB}^{(3)} (r_{AB} - r_{AB,eq}) + k_{AB}^{(4)} (r_{AB} - r_{AB,eq})^2 \right] \cdot (r_{AB} - r_{AB,eq})^2$

Morse  $U(r_{AB}) = D_{AB} \left[ 1 - e^{-\alpha_{AB}(r_{AB} - r_{AB,eq}^2)} \right]$

### Valence angle bending

Potential  $U(\theta_{ABC}) = \frac{1}{2} k_{ABC} + k_{ABC}^{(3)} (\theta_{ABC} - \theta_{ABC,eq}) + k_{ABC}^{(4)} (\theta_{ABC} - \theta_{ABC,eq})^2 + \dots [(\theta_{ABC} - \theta_{ABC,eq})^2]$

$U(\theta_{ABC}) = \sum_{\{j\}_{ABC}} k_{j,ABC}^{fourier} [1 + \cos(j\theta_{ABC} + \psi_j)]$

Fourier  $k_{j,ABC}^{fourier} = \frac{2k_{ABC}^{harmonic}}{j^2}$

### Torsions

Potential  $U(\omega_{ABCD}) = \frac{1}{2} \sum_{\{j\}_{ABCD}} V_{j,ABCD} [1 + (-1)^{j+1} \cos(j\omega_{ABCD} + \psi_{j,ABCD})]$

Improper  $U(\omega_{ABCD}) = \frac{1}{2} \sum_{\{j\}_{ABCD}} V_{j,ABCD} [1 + (-1)^{j+1} \cos(j\omega_{ABCD} + \psi_{j,ABCD})]$

### Van der Waals

Lennard-Jones  $U(r_{AB}) = 4\epsilon_{AB} \left[ \left( \frac{\sigma_{AB}}{r_{AB}} \right)^{12} - \left( \frac{\sigma_{AB}}{r_{AB}} \right)^6 \right]$

Morse  $U(r_{AB}) = D_{AB} \left[ 1 - e^{-\alpha_{AB}(r_{AB} - r_{AB,eq}^{\lambda})} \right]^2$

Hill  $U(r_{AB}) = \epsilon \left[ \frac{6}{\beta_{AB}-6} e^{\beta_{AB} \frac{1-r_{AB}}{r_{AB}}} - \frac{\beta_{AB}}{\beta_{AB}-6} \left( \frac{r_{AB}}{r_{AB}} \right)^6 \right]$

### Electrostatic interactions

Distribution of charges  $U_{AB} = \sum_A \sum_{B>A} \vec{M}^{(A)} \vec{V}^{(B)}$

Point like  $U_{AB} = \frac{q_A q_B}{\epsilon_{AB} r_{AB}}$

Dipolar interactions  $U_{AB/CD} = \frac{\mu_{AB} \mu_{CD}}{\epsilon_{AB/CD} r_{AB/CD}^3} (\cos \chi_{AB/CD} - 3 \cos \alpha_{AB} \cos \alpha_{CD})$

### Parameterization

Parameters  $Z = \sqrt{\sum_i \frac{\text{observables occurrences}}{j} \sum_j \frac{(\text{calc}_{i,j} - \text{expt}_{i,j})^2}{w_i^2}}$

$\sigma_{AB} = \sigma_A + \sigma_B$

$\epsilon_{AB} = \sqrt{\epsilon_A \epsilon_B}$

## Classical mechanics

### Newton's laws

$\vec{F} = m\vec{a}$   $\vec{F}_{BA} = -\vec{F}_{AB}$

$\vec{v}(t) = \frac{d\vec{r}}{dt}$   $\vec{a}(t) = \frac{d\vec{v}}{dt} = \frac{d^2\vec{r}}{dt^2}$   $m \frac{d^2\vec{r}}{dt^2} = \vec{F}$

Force acting on atom  $\vec{F}_i(\vec{r}_1, \dots, \vec{r}_N, \vec{r}_i) = \sum_{j \neq i} \vec{F}_{ij}(\vec{r}_i - \vec{r}_j) + \vec{F}^{(ext)}(\vec{r}_i, \vec{r}_i)$

Bond stretching:  $U = \frac{k_b}{2} (l - l^0)^2$

Bond bending:  $U = \frac{k_\theta}{2} (\theta - \theta^0)^2$

Bond torsion:  $U = k_\phi [1 + \cos(n\phi - \phi^0)]$

Van der Waals interactions:  $U = \left[ \frac{a_{ij}}{r_{ij}^{12}} - \frac{b_{ij}}{r_{ij}^6} \right]$

Electrostatic interactions:  $U = \frac{332 q_i q_j}{\epsilon r_{ij}}$

$\vec{p}_i = m_i \vec{v}_i = m \dot{\vec{r}}_i$   $\vec{F}_i = m_i \ddot{\vec{r}}_i = \dot{\vec{p}}_i$

$\vec{x}(t) = \{\vec{r}_1(t), \dots, \vec{r}_N(t), \vec{p}_1(t), \dots, \vec{p}_N(t)\}$

### Lagrangian formulation

$\vec{F}_i(\vec{r}_1, \dots, \vec{r}_N) = -\Delta_i U(\vec{r}_1, \dots, \vec{r}_N)$

$W_{AB} = \int_A^B \vec{F}_i d\vec{l} = U_A - U_B = -\Delta U_{AB}$   $\oint \vec{F}_i d\vec{l} = 0$

Kinetic energy  $K(\dot{\vec{r}}_1, \dots, \dot{\vec{r}}_N) = \frac{1}{2} \sum_i m_i \dot{\vec{r}}_i^2$

$\mathcal{L}(\vec{r}_1, \dots, \vec{r}_N, \dot{\vec{r}}_1, \dots, \dot{\vec{r}}_N) = K(\dot{\vec{r}}_1, \dots, \dot{\vec{r}}_N) - U(\vec{r}_1, \dots, \vec{r}_N)$

Euler-Lagrange  $\frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{r}_i} \right) - \frac{\partial \mathcal{L}}{\partial r_i} = 0$

$E = \frac{1}{2} \sum_i m_i \dot{\vec{r}}_i^2 + U(\vec{r}_1, \dots, \vec{r}_N)$

$quad \frac{dE}{dt} = 0$

### Generalized coordinates

$q_\alpha = f_\alpha(\vec{r}_1, \dots, \vec{r}_N)$   $\alpha = 1, \dots, 3N$   $\vec{r}_i = \vec{g}_i(q_1, d, \dots, q_{3N})$   $i = 1, \dots, N$

$\dot{\vec{r}}_i = \sum_{\alpha=1}^{3N} \frac{\partial \vec{r}_i}{\partial q_\alpha} \dot{q}_\alpha$   $\mathcal{L}(q, \dot{q}) = \frac{1}{2} \sum_{\alpha=1}^{3N} G_{\alpha\beta} \dot{q}_\alpha \dot{q}_\beta - U(q_1, \dots, q_{3N})$

## Classical mechanics (contd)

### Legendre transforms

$s = f'(x) \equiv g(x)$   $f'(x) = g(x) = s \Rightarrow x = g^{-1}(s)$

$b(g^{-1}(s)) = f(g^{-1}(s)) - sg^{-1}(s) \equiv \tilde{f}(s) = f(x(s)) - sx(s)$

$\tilde{f}(s_1, \dots, s_n) = f(x_1(s_1, \dots, s_n), \dots, x_n(s_1, \dots, s_n)) - \sum_i s_i x_i(s_1, \dots, s_n)$

### Hamiltonian formulation

$\mathcal{H}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N) = -\tilde{\mathcal{L}}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N)$

