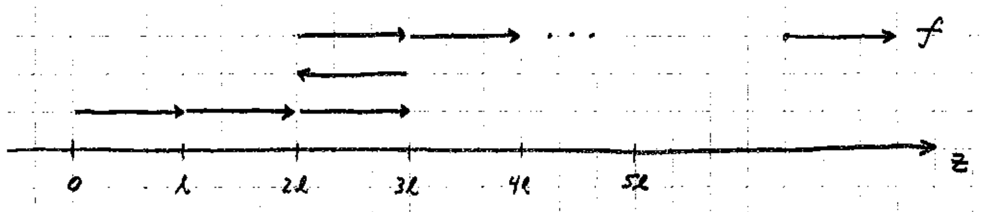
1D cooperative chain model



Introduce variables

$$\sigma_i = \pm 1 \qquad \text{forward / backward step of length } \ell, \quad i = 1, \ldots N$$

End-to-end distance $\quad z = z_N - z_0 = \ell \sum_{i=1}^{N} \sigma_i$

Cooperativity modeled by nearest-neighbor interactions

$$\frac{U_{int}}{k_B T} = -\gamma \sum_{i=1}^{N-1} \sigma_i \sigma_{i+1} \qquad \gamma = \text{stiffness or cooperativity parameter}$$

External force in the $+z$-direction

$$U_{ext} = -fz = -f\ell \sum_{i=1}^{N} \sigma_i \implies \frac{U_{ext}}{k_B T} = -\alpha \sum_{i=1}^{N} \sigma_i \quad \text{where } \alpha = \frac{f\ell}{k_B T}$$

α = the energy of aligning one segment with the external force in units of $k_B T$

Partition function

$$Z = \sum_{\sigma_1 = \pm 1} \sum_{\sigma_2 = \pm 1} \cdots \sum_{\sigma_N = \pm 1} e^{-U/k_B T} = \sum_{\sigma_1 = \pm 1} \sum_{\sigma_2 = \pm 1} \cdots \sum_{\sigma_N = \pm 1} \exp\left\{ \alpha \sum_{i=1}^{N} \sigma_i + \gamma \sum_{i=1}^{N-1} \sigma_i \sigma_{i+1} \right\}$$

Average elongation

$$\langle z \rangle = \frac{\sum_{\sigma_1=\pm 1} \cdots \sum_{\sigma_N = \pm 1} \left(\ell \sum_{i=1}^{N} \sigma_i \right) e^{-U/k_B T}}{\sum_{\sigma_1 = \pm 1} \cdots \sum_{\sigma_N = \pm 1} e^{-U/k_B T}} = \ell \frac{1}{Z} \frac{dZ}{d\alpha} = \ell \frac{d \ln Z}{d\alpha}$$

$$\frac{\langle z \rangle}{L_{TOT}} = \frac{1}{N} \frac{d \ln Z}{d\alpha} \qquad L_{TOT} = N\ell \qquad \text{(relative extension)}$$

We need to find a closed-form expression of $Z(\alpha)$

Calculate Z

$$Z = \sum_{\sigma_1=\pm1} \cdots \sum_{\sigma_N=\pm1} e^{\frac{\alpha}{2}\sigma_1} e^{\frac{\alpha}{2}\sigma_1 + \gamma\sigma_1\sigma_2 + \frac{\alpha}{2}\sigma_2} \cdots e^{\frac{\alpha}{2}\sigma_{N-1} + \gamma\sigma_{N-1}\sigma_N + \frac{\alpha}{2}\sigma_N} e^{\frac{\alpha}{2}\sigma_N}$$

Define functions
$$\begin{cases} V(\sigma) = e^{\frac{\alpha}{2}\sigma} \\ T(\sigma,\sigma') = e^{\frac{\alpha}{2}\sigma + \gamma\sigma\sigma' + \frac{\alpha}{2}\sigma'} \end{cases} \Rightarrow$$

$$Z = \sum_{\sigma_1=\pm1} \cdots \sum_{\sigma_N=\pm1} V(\sigma_1)\,T(\sigma_1\sigma_2)\,T(\sigma_2\sigma_3) \cdots T(\sigma_{N-1}\sigma_N)\,V(\sigma_N)$$

