

### Mechanical quantities 1/13 s07/2

- Temperature (NVE MD):
 
$$T_{\text{kin}} = \frac{E_{\text{kin}}}{fk_B/2}$$
 notation here:  
 $U = U(r^N)$  = potential energy  
 $E = E(T, V)$  = internal energy  
 $f = \#$  of degrees of freedom
- Internal energy:
 
$$E = \langle E_{\text{kin}} + U \rangle \stackrel{NVT}{=} \frac{f}{2} k_B T + \langle U \rangle \equiv E_{\text{id}} + E_{\text{res}}$$
 res = residual  
 see next slide
- Pressure
 
$$p = \frac{N}{V} k_B T - \left\langle \left( \frac{\partial U(V^{1/3} \xi^N)}{\partial V} \right)_{\xi^N} \right\rangle \equiv p_{\text{id}} + p_{\text{res}}$$

$$\beta = 1/k_B T$$

- dimensionless (scaled) coordinates  $\xi_i: \tilde{r}_i = V^{1/3} \xi_i$   
 - red derivative is calculated at constant  $\xi^N$ , whole configurations is uniformly shrank/swelled  
 -  $p_{\text{id}}$  = kinetic contribution (=ideal gas)  
 -  $p_{\text{res}}$  = cohesion contribution

### Entropic quantities 6/13 s07/2

These include  $F, G$  (partition function needed),  $S$  (number of states  $W$ ),  $\mu, \Delta G, \dots$

Useless approach:

$$Q = \frac{\int e^{-\beta U} d\mathbf{r}^N}{1} = \frac{\int e^{-\beta U} d\mathbf{r}^N}{V^{-N} \int e^{-\beta U} e^{+\beta U} d\mathbf{r}^N} = \frac{V^N}{\langle e^{\beta U} \rangle}$$

**Usage:** equilibria in general; solubility, ligand-receptor binding, stability of biomolecules, ...

- thermodynamic integration: over a real variable ( $T, V, P$ ) or coupling parameter
- non-Boltzmann sampling: gradual insertion, alchemical transmutation; umbrella sampling; multiple histogram reweighting; metadynamics
- Widom particle insertion method
- reversible work calculated by the integration of force
- local density method

### Pressure in the NVT ensemble: derivation + 2/13 s07/2

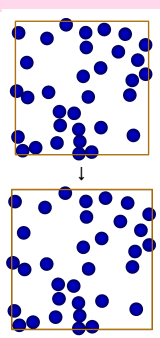
$$dF = -SdT - pdV \quad \langle X \rangle = \frac{1}{Q_N} \int_{V^N} X(\mathbf{r}^N) d\exp[-\beta U(\mathbf{r}^N)] \mathbf{r}^N$$

$$p = - \left( \frac{\partial F}{\partial V} \right)_T, \quad F = -k_B T \ln \frac{Q_N}{N! \Lambda^{3N}}$$

$$Q_N = \int_{V^N} \exp[-\beta U(\mathbf{r}^N)] d\mathbf{r}^N \quad \tilde{r}_i = V^{1/3} \xi_i \quad \int_{1^{3N}} \exp[-\beta U(V^{1/3} \xi^N)] V^N d\xi^N$$

$$p = - \left( \frac{\partial F}{\partial V} \right)_T = k_B T \left( \frac{\partial \ln Q_N}{\partial V} \right)_{\xi^N} = \frac{k_B T}{Q_N} \left( \frac{\partial Q_N}{\partial V} \right)_{\xi^N}$$

$$= \frac{k_B T}{Q_N} \int_{1^{3N}} \exp[-\beta U(V^{1/3} \xi^N)] N V^{N-1} d\xi^N + \frac{k_B T}{Q_N} \int_{1^{3N}} \exp[-\beta U(V^{1/3} \xi^N)] (-\beta) \left( \frac{\partial U(V^{1/3} \xi^N)}{\partial V} \right)_{\xi^N} V^N d\xi^N$$

$$= \frac{N}{V} k_B T - \left\langle \left( \frac{\partial U(V^{1/3} \xi^N)}{\partial V} \right)_{\xi^N} \right\rangle = \text{ideal part (kinetic)} + \text{residual part (correction)}$$


### Thermodynamic integration 7/13 s07/2

Remember physical chemistry:  $dF = -SdT - pdV, dG = -SdT + Vdp$

Canonical ensemble ( $\beta = 1/k_B T$ ):

$$\left( \frac{\partial F}{\partial V} \right)_T = -p, \quad \left( \frac{\partial (\beta F)}{\partial \beta} \right)_V = E, \quad \text{or} \quad \left( \frac{\partial (\beta F_{\text{res}})}{\partial \beta} \right)_V = \langle U \rangle$$

notation here:  
 $U = U(\mathbf{r}^N)$   
 = potential energy  
 $E = E(T, V)$   
 = internal energy