$\mathcal{H}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N) = \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N)$

$\mathcal{H}(q_1, \dots, q_{3N}, p_1, \dots, p_{3N}) = \frac{1}{2} \sum_\alpha \sum_\beta p_\alpha G_{\alpha\beta}^{-1} p_\beta + U(q_1, \dots, q_{3N})$

Hamilton equations  $\dot{q}_\alpha = \frac{\partial \mathcal{H}}{\partial p_\alpha}$   $\dot{p}_\alpha = -\frac{\partial \mathcal{H}}{\partial q_\alpha}$   $\frac{\mathcal{H}}{dt} = 0$   $\mathcal{H} = const$

### Some properties

Conservation laws  $\frac{da}{dt} = \frac{\partial a}{\partial x_i} \dot{x}(t) = \{a, \mathcal{H}\} = 0$

Incompressibility  $\nabla_x(x) = 0$

Symplectic structure  $M = J^T M J$   $J_{kl} = \frac{\partial x_k(t)}{\partial x_l(0)}$

## Theoretical foundations of statistical mechanics

### Thermodynamics

Equilibrium  $g(N, P, V, T) = 0$  First law  $\Delta E = \Delta Q + \Delta W$

State function  $f(n, P, V, T)$  Entropy  $\Delta S = \int_1^2 \frac{dQ_{rev}}{T}$

Reversible work  $dW_{rev} = -PdV + \mu dN$

Heat  $dQ_{rev} = CdT$

### The ensemble

Average  $A = \frac{1}{2} \sum_{\lambda=1}^N a(x_\lambda) \equiv \langle a \rangle$

Microstate  $x_0 = (q_1(0), \dots, q_{3N}(0), p_1(0), \dots, p_{3N}(0))$

Phase space volume  $dx_t = J(x_t; x_0) dx_0$   $\frac{dx_t}{dt} = 0 \Rightarrow J(x_t; x_0) = 1 \Rightarrow dx_t = dx_0$

$f(x_t) : \int f(x) dx = 1 \wedge \frac{df(x_t, t)}{dt} = 0 \Rightarrow$

Distribution function  $f(x_t, t) dx_t = f(x_0, 0) dx_0 \Rightarrow$

$\frac{\partial f(x_t, t)}{\partial t} + \{f(x_t, t), \mathcal{H}(x_t, t)\} = 0$

Equilibrium  $A = \int a(x) f(x, t) dx \Rightarrow \frac{\partial f(x, t)}{\partial t} = 0 \wedge \{f(x, t), \mathcal{H}(x, t) = 0\} \Rightarrow$

$f(x) \propto \mathcal{F}(\mathcal{H}(x))$

$Z = \int dx \mathcal{F}(\mathcal{H}(x)) \Rightarrow f(x) = \frac{1}{Z} \mathcal{F}(\mathcal{H}(x))$

### Microcanonical ensemble

#### State and distribution function

State function  $dS = \frac{1}{T} dE + \frac{P}{T} dV - \frac{\mu}{T} dN$

$\left( \frac{\partial S}{\partial E} \right)_{V,N} = \frac{1}{T}$   $\left( \frac{\partial S}{\partial V} \right)_{N,E} = \frac{P}{T}$   $\left( \frac{\partial S}{\partial N} \right)_{V,N} = \frac{\mu}{T}$

Boltzmann relation  $S(N, V, E) = k \ln \omega(N, V, E)$

$\Omega(N, V, E) = M_N \int d\vec{p} \int_{D(V)} d\vec{r} \delta(\mathcal{H}(\vec{r}, \vec{p}) - E)$

Distribution function  $= M_N \int dx \delta(\mathcal{H}(x) - E)$

$M_N = \frac{E_0}{N! h^{3N}}$

$A = \langle a \rangle = \frac{M_N}{\Omega(N, V, E)} \int dx a(x) \delta(\mathcal{H}(x) - E) = \frac{\int dx a(x) \delta(\mathcal{H}(x) - E)}{\int dx \delta(\mathcal{H} - E)}$

$\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle = \frac{M_N}{\Omega(N, V, E)} \frac{\partial}{\partial E} \int_{\mathcal{H}(x) < E} dx x_i \frac{\partial (\mathcal{H} - E)}{\partial x_j}$

### Virial theorem

$\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle = \delta_{ij} \frac{\Sigma(E)}{\frac{\partial \Sigma(E)}{\partial E}}$

$\Sigma(N, V, E) = \frac{1}{N! h^{3N}} \int dx \theta(E - \mathcal{H})$

$\Omega(N, V, E) = E_0 \frac{\partial \Sigma(N, V, E)}{\partial E}$   $\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle = \delta_{ij} \left( \frac{\ln \Sigma(E)}{\partial E} \right)^{-1}$

$S(N, V, E) = k \ln \Omega(N, V, E) \simeq k \ln \Sigma(N, V, E) = \tilde{S}(N, V, E)$

$\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle \simeq \delta_{ij} \left( \frac{S(E)}{\partial E} \right)^{-1} = kT \delta_{ij}$

### Thermal contact

$\Omega(N, V, E) = M_N \int dx \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E)$

$\Omega(N, V, E) = \int d\vec{E}_1 \Omega_1(N_1, V_1, E_1) \Omega_2(N_2, V_2, E - E_1)$

$S(N, V, E) = k \ln \Omega_1(N_1, V_1, E_1) + k \ln \Omega_2(N_2, V_2, E - E_1)$

$= S_1(N_1, V_1, E_1) + S_2(N_2, V_2, E - E_1)$

$T_1 = T_2$

## Introduction to molecular dynamics

### Verlet algorithm

$\vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i} \vec{F}_i(t)$

$\vec{v}_i(t + \Delta t) = \vec{v}_i(t) + \frac{\Delta t}{2m_i} \left[ \vec{F}_i(t) + \vec{F}_i(t + \Delta t) \right]$

Initial conditions  $f(v) = \sqrt{\frac{m}{2\pi kT}} e^{-\frac{mv^2}{2kT}}$   $f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{x^2}{2\sigma^2}}$

## Introduction to molecular dynamics (contd)

### Action integral

$Q \equiv \{q_1, \dots, q_{3N}\}$   $\dot{Q} \equiv \{\dot{q}_1, \dots, \dot{q}_{3N}\}$

$A[Q] = \int_{t_1}^{t_2} \mathcal{L}(Q(t), \dot{Q}(t)) dt$

$\delta Q(t_1) = \delta Q(t_2) = 0$   $\delta \dot{Q}(t_1) = \delta \dot{Q}(t_2) = 0$

$\delta A = \int_{\alpha=1}^{3N} \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \delta q_\alpha(t) \Big|_{t_1}^{t_2} dt + \int_{t_1}^{t_2} \sum_{\alpha=1}^{3N} \left[ \frac{\partial \mathcal{L}}{\partial q_\alpha} \delta q_\alpha(t) - \frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) \delta q_\alpha(t) \right] dt = 0$

### Constraints

$\sum_{\alpha=1}^{3N} a_{k\alpha} dq_\alpha + a_{kt} dt = 0, k = 1, \dots, N_C$

Holonomic  $a_{k\alpha} = \frac{\partial \sigma_k}{\partial q_\alpha}$   $a_{kt} = \frac{\partial \sigma_k}{\partial t}$

$\frac{1}{2} \sum_i m_i \dot{\vec{r}}_i^2 - C = 0 \Rightarrow \frac{1}{2} \sum_i m_i \dot{\vec{r}}_i d\vec{r}_i - C dt = 0$