Compare with matrix multiplication

$$\sum_{i_1}\sum_{i_2} u_{i_1} W_{i_1 i_2} u_{i_2} = u^T W u$$

$$\sum_{i_1}\sum_{i_2}\sum_{i_3} u_{i_1} W_{i_1 i_2} W_{i_2 i_3} u_{i_3} = u^T W W u$$

$$\vdots$$

The same for Z because $\sigma_1 \sigma_2 \dots$ are just dummy variables

Define matrices

$$V = \begin{pmatrix} e^{\frac{\alpha}{2}} \\ e^{-\frac{\alpha}{2}} \end{pmatrix} \begin{array}{l} \longleftarrow \sigma = +1 \\ \longleftarrow \sigma = -1 \end{array}$$

$$T = \begin{pmatrix} e^{\alpha+\gamma} & e^{-\gamma} \\ e^{-\gamma} & e^{-\alpha+\gamma} \end{pmatrix}$$ <u>the transfer matrix</u>

Then

$$Z = V^T T^{N-1} V$$

Diagonalize T

T is real and symmetric $\Rightarrow$

$$T\bar{e}_\pm = \lambda_\pm \bar{e}_\pm \qquad \bar{e}_\pm \text{ orthonormal eigenvectors } \left(\bar{e}_+\cdot\bar{e}_- = 0,\ |\bar{e}_\pm| = 1\right)$$

Express V as a linear combination of $\bar{e}_+$ and $\bar{e}_-$

$$V = v_+\bar{e}_+ + v_-\bar{e}_- \qquad \text{for some constants } v_+ \text{ and } v_-$$

$$\begin{aligned} Z &= \left(v_+\bar{e}_+ + v_-\bar{e}_-\right) T^{N-1} \left(v_+\bar{e}_+ + v_-\bar{e}_-\right) \\ &= \left(v_+\bar{e}_+ + v_-\bar{e}_-\right)\left(v_+\lambda_+^{N-1}\bar{e}_+ + v_-\lambda_-^{N-1}\bar{e}_-\right) \\ &= v_+^2\lambda_+^{N-1} + v_-^2\lambda_-^{N-1} \end{aligned}$$

Assume $\lambda_+ > \lambda_-$ and N large

$$\ln Z = \ln v_+^2 + (N-1)\ln\lambda_+$$

$$\frac{\langle z\rangle}{L_{TOT}} = \frac{d}{d\alpha}\frac{\ln Z}{N} = \frac{d\ln\lambda_+}{d\alpha} \qquad N\to\infty$$

Note: For large N, it is sufficient to know λ_+

($\bar{e}_+$, $\bar{e}_-$, v_+, v_-, and λ_- not needed)

Find the eigenvalues of T

$$\det(T-\lambda I) = \begin{vmatrix} e^{\alpha+\gamma}-\lambda & e^{-\gamma} \\ e^{-\gamma} & e^{-\alpha+\gamma}-\lambda \end{vmatrix} = 0$$

$$(e^{\alpha+\gamma}-\lambda)(e^{-\alpha+\gamma}-\lambda) - e^{-2\gamma} = 0$$

$$\lambda^2 \underbrace{- \lambda\left(e^{\alpha+\gamma}+e^{-\alpha+\gamma}\right)}_{-\lambda(e^{\alpha}+e^{-\alpha})e^{\gamma}} + e^{2\gamma} - e^{-2\gamma} = 0$$

$$\lambda^2 - 2\lambda\cosh\alpha\, e^{\gamma} + e^{2\gamma} - e^{-2\gamma} = 0$$

$$(\lambda - e^{\gamma}\cosh\alpha)^2 \underbrace{- e^{2\gamma}\cosh^2\alpha + e^{2\gamma}}_{-e^{2\gamma}\sinh^2\alpha} - e^{-2\gamma} = 0 \qquad (\cosh^2 x - \sinh^2 x = 1)$$

$$(\lambda - e^{\gamma}\cosh\alpha)^2 - e^{2\gamma}\sinh^2\alpha - e^{-2\gamma} = 0$$

$$\lambda = e^{\gamma}\left(\cosh\alpha \pm \sqrt{\sinh^2\alpha + e^{-4\gamma}}\right)$$