- Numerically integrated:  $p, E$  must be determined in many points
- Start from a suitable reference state (ideal gas, hard spheres, Lennard-Jones, Einstein crystal)

Proof # 1 of  $\frac{\partial (\beta F)}{\partial \beta} = E$ :

$$\frac{\partial (\beta F)}{\partial \beta} = \frac{\partial (F/T)}{\partial (1/T)} = \frac{\partial (F/T)}{\partial T} \cdot \frac{\partial (1/T)}{\partial T} = \frac{-ST - F}{T^2} \cdot \left( \frac{-1}{T^2} \right) = ST + F = E$$

Proof # 2 of  $\frac{\partial (\beta F)}{\partial \beta} = E$ :

$$\frac{\partial (\beta F)}{\partial \beta} = -\frac{\partial \ln Z}{\partial \beta} = -\frac{1}{Z} \frac{\partial Z}{\partial \beta} = -\frac{\partial \sum_{\psi} e^{-\beta \mathcal{E}(\psi)} / \partial \beta}{\sum_{\psi} e^{-\beta \mathcal{E}(\psi)}} = \frac{\sum_{\psi} [-\mathcal{E}(\psi) e^{-\beta \mathcal{E}(\psi)}]}{\sum_{\psi} e^{-\beta \mathcal{E}(\psi)}} = \langle \mathcal{E} \rangle = E$$

### Residual quantities 3/13 s07/2

= with respect to the standard state of ideal gas at the same temperature, volume (= density), and composition as the given system. Usefull in the canonical (NVT) ensemble.  
 sometimes called "excess"

For the Helmholtz energy: ideal gas:  $Q_N = V^N$

$$F = -k_B T \ln Z_N = -k_B T \ln \frac{Q_N}{N! \Lambda^{3N}} = -k_B T \ln \frac{V^N}{N! \Lambda^{3N}} - k_B T \ln \frac{Q_N}{V^N} \equiv F_{\text{id}} + F_{\text{res}}$$

**Refresh:**  
 de Broglie thermal wavelength:

$$\Lambda = \frac{h}{\sqrt{2\pi m k_B T}}$$

chemical potential of ideal gas:

$$\mu_{\text{id}} = \left( \frac{\partial F_{\text{id}}}{\partial N} \right)_{T, V} = k_B T \ln \frac{N \Lambda^3}{V}$$

### Integration over a coupling parameter + 8/13 s07/2

Let us consider any dependence ( $\beta U$ )( $\lambda$ ), e.g.:

$$(\beta U)(\lambda) = \begin{cases} \beta[U_0 + \lambda(U_1 - U_0)] & \lambda = \text{coupling parameter, } \lambda \in [0, 1] \\ \lambda U & \lambda \equiv \beta: \text{ see previous slide} \end{cases}$$

then

$$\frac{\partial \beta F_{\text{res}}}{\partial \lambda} = -\frac{\partial \ln Q}{\partial \lambda} = -\frac{1}{Q} \int \frac{\partial e^{-\beta U}}{\partial \lambda} d\mathbf{r}^N = \frac{1}{Q} \int \frac{\partial (\beta U)(\lambda)}{\partial \lambda} e^{-\beta U(\lambda)} d\mathbf{r}^N = \left\langle \frac{\partial (\beta U)(\lambda)}{\partial \lambda} \right\rangle_{\lambda}$$

$$(\beta F_{\text{res}})(\lambda_1) = (\beta F_{\text{res}})(\lambda_0) + \int_{\lambda_0}^{\lambda_1} \left\langle \frac{\partial (\beta U)(\lambda)}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

where  $\langle \cdot \rangle_{\lambda}$  = mean value in the ensemble (simulation) with potential  $U(\lambda)$

**Example 1:** for  $\lambda = \beta$  we get as before:

$$\beta_1 F_{\text{res}}(\beta_1) - \beta_0 F_{\text{res}}(\beta_0) = \int_{\beta_0}^{\beta_1} \langle U \rangle d\beta$$

**Example 2:** integration from an Einstein crystal to a real crystal.  
 NB: Einstein crystal = independent harmonic oscillators at lattice sites

### Pressure - virtual volume change method 4/13 s07/2

$$p = \frac{N}{V} k_B T - \left\langle \left( \frac{\partial U(V^{1/3} \xi^N)}{\partial V} \right)_{\xi^N} \right\rangle$$

**Numerical derivative** (for a selected series of configurations)

$$\frac{\partial U}{\partial V} = \frac{U(V + \Delta V) - U(V)}{\Delta V} + \mathcal{O}(\Delta V) \equiv \frac{U(\xi^N) - U(\xi^N)}{\Delta V} + \mathcal{O}(\Delta V)$$

$$\frac{\partial U}{\partial V} = \frac{U(V + \Delta V) - U(V - \Delta V)}{2\Delta V} + \mathcal{O}(\Delta V^2)$$

**Implementation:**  $U(V + \Delta V)$  means that the whole configuration (all distances) is swelled by the same ratio; for molecules w.r.t. a reference point (then,  $N = \#$  of molecules):

$$\left( \frac{V + \Delta V}{V} \right)^{1/3}$$

The scaled configuration is not included in the trajectory.