Non-holonomic  $\Rightarrow a_{1i} = \frac{1}{2} m_i \dot{\vec{r}}_i \wedge a_{1t} = -C$

Lagrange multiplier  $\frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) - \frac{\partial \mathcal{L}}{\partial q_\alpha} = \sum_{k=1}^{N_C} \lambda_k a_{k\alpha}$

$\dot{q}_\alpha = \frac{\partial \mathcal{H}}{\partial p_\alpha}$   $\dot{p}_\alpha = -\frac{\partial \mathcal{H}}{\partial q_\alpha} - \sum_{k=1}^{N_C} \lambda_k a_{k\alpha}$   $\sum_{\alpha=1}^{3N} a_{k\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha} = 0$

Simulation  $m_i \ddot{\vec{r}}_i = \vec{F}_i + \sum_{k=1}^{N_C} \lambda_k \nabla_i \sigma_k$   $\dot{\sigma}_k = \sum_{i=1}^N \nabla_i \sigma_k \cdot \dot{\vec{r}}_i = 0$

Velocity Verlet  $\vec{r}_i(\Delta t) = \vec{r}_i(0) + \Delta t \vec{v}_i(0) + \frac{\Delta t^2}{2m_i} \vec{F}_i(0) + \frac{\Delta t^2}{2m_i} \sum_k \lambda_k \nabla_i \sigma_k(0)$

$\vec{r}_i(\Delta t) = \vec{r}_i + \frac{1}{m_i} \sum_k \tilde{\lambda}_k \nabla_i \sigma_k(0)$   $\tilde{\lambda}_k = \frac{\Delta t^2}{2} \lambda_k$

$\sigma_l \left( \vec{r}_1^{(1)}, \dots, \vec{r}_N^{(1)} \right) + \sum_{i=1}^N \sum_{k=1}^{N_C} \frac{1}{m_i} \nabla_i \sigma_k \left( \vec{r}_1^{(1)}, \dots, \vec{r}_N^{(1)} \right) \cdot \nabla_i \sigma_k \left( \vec{r}_1(0), \dots, \vec{r}_N(0) \right) \delta \tilde{\lambda}_k \approx 0$

### Direct translation

#### Liouville operator

Computable on  $a$ :  $\frac{da}{dt} = \{a, \mathcal{H}\}$

$iL = \sum_\alpha \left[ \frac{\partial \mathcal{H}}{\partial q_\alpha} \frac{\partial}{\partial q_\alpha} - \frac{\partial \mathcal{H}}{\partial q_\alpha} \frac{\partial}{\partial p_\alpha} \right] \Rightarrow iLa = \{a, \mathcal{H}\} \Rightarrow \frac{da}{dt} = iLa \Rightarrow a(x_t) = e^{iLt} a(x_0)$

Split  $iL_1 = \sum_\alpha \frac{\partial \mathcal{H}}{\partial p_\alpha} \frac{\partial}{\partial q_\alpha}$   $iL_2 = -\sum_\alpha \frac{\partial \mathcal{H}}{\partial q_\alpha} \frac{\partial}{\partial p_\alpha}$

$iL_1 iL_2 \phi(x) \neq iL_2 iL_1 \phi(x) \Rightarrow iL_1 iL_2 - iL_2 iL_1 \equiv [iL_1, iL_2] \neq 0$

### Trotter theorem

$[iL_1, iL_2] \neq 0 \Rightarrow e^{iLt} \neq e^{iL_1 t} e^{iL_2 t}$

$e^{A+B} = \lim_{P \rightarrow \infty} \left[ e^{\frac{A}{2P}} e^{\frac{B}{P}} e^{\frac{B}{2P}} \right]^P$   $e^{iLt} = \lim_{P \rightarrow \infty} \left[ e^{\frac{iL_2 t}{2P}} e^{\frac{iL_1 t}{P}} e^{\frac{iL_2 t}{2P}} \right]^P$

$e^{iLt} \approx e^{\frac{iL_2 \Delta t}{2}} e^{iL_1 \Delta t} e^{\frac{iL_2 \Delta t}{2}}$

### Trotter algorithm

Exponential operator  $e^{c \frac{\partial}{\partial x}} g(x) = g(x + c)$

$\begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix} = \begin{pmatrix} x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right) \\ p(0) + \frac{\Delta t}{2} F(x(0)) + \frac{\Delta t}{2} F \left( x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right) \right) \end{pmatrix}$

$x(\Delta t) = x(0) + v(0) \Delta t + \frac{\Delta t^2}{2m} F(0)$   $p(\Delta t) = v(0) + \frac{\Delta t}{2m} [F(0) + F(\Delta t)]$

### RESPA

$iL = \frac{p}{m} \frac{\partial}{\partial x} + [F_{fast}(x) + F_{slow}(x)] \frac{\partial}{\partial p} = iL_{fast} + iL_{slow}$   $\mathcal{H}_{ref} = \frac{p^2}{2m} + U_{fast}(x)$

$e^{iL \Delta t} = e^{iL_{slow} \frac{\Delta t}{2}} e^{iL_{fast} \Delta t} e^{iL_{slow} \frac{\Delta t}{2}}$

$e^{iL_{fast} \Delta t} = \left[ e^{\frac{\Delta t}{2} F_{fast} \frac{\partial}{\partial p}} e^{\delta t \frac{p}{m} \frac{\partial}{\partial x}} e^{\frac{\delta t}{2} F_{fast} \frac{\partial}{\partial p}} \right]^n$   $\delta t = \frac{\Delta t}{n}$

## Evaluation of energy and forces

### Periodic boundary condition

Non bonded interaction  $U_{nb}(\vec{r}_1, \dots, \vec{r}_N) = \sum_{i < j \in nb} \left\{ 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{r_{ij}} \right\}$

Error function  $erf(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} dt$   $\lim_{x \rightarrow \infty} erf(x) = 1$   $erf(0) = 0$

Complement error  $erfc(x) = 1 - erf(x) = \frac{2}{\sqrt{\pi}} \int_x^\infty e^{-t^2} dt$   $\lim_{x \rightarrow \infty} erf(x) = 0$

$erf(0) = 1$

$\frac{1}{r} = \frac{\text{short-ranged}}{erfc(\alpha r)} + \frac{\text{long-ranged}}{erf(\alpha r)}$   $U_{nb} = U_{short} + U_{long}$   $\vec{r}_{ij} = |\vec{r}_i - \vec{r}_j + \vec{S}|$   $\vec{S} = \vec{m}L$

$U_{short}(\vec{r}_1, \dots, \vec{r}_N) = \sum_{\vec{S}} \sum_{i > j \in nb} \left\{ 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij, \vec{S}}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij, \vec{S}}} \right)^6 \right] + \frac{q_i q_j erf c(\alpha r_{ij, \vec{S}})}{r_{ij, \vec{S}}} \right\}$

$U_{long}(\vec{r}_1, \dots, \vec{r}_N) = \sum_{\vec{S}} \sum_{i > h \in nb} \frac{q_i q_h erf(\alpha r_{ij, \vec{S}})}{r_{ij, \vec{S}}}$

### Short range forces

$\vec{U}_{short} = U_{short}(\vec{r}_{ij}) S(\vec{r}_{ij})$   $S(r) = \begin{cases} 1 & r < r_C - \lambda \\ 1 + \left( \frac{r - r_C + \lambda}{\lambda} \right)^2 (2 \frac{r - r_C + \lambda}{\lambda} - 3) & r_C - \lambda \leq r < r_C \\ 0 & r > r_C \end{cases}$