The relative extension

$$\frac{\langle z\rangle}{L_{TOT}} = \frac{d\ln\lambda_+}{dz} = \frac{\sinh\alpha + \dfrac{\sinh\alpha\cosh\alpha}{\sqrt{\sinh^2\alpha + e^{-4\gamma}}}}{\cosh\alpha + \sqrt{\sinh^2\alpha + e^{-4\gamma}}}$$

$$= \frac{\sinh\alpha}{\sqrt{\sinh^2\alpha + e^{-4\gamma}}} \qquad \text{(long-dash curve in Fig. 9.5)}$$

3D random walk with an external force f (3D FJC model)

N steps $\bar{a}_i$ of length $|\bar{a}_i| = a$

The energy is $E = -\bar{f}\cdot\bar{R}$ where $\bar{R} = \sum_{i=1}^{N} \bar{a}_i$ is the end-to-end vector

Partition function

$$Z = \int_{\bar{a}_1} d\bar{a}_1 \dots \int_{\bar{a}_N} d\bar{a}_N \, e^{\bar{f}\cdot\bar{R}/k_BT} = \int_{\bar{a}_1} d\bar{a}_1 \dots \int_{\bar{a}_N} d\bar{a}_N \exp\left(\bar{f}\cdot\sum_{i=1}^{N}\bar{a}_i / k_BT\right)$$

$$= \int_{\bar{a}_1} d\bar{a}_1 \exp\left(\bar{f}\cdot\bar{a}_1/k_BT\right) \dots \int_{\bar{a}_N} d\bar{a}_N \exp\left(\bar{f}\cdot\bar{a}_N/k_BT\right)$$

Each step $\bar{a}_i$ is independent of the other

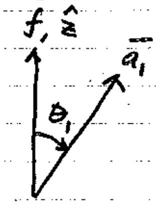
$$Z = \left[Z_1\right]^N \qquad Z_1 = \int_{\bar{a}_1} d\bar{a}_1 \exp\left(fa\cos\theta_1/k_BT\right)$$

Relative extension in f-direction

$$\left\langle \frac{\bar{f}\cdot\bar{R}}{f L_{TOT}} \right\rangle = \left\langle \frac{\bar{f}\cdot\sum a_i}{fNa} \right\rangle = \left\langle \frac{fa\sum_i \cos\theta_i}{fNa} \right\rangle = \langle \cos\theta_1 \rangle$$

$$\langle \cos\theta_1 \rangle = \frac{\int_{\bar{a}_1} d\bar{a}_1 \cos\theta_1 \exp\left(fa\cos\theta_1/k_BT\right)}{\int_{\bar{a}_1} d\bar{a}_1 \exp\left(fa\cos\theta_1/k_BT\right)} = \frac{k_BT}{a}\frac{\partial \ln Z_1}{\partial f}$$

Calculate Z_1



$dA = \sin\theta_1 \, d\theta_1 \, d\phi_1$

Choose $\hat{z}$ in $\bar{f}$-direction:

$$Z_1 = \int_0^{\pi} d\theta_1 \int_{-\pi}^{2\pi} d\phi_1 \sin\theta_1 \exp\left(fa\cos\theta_1 / k_BT\right)$$

$$= 2\pi \left(-\frac{k_BT}{fa}\right) \left[\exp\left(fa\cos\theta_1 / k_BT\right)\right]_0^{\pi}$$

$$= 2\pi \left(-\frac{k_BT}{fa}\right) \left(e^{-fa/k_BT} - e^{fa/k_BT} \right)$$

$$= \frac{4\pi k_BT}{fa} \sinh\left(\frac{fa}{k_BT}\right)$$

$$\frac{\partial Z_1}{\partial f} = \frac{4\pi k_BT}{a} \left(-\frac{1}{f^2} \sinh\left(\frac{fa}{k_BT}\right) + \frac{1}{f} \cosh\left(\frac{fa}{k_BT}\right) \cdot \frac{a}{k_BT} \right) \quad \Longrightarrow$$

$$\frac{\partial \ln Z_1}{\partial f} = \frac{1}{Z_1} \frac{\partial Z_1}{\partial f} = \frac{a}{k_BT} \coth \frac{fa}{k_BT} - \frac{1}{f}$$