For models with a hard core such that swelling the box cannot cause an overlap, shrinking can be used:  $P = Nk_B T/V + \frac{k_B T}{\Delta V} (e^{-[U(V-\Delta V) - U(V)]/k_B T} + \mathcal{O}(\Delta V))$

### Non-Boltzmann sampling 9/13 s07/2

We want  $\langle \beta U \rangle_1$ , but we simulate  $\langle \beta U \rangle_0$  (can change  $\beta/U$  both)

$$\Delta(\beta U) = (\beta U)_1 - (\beta U)_0$$

$$\langle X \rangle_{(\beta U)_1} = \frac{\int X e^{-(\beta U)_1} d\mathbf{r}^N}{\int e^{-(\beta U)_1} d\mathbf{r}^N} = \frac{\int X e^{-(\beta U)_0} e^{-\Delta(\beta U)} d\mathbf{r}^N}{\int e^{-(\beta U)_0} e^{-\Delta(\beta U)} d\mathbf{r}^N} = \frac{\langle X e^{-\Delta(\beta U)} \rangle_0}{\langle e^{-\Delta(\beta U)} \rangle_0}$$

Helmholtz energy:

$$\Delta(\beta F_{\text{res}}) = \beta_1 F_{\text{res}}((\beta U)_1) - \beta_0 F_{\text{res}}((\beta U)_0)$$

$$= -\ln \left( \frac{Q_1}{Q_0} \right) = -\ln \left( \frac{\int e^{-(\beta U)_1} d\mathbf{r}^N}{\int e^{-(\beta U)_0} d\mathbf{r}^N} \right)$$

$$= -\ln \frac{\int e^{-(\beta U)_0} e^{-\Delta(\beta U)} d\mathbf{r}^N}{\int e^{-(\beta U)_0} d\mathbf{r}^N} = -\ln \langle e^{-\Delta(\beta U)} \rangle_0$$

$$= \ln \langle e^{+\Delta(\beta U)} \rangle_1$$

where the last equation follows from  $0 \leftrightarrow 1$  interchange

### Pressure from the virial of force + 5/13 s07/2

**The derivative expanded:**

$$\frac{\partial U(V^{1/3} \xi^N)}{\partial V} = \sum_{i=1}^N \frac{1}{3} V^{-2/3} \xi_i \cdot \frac{\partial U}{\partial \tilde{r}_i} = \frac{1}{3V} \sum_{i=1}^N \tilde{r}_i \cdot \frac{\partial U}{\partial \tilde{r}_i}$$

The result is

$$p = \frac{N}{V} k_B T + \frac{1}{3V} \langle W_f \rangle, \quad W_f = - \sum_{i=1}^N \tilde{r}_i \cdot \frac{\partial U}{\partial \tilde{r}_i} = \sum_{i=1}^N \tilde{r}_i \cdot \tilde{f}_i \quad (\text{virial of force})$$

... cannot be directly applied in the periodic boundary conditions.

- Pair additivity in the periodic boundary conditions  $\Rightarrow$

$$p = \frac{N}{V} k_B T - \frac{1}{3V} \sum_{i < j} \langle r_{ij} U'(r_{ij}) \rangle \equiv p_{\text{id}} + p_{\text{res}}$$

- For molecular models one can use either the site-frame ( $N = \#$  of sites/atoms) or molecular frame ( $N = \#$  of molecules; typically, ref. point = center of mass). Of course, the formulas differ.

### Non-Boltzmann sampling contd. 10/13 s07/2

- $\Delta(\beta U)$  must not be too large  $e^x = 1 + x + \dots$   
 $\ln(1+x) = x + \dots$
- the thermodynamic integration is recovered for infinitesimally small  $\Delta(\beta U)$ :

$$\Delta(\beta F_{\text{res}}) = -\ln \langle e^{-\Delta(\beta U)} \rangle_0$$

$$\approx -\ln(1 - \Delta(\beta U))_0$$

$$= -\ln(1 - \langle \Delta(\beta U) \rangle_0)$$

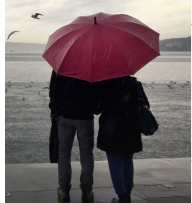
$$\approx \langle \Delta(\beta U) \rangle_0$$

$$\Rightarrow \partial(\beta F_{\text{res}})/\partial \lambda = \langle \partial(\beta U)/\partial \lambda \rangle_{\lambda}$$