## Evaluation of energy and forces (contd)

### Long range forces

$C_{\vec{g}} = \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}}$   $\frac{1}{V} \sum_{\vec{g}} C_{\vec{g}} e^{i\vec{g} \cdot \vec{r}} = \frac{1}{V} \sum_{i \neq j} q_i q_j \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} e^{i\vec{g} \cdot (\vec{r}_i - \vec{r}_j)}$

$U_{long} = \frac{1}{V} \sum_{i,j} q_i q_j \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} e^{i\vec{g} \cdot (\vec{r}_i - \vec{r}_j)} - \frac{1}{V} \sum_i q_i^2 \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}}$

$U_{long} = \frac{1}{V} \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} |S(\vec{g})|^2 - \frac{\alpha}{\sqrt{\pi}} \sum_i q_i^2$

### Particle-particle particle-mesh Ewald

$\rho(\vec{r}) = \sum_i q_i \delta(\vec{r} - \vec{r}_i)$   $\rho(\vec{g}) = \int d\vec{r} \rho(\vec{r}) e^{i\vec{g} \cdot \vec{r}} = \sum_i q_i e^{i\vec{g} \cdot \vec{r}_i}$

$\nabla^2 \phi(\vec{r}) = -\nabla \cdot \vec{E} = -4\pi \rho(\vec{r})$   $g^2 \phi(\vec{g}) = -4\pi \rho(\vec{g}) = 4\pi S(\vec{g})$

## Canonical ensemble

### Thermodynamics

Helmholtz free energy  $A(N, V, T) = E(N, V, T) - TS(N, V, T)$

$dA = SdT - PdV + \mu dN$   $S = -\left( \frac{\partial A}{\partial T} \right)_{N,V}$   $P = -\left( \frac{\partial A}{\partial V} \right)_{N,T}$   $\mu = \left( \frac{\partial A}{\partial N} \right)_{V,T}$

### Thermal contact

Microcanonical  $\Omega(N, V, E) = M_N \int dx_1 dx_2 \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E)$

Distribution function  $\ln f(x_1) = \ln \int dx_2 \delta(\mathcal{H}_2(x_2) - E) = \frac{\partial}{\partial E} \ln \int dx_2 \delta(\mathcal{H}_2(x_2) - E) \mathcal{H}_1(x_1)$

$Q(N, V, T) = \frac{1}{N! h^{3N}} \int dx e^{-\beta \mathcal{H}(x)}$   $\beta = \frac{1}{kT}$

### From micro to macro

$A = E - \beta \left( \frac{\partial A}{\partial \beta} \right)_{N,V}$

$E = \langle \mathcal{H} \rangle = \frac{1}{N! h^{3N}} \frac{\int dx \mathcal{H}(x) e^{-\beta \mathcal{H}(x)}}{\int dx e^{-\beta \mathcal{H}(x)}} = -\frac{1}{Q(N, V, \beta)} \frac{\partial Q(N, V, \beta)}{\partial \beta} = -\frac{\partial \ln Q(N, V, \beta)}{\partial \beta}$

$A + \frac{\partial \ln Q}{\partial \beta} + \beta \frac{\partial A}{\partial \beta} = 0 \Rightarrow \ln Q(N, V, \beta) = -\beta A(N, V, \beta)$

$A(N, V, T) = -kT \ln Q(N, V, T)$   $C_N = \frac{1}{N! h^{3N}}$

Energy  $E = \langle \mathcal{H} \rangle = \frac{1}{Q} \frac{\partial Q}{\partial \beta} = 0$

Temperature estimator  $\mathcal{T}(x) + \frac{1}{3Nk} \sum_i \frac{\vec{p}_i^2}{m_i}$   $T = \langle \mathcal{T}(x) \rangle = \frac{C_N \int dx \mathcal{T}(x) e^{-\beta \mathcal{H}(x)}}{C_N \int dx e^{-\beta \mathcal{H}(x)}}$

Energy fluctuation  $\Delta E^2 = \frac{\partial^2 \ln Q}{\partial \beta^2} = kT^2 C_V$   $\frac{\Delta E}{E} \sim \frac{1}{\sqrt{N}}$

Pressure estimator  $\mathcal{P}(\vec{r}, \vec{p}) = \frac{1}{3V} \sum_i \left[ \frac{\vec{p}_i^2}{m_i} + \vec{F}_i \cdot \vec{r}_i \right]$

## Thermostats

### Velocity rescaling

$\bar{K} = \frac{N_j}{2\beta}$   $K = \frac{1}{2} \sum_i m_i \vec{v}_i^2$   $\vec{v}_i \rightarrow \frac{\vec{v}_i}{\alpha}</$

## Thermostats (contd)

## Nosè-Hoover equations

$$\begin{aligned}\vec{p}'_i &= \frac{\vec{p}_i}{s} & \vec{p}'_s &= \frac{p_s}{s} & dt' &= \frac{dt}{s} & \frac{d\vec{r}'_i}{dt'} &= \frac{\vec{p}'_i}{m_i} & \frac{d\vec{p}'_i}{dt'} &= \vec{F}_i - \frac{s\vec{p}'_i}{Q}\vec{p}'_i \\ \frac{ds}{dt'} &= \frac{s^2\vec{p}'_s}{Q} & \frac{dp'_s}{dt'} &= \frac{1}{2} \left[ \sum_i \frac{(\vec{p}'_i)^2}{m_i} - gkT \right]^2 - \frac{s(\vec{p}'_s)^2}{2} & \frac{1}{2} \frac{ds}{dt'} &= \frac{d\eta}{dt'} & p_s &= p_\eta = s\vec{p}'_s \\ \dot{\vec{r}}'_i &= \frac{\vec{p}'_i}{m_i} & \dot{\vec{p}}'_i &= \vec{F}_i - \frac{p'_s}{Q}\vec{p}_i & \dot{\eta} &= \frac{p_\eta}{Q} & \dot{p}_\eta &= \sum_i \frac{\vec{p}'_i}{m_i} - dNkT\end{aligned}$$

## Non Hamiltonian statistical mechanics

$$\begin{aligned}\dot{x} &= \xi(x, t) & \nabla \cdot \dot{x} &= \nabla \cdot \xi(x, t) = \kappa(x, t) \neq 0 \\ J(x_t; x_0) &= e^{\int_0^t ds \kappa(x_s, s)} & \kappa(x_t, t) &= \frac{dw(x_t, t)}{dt} \Rightarrow J(x_t; x_0) = e^{w(x_t, t) - w(x_0, 0)} \\ e^{-w(x_t, t) - w(x_0, 0)} &= e^{-w(x_t, t)} dx_t = e^{-w(x_0, 0)} dx_0 \\ J(x_t; x_0) &= \frac{\sqrt{g(x_0, 0)}}{\sqrt{g(x_t, t)}} & \sqrt{g(x_t, t)} &= e^{-w(x_t, t)} \\ \frac{\partial}{\partial t} \left[ f(x, t) \sqrt{g(x, t)} \right] &+ \nabla \cdot \left[ \dot{x} \sqrt{g(x, t)} f(x, t) \right] &= 0 & f(x_t, t) \sqrt{g(x_t, t)} dx_t = f(x_0) \sqrt{g(x_0, 0)} dx_0 \\ \Lambda_k(x_t) - C_k &= 0 & \frac{d\Lambda_k(x_t)}{dt} = 0 &\Rightarrow f(x) = \prod_{k=1}^{N_C} \delta(\Lambda_k(x_t) - C_k)\end{aligned}$$

$$\text{Microcanonical } \mathcal{E} = \int dx \sqrt{g(x)} f(x) = \int dx \sqrt{g(x)} \prod_{k=1}^{N_C} \delta(\Lambda_k(x_t) - C_k)$$

$$\text{Nosè=Hoover: } \mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta) = \mathcal{H}(\vec{r}, \vec{P}) + \frac{p_\eta^2}{2Q} + dNkT\eta \quad \frac{d\mathcal{H}'}{dt} = 0$$

$$\kappa = -Nd\dot{\eta} \Rightarrow \sqrt{g} = e^{dN\eta}$$

$$\text{Partition function } \mathcal{E}_T(N, V, C_1) = \frac{e^{\beta C_1 \sqrt{2\pi QkT}}}{dNkT} \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})}$$