Relative extension

$$\coth \frac{fa}{k_BT} - \frac{k_BT}{fa}$$

(short-dash curve in Fig. 9.5)

large f: $\langle \cos\theta_1 \rangle \to 1$ Ok.

small f: $\langle \cos\theta_1 \rangle \to \frac{k_BT}{fa} - \frac{k_BT}{fa} \to 0$ Ok.

$$\left(\coth x \to \frac{1}{x} + \cdots \qquad x \to 0 \right)$$

Helix-coil transition 9.5

Amino acids (like many biomolecules) are chiral, i.e. assymmetric with respect to reflection.

Formation of α-helices (which are right-handed) changes the degree of reflection assymmetry

Measurements of the difference in absorption of right- and left-circularly polarized light (circular dichroism) can be used to detect the α-helix content (and β-sheet content but not as accurately).

Simple model for the helix-coil transition

Variables:

$$\sigma_i = \begin{cases} +1 & \text{if } H \text{ bond between } CO(i) \text{ and } NH(i+4) \\ -1 & \text{if } H \text{ bond not present} \end{cases}$$

helix state

$$Z = \sum_{\text{all states}} e^{-G/k_B T}$$

G = free energy (include solvent effects)

$$-\frac{G}{k_B T} = \alpha \sum_{i=1}^{N} \sigma_i + \gamma \sum_{i=1}^{N-1} \sigma_i \sigma_{i+1}$$

Zimm - Bragg model (1950s)

bias parameter

cooperativity parameter

Bias parameter α

$$2\alpha = -\frac{\Delta G}{k_B T}$$ where ΔG is the free energy change when a H bond is formed, $\sigma_i = -1 \to +1$ $(\gamma = 0)$.

$\Delta G = \Delta E - T\Delta S$ naive guess: $\Delta E < 0$ and $\Delta S < 0$
(not necessarily so, see Fig. 9.7 on pg. 365)

ΔE: formation of a H bond $\Rightarrow$ energy reduction
BUT, H bonds to solvent molecules break so
net change ΔE depends on solvent conditions.
($\Delta E > 0 \Rightarrow$ random coil at low T)

ΔS: chain entropy decreases upon coil $\to$ helix transition.
BUT, still possible that $\Delta S > 0$ due to entropy
changes in the solvent.
($\Delta S > 0 \Rightarrow$ helix formation favorable at high T)

α is temperature dependent

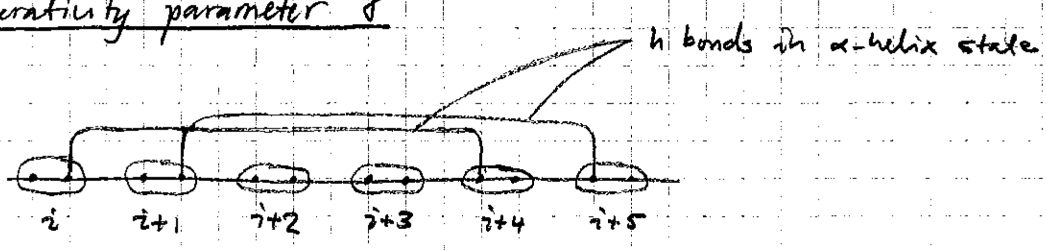
$$\alpha = -\frac{\Delta E - T\Delta S}{2k_B T}$$

Define: $T = T_m = \dfrac{\Delta E}{\Delta S} \Rightarrow \alpha = 0$ midpoint temperature

$T < T_m \Rightarrow \alpha < 0$ coil favorable (stat. weight $\propto e^{\alpha \sum \sigma_i}$)
assume $\Delta E > 0$ and $\Delta S \geq 0$ as in Fig. 9.7