- Several discrete  $\lambda$ : a) Fit + integrate; b) Simpson or similar rule
- Slow change of  $\lambda$  every MD step and integrate

**Umbrella sampling**

The system in the middle is sampled: mid =  $(\beta U)_0 + \Delta(\beta U)/2 = (\beta_0 U_0 + \beta_1 U_1)/2$ :

$$\Delta(\beta F_{\text{res}}) = \ln \langle e^{+\Delta(\beta U)/2} \rangle_{\text{mid}} - \ln \langle e^{-\Delta(\beta U)/2} \rangle_{\text{mid}}$$


https://positivestartup.com/2015/01/30/surviving-the-storm-together

## Widom particle insertion method I

11/13  
s07/2

Open system

$$dF = -SdT - pdV + \mu dN$$

$$\beta\mu = \left( \frac{\partial(\beta F)}{\partial N} \right)_{V,T} = - \left( \frac{\partial \ln Z_N}{\partial N} \right)_{V,T}$$

$$\beta\mu_{res} = \left( \frac{\partial(\beta F_{res})}{\partial N} \right)_{V,T} = - \left( \frac{\partial \ln(Q_N/V^N)}{\partial N} \right)_{V,T} \approx - \left( \ln \frac{Q_{N+1}}{V^{N+1}} - \ln \frac{Q_N}{V^N} \right)$$

$$\exp(-\beta\mu_{res}) = \frac{1}{V} \frac{Q_{N+1}}{Q_N}$$

Or for the full chemical potential:

$$e^{-\beta\mu} = \frac{Z_{N+1}}{Z_N} = \frac{Q_{N+1}/[(N+1)! \Lambda^{3(N+1)}]}{Q_N/[N! \Lambda^{3N}]} = \frac{1}{(N+1)\Lambda^3} \frac{Q_{N+1}}{Q_N} \approx \frac{1}{N\Lambda^3} \frac{Q_{N+1}}{Q_N}$$

then by subtracting  $\mu^{id} = k_B T \ln \left( \frac{N\Lambda^3}{V} \right)$  we get the same  $\mu_{res} = \mu - \mu^{id}$

## Reversible work by integrating the mean force

13/13  
s07/2

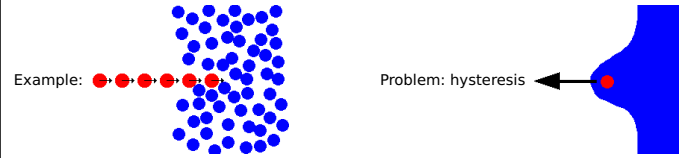
From thermodynamics:

$$\Delta G = W_{\text{other than pressure-volume}} [p, T]$$

$$\Delta\mu_i = - \int_{r_i(1)}^{r_i(2)} \langle \vec{f}_i \rangle \cdot d\vec{r}_i$$

where  $\vec{f}_i = -\partial U / \partial \vec{r}_i$  is the force acting on particle  $i$

Molecules: the force applies to the center of mass or other reference point



## Widom particle insertion method II

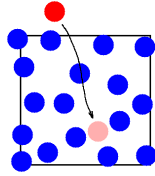
12/13  
s07/2

$$\exp(-\beta\mu_{res}) = \frac{1}{V} \frac{Q_{N+1}}{Q_N}$$

$$N \rightarrow N+1 \quad U_{N+1} = U_N + \psi(N)$$

$$\frac{1}{V} \frac{Q_{N+1}}{Q_N} = \frac{1}{V Q_N} \int \exp(-\beta U_N - \beta \psi) d\vec{r}_1 \dots d\vec{r}_{N+1} = \frac{1}{V} \int (e^{-\beta \psi})_N d\vec{r}_{N+1}$$

$$\exp(-\beta\mu_{res}) = \frac{1}{V} \int (e^{-\beta \psi})_N d\vec{r}_{N+1} = \langle (e^{-\beta \psi})_N \rangle_{\text{random } \vec{r}_{N+1}}$$



where  $\frac{1}{V} \int X d\vec{r}_{N+1} = \langle X \rangle_{\text{random } \vec{r}_{N+1}}$  = mean value of  $X$  over positions of the  $(N+1)$ -th particle in volume  $V$ , calculated by MC integration (inserting a particle at random place)

●  $(N+1)$ -th particle does not influence the system – it is virtual (fictitious, ghost)

● Problem: dense systems, large solutes

Remedy: gradual insertion (thermodynamic integration or by finite steps)

**Similar:** solute insertion  $\Rightarrow$  solubility, Henry constant