## Nosè-Hoover chains

$$\begin{aligned}\dot{\vec{r}}'_i &= \frac{\vec{p}_i}{m_i} & \dot{\vec{p}}'_i &= \vec{F}_i - \frac{p_{\eta_1}}{Q_1} \vec{p}_i & \dot{\eta}_j &= \frac{p_{\eta_j}}{Q_j} & j &= 1, \dots, M \\ \dot{p}_{\eta_1} &= \left[ \sum_i \frac{\vec{p}'_i}{m_i} - dNkT \right] - \frac{p_{\eta_2}}{Q_2} p_{\eta_1} & \dot{p}_{\eta_j} &= \left[ \sum_i \frac{\vec{p}'_{j+1}}{Q_{j+1}} - kT \right] - \frac{p_{\eta_{j+1}}}{Q_{j+1}} p_{\eta_j} & j &= 2, \dots, M-1 \\ \dot{p}_{\eta_M} &= \frac{p_{\eta_{M-1}}}{Q_{M-1}} - kT \\ \mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta) &= \mathcal{H}(\vec{r}, \vec{p}) + \sum_{j=1}^M \frac{p_{\eta_j}^2}{2Q_j} + dNkT\eta_1 + kT \sum_{j=2}^M \eta_j \\ \kappa &= -dN\dot{\eta}_1 - \dot{\eta}_c & \eta_c &= \sum_{j=2}^M \eta_j & \sqrt{g} &= e^{dN\eta_1 + \eta_c} \\ \text{Partition function } \mathcal{E}_T(N, V, C_1) &= \mathcal{M} \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})}\end{aligned}$$

## Isobaric ensemble

## Legendre transforms

$$\begin{aligned}\text{Enthalpy } dH &= TdS + \mu dN + VdP & T &= \left( \frac{\partial H}{\partial S} \right)_{N,P} & \langle V \rangle &= \left( \frac{\partial H}{\partial P} \right)_{N,S} & \mu &= \left( \frac{\partial H}{\partial N} \right)_{P,S} \\ \text{Gibbs } dG &= \mu dN + VdP - SdT & S &= - \left( \frac{\partial G}{\partial T} \right)_{N,P} & \langle V \rangle &= - \left( \frac{\partial G}{\partial P} \right)_{N,T} & \mu &= - \left( \frac{\partial G}{\partial N} \right)_{P,T}\end{aligned}$$

## Isoenthalpic-isobaric ensemble

$$\begin{aligned}H &= \mathcal{H}(v) + PV & f(x) &= F(\mathcal{H}(x)) = \mathcal{M} \delta(\mathcal{H}(x) + PV - H) \\ \Gamma(N, P, H) &= \mathcal{M} \int_0^\infty dV \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} \delta(\mathcal{H}(\vec{r}, \vec{p}) + PV - H) \\ S(N, P, H) &= k \ln \Gamma(N, P, H) & \frac{1}{T} &= \left( \frac{\partial S}{\partial H} \right)_{N,P} & \left( \frac{V}{T} \right) &= - \left( \frac{\partial S}{\partial P} \right)_{N,H} & \frac{\mu}{T} &= - \left( \frac{\partial S}{\partial N} \right)_{P,H}\end{aligned}$$

## Isothermal-isobaric ensemble

$$\begin{aligned}Q(N, V, T) &\propto Q(N_1, V_1, T) Q(N_2, V_2, T) \\ f(x_1) &= I_{N_1} e^{\beta \mu N_1} e^{-\beta PV_1} C_{N_1} e^{-\beta \mathcal{H}_1(x_1)} & I_{N_1} &= \frac{1}{V_0 N_1! h^{3N_1}} \\ \Delta(N, P, T) &= \frac{1}{V_0} \int_0^\infty dV e^{-\beta PV} Q(N, V, T) \\ G(N, P, \beta) &= - \frac{\partial \ln \Delta(N, P, \beta)}{\partial \beta} - \beta \frac{\partial G}{\partial \beta}\end{aligned}$$

## Virial theorems

$$\text{Pressure } \langle P^{(int)} \rangle = \frac{P}{\Delta(N, P, T)} \int_0^\infty dV e^{-\beta PV} Q(N, V, T) = P \text{ Work } \langle P^{(int)} V \rangle + kT = P \langle V \rangle$$

## Andersen's Hamiltonian

$$\begin{aligned}\mathcal{H}_A &= \sum_{i=1}^N \frac{V^{-\frac{3}{2}} \pi_i^2}{2m_i} + U(V^{\frac{1}{3}} s_1, \dots, V^{\frac{1}{3}} s_N) + \frac{p_s^2}{2W} + PV & W &= (3N+1)kT\tau_b^2 \\ \dot{s}_i &= \frac{p_i}{m_i} + \frac{\dot{V}}{3V} r_i & \dot{\pi}_i &= -\frac{\partial U}{\partial r_i} - \frac{\dot{V}}{3V} p_i & \dot{V} &= \frac{p_V}{W} & \dot{p}_V &= \frac{1}{3V} \sum_{i=1}^N \left[ \frac{p_i^2}{m_i} - \frac{\partial U}{\partial r_i} r_i \right] - P \\ \dot{\vec{r}}'_i &= \frac{\vec{p}_i}{m_i} + \frac{\dot{V}}{3V} \vec{r}_i & \dot{\vec{p}}'_i &= -\frac{\partial U}{\partial \vec{r}_i} - \frac{\dot{V}}{3V} \vec{p}_i & \dot{V} &= \frac{p_V}{W} & \dot{p}_V &= \frac{1}{3V} \sum_{i=1}^N \left[ \frac{\vec{p}_i^2}{m_i} - \frac{\partial U}{\partial \vec{r}_i} \cdot \vec{r}_i \right] - P \\ \left\langle \frac{p_V^2}{2W} \right\rangle &= k\frac{T}{2} \Rightarrow \mathcal{H}(\vec{r}, \vec{p}) + PV && \text{is conserved}\end{aligned}$$

## MTK algorithm

$$\begin{aligned}\epsilon &= \frac{1}{3} \ln \frac{V}{V_0} \Rightarrow \dot{\epsilon} = \frac{\dot{V}}{3V} = \frac{p_\epsilon}{W} \\ \dot{\vec{r}}'_i &= \frac{\vec{p}_i}{m_i} + \frac{p_\epsilon}{W} \vec{r}_i & \dot{\vec{p}}'_i &= -\frac{\partial U}{\partial \vec{r}_i} - \frac{p_\epsilon}{W} \vec{p}_i & \dot{V} &= \frac{dV p_\epsilon}{dW} & \dot{p}_\epsilon &= dV(\mathcal{P}^{(int)} - P) \\ \kappa &= \frac{\dot{V}}{V} & \dot{\pi}_i &= -\frac{\partial U}{\partial r_i} - \left( 1 + \frac{d}{dV} \right) \frac{p_\epsilon}{W} \vec{p}_i & \dot{p}_\epsilon &= dV(\mathcal{P}^{(int)} - P) + \frac{d}{dV} \sum_{i=1}^N \frac{\vec{p}_i^2}{m_i} \\ \text{Langevin piston } \dot{\vec{r}}'_i &= \frac{\vec{p}_i}{m_i} + \frac{\dot{V}}{3V} \vec{r}_i & \dot{\vec{p}}'_i &= -\frac{\partial U}{\partial \vec{r}_i} - \frac{\dot{V}}{3V} \vec{p}_i & \dot{V} &= \frac{p_V}{W} \\ \dot{p}_V &= \frac{1}{3V} \sum_{i=1}^N \left[ \frac{\vec{p}_i^2}{m_i} - \frac{\partial U}{\partial \vec{r}_i} \cdot \vec{r}_i \right] - P - \gamma \dot{V} + R(t) & \langle R(0)R(t) \rangle &= \frac{2\gamma kT}{W} \delta(t)\end{aligned}$$

## Grand canonical ensemble

## Euler's theorem

$$\begin{aligned}U(\lambda N, \lambda V, \lambda S) &= \lambda U(N, V, S) \Rightarrow U(N, V, S) = \mu N - PV + TS \\ A(\lambda N, \lambda V, T) &= \lambda A(N, V, T) \Rightarrow A(N, V, T) = \mu N - PV \\ H(\lambda N, \lambda S, P) &= \lambda H(N, S, P) \Rightarrow H(N, S, P) = \mu N + TS \\ G(\lambda N, P, T) &= \lambda G(N, P, T) \Rightarrow G(N, P, T) = \mu N\end{aligned}$$

## Thermodynamics

$$\begin{aligned}\tau(A) \left( \frac{\partial A}{\partial N}, V, T \right) &= -PV & d\tilde{A} &= -PdVpSdT - Nd\mu & \tilde{A}(\mu, \lambda V, T) &= \lambda \tilde{A}(\mu, V, T) \\ \text{Partition function } \sum_{N=0}^{\infty} \frac{1}{N! h^{3N}} e^{\beta \mu N} \int dx e^{-\beta \mathcal{H}(x, N)} &= e^{\beta PV}\end{aligned}$$

$$\begin{aligned}\mathcal{E}(\mu, V, T) &= \sum_{N=0}^{\infty} \frac{1}{N! h^{3N}} e^{\beta \mu N} \int dx e^{-\beta \mathcal{H}(x, N)} = \sum_{N=0}^{\infty} e^{\beta \mu N} Q(N, V, T) = e^{\beta PV} \\ \frac{PV}{kT} &= \ln \mathcal{E}(\mu, V, T) & z &= e^{\beta \mu} & \mathcal{E}(z, V, T) &= \sum_{N=0}^{\infty} z^N Q(N, V, T) \\ \langle N \rangle &= \frac{1}{\mathcal{E}(\mu, V, T)} \sum_{N=0}^{\infty} N e^{\beta \mu N} Q(N, V, T) = kT \left( \frac{\partial}{\partial \mu} \ln \mathcal{E}(\mu, V, T) \right)_{V, T} \\ \langle N \rangle &= z \frac{\partial}{\partial z} \ln \mathcal{E}(z, V, T)\end{aligned}$$

## Ideal gas

$$\begin{aligned}Q(N, V, T) &= \frac{1}{N!} \left[ V \left( \frac{2\pi m}{\beta h^2} \right)^{\frac{3}{2}} \right]^N = \frac{1}{N!} \left( \frac{V}{\lambda^3} \right)^N & \mathcal{E}(z, V, T) &= e^z V \lambda^3 \\ \langle N \rangle &= V \frac{\lambda^3}{z^3} \Rightarrow z = \frac{\langle N \rangle \lambda^3}{V} & \frac{PV}{kT} &= \ln \mathcal{E}(z, V, T) = \frac{V}{\lambda^3} z = \langle N \rangle\end{aligned}$$

## Particle number fluctuations

$$\begin{aligned}\Delta N &= \sqrt{\langle N^2 \rangle - \langle N \rangle^2} & z \frac{\partial}{\partial z} z \frac{\partial}{\partial z} \ln \mathcal{E}(z, V, T) &= \langle N^2 \rangle - \langle N \rangle^2 \\ \Delta N^2 &= kTV \frac{\partial^2 P}{\partial \mu^2} & a(v, T) &= \frac{1}{N} A \left( N, \frac{V}{N}, T \right) \Rightarrow \mu = a(v, T) - V \frac{\partial a}{\partial v} \\ P &= -\frac{\partial a}{\partial v} & \frac{\partial P}{\partial \mu} &= -\frac{\partial^2 a}{\partial v^2} \frac{\partial v}{\partial \mu} & \frac{\partial \mu}{\partial v} &= \frac{\partial a}{\partial v} - \frac{\partial a}{\partial v} v \frac{\partial^2 a}{\partial v^2} \Rightarrow \frac{\partial P}{\partial \mu} = \frac{1}{v} \\ \frac{\partial^2 P}{\partial \mu^2} &= -\frac{1}{v^3} \frac{\partial P}{\partial v} & \kappa_T &= -\frac{1}{v} \frac{\partial P}{\partial v} \Rightarrow \Delta N^2 = \frac{\langle N \rangle kT}{v} \kappa_T & \frac{\Delta N}{\langle N \rangle} &\sim \frac{1}{\sqrt{\langle N \rangle}}\end{aligned}$$

## Quantifying uncertainties and sampling quality

## Autocorrelation analysis

$$\begin{aligned}C_f(t') &= \frac{\langle (f(x) - \langle f \rangle)(f(t+t') - \langle f \rangle) \rangle}{\sigma_f^2} \\ C_f(t') &= \frac{1}{\sigma_f^2} \frac{1}{N} \sum_{i=1}^{N-t'} (f(j\Delta t) - \langle f \rangle)(f(j\Delta t + t') - \langle f \rangle) & \tau_f &= \int_0^{+\infty} dt' C_f(t') \\ N_f^{ind} &\simeq \frac{t_{sim}}{\tau_f} & SE(f) &= \frac{\sigma_f}{\sqrt{N_f^{ind}}} \sim \sigma_f \sqrt{\frac{\tau_f}{t_{sim}}}\end{aligned}$$

## Block averaging analysis

$$BSE(f, n) = \frac{\sigma_n}{\sqrt{M}}$$

## Protein motions

## Gaussian network models

$$\begin{aligned}U_{ij} &= \gamma_{ij} (\Delta \vec{r}_j - \Delta \vec{r}_i) \cdot (\Delta \vec{r}_j - \Delta \vec{r}_i) = \gamma_{ij} \Delta \vec{r}_{ij}^2 & U_{GNM} &= \frac{\gamma}{2} \sum_i \sum_j \Delta \vec{r}_{ij}^2 \\ U_{GNM} &= \frac{\gamma}{2} \Delta \vec{r}(t)^T \Gamma \Delta \vec{r}(t) & \langle \Delta \vec{r}_i \cdot \Delta \vec{r}_j \rangle &= \frac{3kT}{\gamma} [\Gamma^{-1}]_{ij} \\ \langle \Delta \vec{r}_i \cdot \Delta \vec{r}_i \rangle &= \sum_k [\Delta r_i^2]_k & B_i &= \frac{8\pi^2}{3} \langle \Delta r_i^2 \rangle \\ \text{Normal mode analysis: } U &= \frac{1}{2} \sum_i \sum_j H_{ij} (q_i - q_i^0)(q_j - q_j^0) \\ C &= \langle \Delta \vec{q} \Delta \vec{q}^T \rangle = \frac{1}{Q} \int d\vec{q} \Delta \vec{q} \Delta \vec{q}^T e^{-\frac{\Delta \vec{q}^T H \Delta \vec{q}}{2kT}} d^N \Delta \vec{q} = kTH^{-1}\end{aligned}$$

## Anisotropic network model

$$\begin{aligned}U_{ANM} &= \frac{1}{2} \sum_{ij} \gamma(r_{ij} - r_{ij}^0)^2 \Rightarrow \frac{\partial^2 U}{\partial x_i \partial x_j} = -\gamma \frac{(x_i - x_j)(y_i - y_j)}{r_{ij}^2} & \langle \Delta \vec{r}_i \cdot \Delta \vec{r}_j \rangle &= \frac{3kT}{\gamma} \sum_k \lambda_k^{-1} [\vec{u}_k \vec{u}_k^T]_{ij} \\ \text{Correlation cosine } I_k &= \frac{\Delta \vec{q}_{AB} \cdot \vec{u}_k}{|\Delta \vec{q}_{AB}|} & C_0 &= \sqrt{\sum_k I_k^2} \\ \text{Degree of connectivity } \kappa_k &= N^{-1} e^{-\sum_{i=1}^N \alpha(\Delta r_i)^2} \log(\alpha(\Delta r_i)^2|_k) & \sum_{i=1}^N \alpha(\Delta r_i)^2|_k &= 1\end{aligned}$$

## Essential dynamics

$$\begin{aligned}\text{Covariance matrix } C_{ij} &= \overline{(x_i(t) - \overline{x_i(t)})(x_j(t) - \overline{x_j(t)})} \\ \text{Correlation matrix } R_{ij} &= \frac{\overline{(x_i(t) - \overline{x_i(t)})(x_j(t) - \overline{x_j(t)})}}{\sigma_{x_i} \sigma_{x_j}} \\ PC_k(t) &= \sum_{i=1}^N \vec{d}_i(t) \cdot \vec{u}_i^T & c_k &= \frac{2}{T_{sim}} \left( \int_0^{T_{sim}} \cos \left( \pi \frac{k_B T}{\lambda_k} t \right) PC_k(t) dt \right)^2 \left( \int_0^{T_{sim}} PC_k^2(t) dt \right)^{-1} \\ \Omega_{A,B} &= 1 - \left[ \frac{\sum_{k=1}^{3N-6} (\lambda_k^A + \lambda_k^B) - 2 \sum_{k=1}^{3N-6} \sum_{j=1}^{3N-6} \sqrt{\lambda_k^A \lambda_j^B} (\vec{u}_k^A \cdot \vec{u}_j^B)^2}{\sum_{k=1}^{3N-6} (\lambda_k^A + \lambda_k^B)} \right]^{\frac{1}{2}}\end{aligned}$$

## Monte Carlo methods

## Introduction

$$\begin{aligned}f(x) &\geq 0 \wedge \int f(x) dx = 1 & I &= \int dx \phi(x) f(x) \equiv \langle \phi \rangle_f \\ \tilde{I}_M &= \frac{1}{M} \int_{i=1}^M \phi(x_i) & \lim_{M \rightarrow \infty} \tilde{I}_M &= I \\ \int dx \phi(x) f(x) &= \frac{1}{M} \int_{i=1}^M \phi(x_i) \pm \frac{1}{\sqrt{M}} \left[ \langle \phi^2 \rangle_f - \langle \phi \rangle_f^2 \right]^{\frac{1}{2}} \\ P(X) &= \int_a^X f(x) dx & f(X) &= \frac{dP}{dX} & X \geq x \Rightarrow g(X) \geq g(x) & \tilde{P}(Y = g(X)) = P(X)\end{aligned}$$

## Monte Carlo methods (contd)

## Importance sampling

$$\begin{aligned}I &= \int dx \phi(x) f(x) = \int dx \left[ \frac{\phi(x) f(x)}{h(x)} \right] h(x) = \int dx \psi(x) h(x) = \frac{1}{M} \sum_{i=1}^M \psi(x_i) \pm \frac{1}{\sqrt{M}} \left[ \langle \psi^2 \rangle_h - \langle \psi \rangle_h^2 \right]^{\frac{1}{2}} \\ \sigma^2[h] &= \int dx \frac{\phi^2(x) f^2(x)}{h(x)} - \left[ \int dx \phi(x) f(x) \right]^2 \\ \delta F[h] &= -\frac{\phi^2(x) f^2(x)}{h^2(x)} \delta h(x) - \lambda \delta h(x) & \frac{\delta F[h]}{\delta h(x)} &= 0 \Rightarrow h(x) = \frac{1}{\sqrt{-\lambda}} \phi(x) f(x)\end{aligned}$$

## Markov chains

$$\begin{aligned}\text{Detailed balance } R(x|y)f(y) &= R(y|x)f(x) \\ \text{Rejection method } R(x|y) &= A(x|y)T(x|y) & r(x|y) &= \frac{T(y|x)f(x)}{T(x|y)f(y)} \\ A(x|y) &= \min[1, r(x|y)] \\ \text{Metropolis algorithm } r(x_{k+1}|x_k) &= \frac{T(x_k|x_{k+1})f(x_{k+1})}{T(x_{k+1}|x_k)f(x_k)} \\ \text{Canonical distribution } A(r'|r) &= \min \left[ 1, e^{-\beta(U(r') - U(r))} \right]\end{aligned}$$

$$\begin{aligned}\text{Trial move } \begin{cases} x'_i = x_i + \frac{1}{\sqrt{3}}(\xi_x - 0.5)\Delta \\ y'_i = y_i + \frac{1}{\sqrt{3}}(\xi_y - 0.5)\Delta \\ z'_i = z_i + \frac{1}{\sqrt{3}}(\xi_z - 0.5)\Delta \end{cases} \\ \text{Isothermal-isobaric } A(V'|V) &= \min \left[ 1, e^{-\beta P(V' - V)} e^N \ln \frac{V'}{V} e^{-\beta(U(r') - I)} \right]\end{aligned}$$

$$\begin{aligned}\text{Gran canonical } \begin{cases} A(N+1|N) = \min \left[ 1, \frac{V}{\lambda^3(N+1)} e^{\beta \mu} e^{-\beta(U(r') - U(r))} \right] \\ A(N-1|N) = \min \left[ 1, \frac{\lambda^3 N}{V} e^{-\beta \mu} e^{-\beta(U(r') - U(r))} \right] \end{cases}\end{aligned}$$

## Hybrid Monte Carlo

$$\begin{aligned}A(r', p'|r, p) &= \min \left[ 1, e^{-\beta \Delta \mathcal{H}} \right] & T(r', p'|r, p) &= T(r, -p|r', -p') \\ \int d^N p d^N p' T(r', p'|r, p) A(r', p'|r, p) f(r, p) &= \int d^N p d^N p' T(r, p|r', p') A(r, p|r', p') f(r', p')\end{aligned}$$

## Free energy calculations

## Free energy perturbation theory

$$\begin{aligned}\Delta A_{AB} &= -kT \ln \frac{Z_B}{Z_A} & \frac{Z_B}{Z_A} &= \langle e^{-\beta[U_B(\vec{r}_1, \dots, \vec{r}_N) - U_A(\vec{r}_1, \dots, \vec{r}_N)]} \rangle_A \\ \Delta A_{AB} &= -kT \ln \langle e^{-\beta[U_B(\vec{r}_1, \dots, \vec{r}_N) - U_A(\vec{r}_1, \dots, \vec{r}_N)]} \rangle_A \\ \text{Adiabatic switching: } \frac{kT}{Z} \frac{\partial Z}{\partial \lambda} &= \frac{kT}{Z} \int d^N \vec{r} \left( -\beta \frac{\partial U}{\partial \lambda} \right) e^{-\beta U(\vec{r}_1, \dots, \vec{r}_N)} = -\langle \frac{\partial U}{\partial \lambda} \rangle \\ \text{Thermodynamics integration: } \Delta A_{AB} &= \int_0^1 \left( \frac{\partial A}{\partial \lambda} \right) d\lambda = \int_0^1 \langle \frac{\partial U}{\partial \lambda} \rangle_\lambda d\lambda \\ \text{Adiabatic free energy dynamics: } \left\langle \frac{p_\lambda^2}{2m_\lambda} \right\rangle &= kT\lambda & Z(\lambda, \beta) &= \int d^N \vec{r} e^{-\beta U(\vec{r}, \lambda)} \\ \mathcal{H}_{eff}(\lambda, p_\lambda) &= \frac{p_\lambda^2}{2m_\lambda} - \frac{1}{\beta} \ln Z(\lambda, \beta) & \tilde{P}_{adb}(\lambda, \beta, \beta_\lambda) &= [Z(\lambda, \beta)]^{\frac{\beta_\lambda}{\beta}} \\ A(\lambda) &= -kT \ln Z(\lambda, \beta) + const\end{aligned}$$

## Jarzynski's equality

$$\begin{aligned}W_{AB} &= \langle W_{AB}(x) \rangle_A \geq \Delta A_{AB} & \langle e^{-\beta W_{AB}(x_0)} \rangle_A &= e^{-\beta \Delta A_{AB}} \\ \text{Pulling experiment: } U(\vec{r}_1, \dots, \vec{r}_N, t) &= U_0(\vec{r}_1, \dots, \vec{r}_N) + \frac{1}{2} k(|\vec{r}_1 - \vec{r}_N| - r_{eq} - vt)^2 \\ \langle e^{-\beta W_\tau} \rangle &= \int \mathcal{W}_\tau P(\mathcal{W}_\tau) e^{-\beta W_\tau} \\ P(\mathcal{W}_\tau) \sim N &\Rightarrow \ln \langle e^{-\beta W_\tau} \rangle \simeq -\beta \langle W_\tau \rangle + \frac{\beta^2}{2} (\langle W_\tau^2 \rangle - \langle W_\tau \rangle^2)\end{aligned}$$

## Replica exchange Monte Carlo

$$\begin{aligned}F(\vec{r}^{(1)}, \dots, \vec{r}^{(M)}) &= \prod_{K=1}^M f_K(\vec{r}^{(K)}) & f_K(\vec{r}^{(K)}) &= \frac{e^{-\beta_K U(\vec{r}^{(K)})}}{Q(N, V, T_K)} \\ T(\vec{r}^{(K)}, \vec{r}^{(K+1)} | \vec{r}^{(K)}, \vec{r}^{(K+1)}) &= T(\vec{r}^{(K)}, \vec{r}^{(K+1)} | \vec{r}^{(K)}, \vec{r}^{(K+1)}) \\ A(\vec{r}^{(K+1)}, \vec{r}^{(K)} | \vec{r}^{(K)}, \vec{r}^{(K+1)}) &= \min \left[ 1, e^{-\Delta \kappa_{K, K+1}} \right] \\ \Delta_{K, K+1} &= (\beta_K - \beta_{K+1}) \left[ U(\vec{r}^{(K+1)}) - U(\vec{r}^{(K)}) \right] \\ \text{Wang-Landau sampling } Q(\beta) &= \int_0^\infty dE e^{-\beta E} \Omega(E) & A(E_2|E_1) &= \min \left[ 1, \frac{\Omega(E_2)}{\Omega(E_1)} \right]\end{aligned}$$

## Rare events

## Reaction coordinates

$$\begin{aligned}P(s_1, \dots, s_n) &= \frac{C_N}{Q(N, V, T)} \int d^N \vec{p} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})} \prod_{\alpha=1}^n \delta(f_\alpha(\vec{r}_1, \dots, \vec{r}_N) - s_\alpha) \\ A(s_1, \dots, s_n) &= -fT \ln P(s_1, \dots, s_n)\end{aligned}$$

## Blue moon ensemble

$$\begin{aligned}\frac{dA}{ds} &= -\frac{kT}{P(s)} \frac{dP}{ds} & A(q) &= A(s^{(i)}) + \int_{s^{(i)}}^q \frac{dA}{ds} ds & \Delta A &= \int_{s^{(i)}}^{s^{(f)}} \frac{dA}{ds} ds \\ P(s) &= \langle \delta(f_1(\vec{r}_1, \dots, \vec{r}_N) - s) \rangle & \frac{1}{P(s)} \frac{dP}{ds} &= -\beta \left\langle \frac{\partial \mathcal{H}}{\partial q_1} \right\rangle^{cond} \\ A(q) &= A(s^{(i)}) + \int_{s^{(i)}}^q \left\langle \frac{\partial \mathcal{H}}{\partial q_1} \right\rangle_s^{cond} ds\end{aligned}$$

## WHAM

$$\begin{aligned}\text{Umbrella sampling } W_k(f_1(\vec{r}_1, \dots, \vec{r}_N), s_k) &= \frac{1}{k} [f_1(\vec{r}_1, \dots, \vec{r}_N) - s_k]^2 \Rightarrow P(s, s^{(k)}) \\ \tilde{P}(q, s^{(k)}) &= e^{\beta A_k} \int d^N \vec{r} e^{-\beta U(\vec{r})} e^{-\beta W_k(f_1(\vec{r}), s^{(k)})} \delta(f_1(\vec{r}) - q) \\ e^{-\beta A_k} &= e^{-\beta A_0} \left\langle e^{-\beta W_k(f_1(\vec{r}), s^{(k)})} \right\rangle & e^{-\beta A_0} &= \int d^N \vec{r} e^{-\beta U(\vec{r})} \\ P_k(q) &= e^{-\beta(A_k - A_0) \beta W_k(q, s^{(k)})} \tilde{P}(q, s^{(k)}) \\ P(q) &= \sum_{k=1}^n C_k(q) P_k(q) & \sum_{k=1}^n C_k(q) &= 1 & \tilde{P}(q, s^{(k)}) &\sim \frac{1}{n_k \Delta q} \tilde{H}_k(q) \\ \hat{\sigma}_k^2 &= \frac{\epsilon_k(q) \tilde{H}_k(q)}{n_k \Delta q} & \hat{\sigma}_k^2 &= e^{-2\beta(A_k - A_0)} e^{2\beta W_k(q, s^{(k)})} \hat{\sigma}_k^2 & \sigma^2 &= \sum_{k=1}^n C_k^2(q) \hat{\sigma}_k^2 \\ C_k(q) &= \frac{n_k e^{\beta A_k} e^{-\beta W_k(q, s^{(k)})}}{\sum_{j=1}^n n_j e^{\beta A_k} e^{-\beta W_k(q, s^{(j)})}} \\ P(q) &= \frac{\sum_{k=1}^n n_k \tilde{P}(q, s^{(k)})}{\sum_{k=1}^n n_k e^{\beta(A_k - A_0)} e^{-\beta W_k(q, s^{(k)})}} & e^{\beta(A_k - A_0$$