$T > T_m \Rightarrow \alpha > 0$ helix favorable

Cooperativity parameter γ



Overlapping H bonds $\Rightarrow$ cooperativity ($\gamma > 0$)

Largely an entropic effect $\Rightarrow$ γ only weakly T dependent

End effects. Consider two different configurations with n consecutive H bonds.

$$- - - \;\ldots\; - \;\Rightarrow\; - + + \;\ldots\; + - \qquad \Delta G / k_B T = -2n\alpha + 4\gamma$$

$$- - - \;\ldots\; - \;\Rightarrow\; - - + \;\ldots\; + + \qquad \Delta G / k_B T = -2n\alpha + 2\gamma$$

Should be equivalent. Change boundary conditions.

Add two auxiliary amino acids $\sigma_0 = \sigma_{N+1} = -1$.

Now, helix initiation costs as much at the beginning of the chain as in the middle (as it should).

$$Z = \sum_{\sigma_1=\pm1} \cdots \sum_{\sigma_N=\pm1} \exp\left\{ \alpha \sum_{i=1}^{N} \sigma_i + \gamma \sum_{i=0}^{N} \sigma_i \sigma_{i+1} \right\}$$

$$= \sum_{\sigma_1=\pm1} \cdots \sum_{\sigma_N=\pm1} e^{-\frac{\alpha}{2}\sigma_0} e^{\frac{\alpha}{2}\sigma_0} \exp\left\{ \alpha \sum_{i=1}^{N} \sigma_i + \gamma \sum_{i=0}^{N} \sigma_i \sigma_{i+1} \right\} e^{\frac{\alpha}{2}\sigma_{N+1}} e^{-\frac{\alpha}{2}\sigma_{N+1}}$$

$$= \sum_{\sigma_1=\pm1} \cdots \sum_{\sigma_N=\pm1} e^{-\frac{\alpha}{2}\sigma_0} T(\sigma_0 \sigma_1) T(\sigma_1 \sigma_2) \cdots T(\sigma_N, \sigma_{N+1}) e^{-\frac{\alpha}{2}\sigma_{N+1}}$$

$$= \begin{pmatrix} 0 & e^{\frac{\alpha}{2}} \end{pmatrix} T^{N+1} \begin{pmatrix} 0 \\ e^{\frac{\alpha}{2}} \end{pmatrix} \quad ; \quad T = \begin{pmatrix} e^{\alpha+\gamma} & e^{-\gamma} \\ e^{-\gamma} & e^{-\alpha+\gamma} \end{pmatrix}$$

transfer matrix (as before)

Helix content $\quad \langle \theta \rangle = \frac{1}{N} \langle \sum_{i=1}^{N} \frac{1+\sigma_i}{2} \rangle = \frac{1}{2} + \frac{1}{2N} \langle \sum_{i=1}^{N} \sigma_i \rangle$

Need to calculate

$$\frac{1}{N} \langle \sum_{i=1}^{N} \sigma_i \rangle = \frac{1}{N} \frac{d \ln Z}{d\alpha} = \frac{d \ln \lambda_+}{d\alpha}$$

Diagonalize T

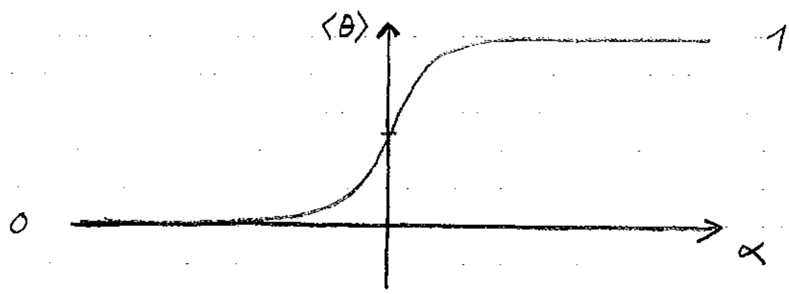
⋮

Get eigenvalues λ_+, λ_-

⋮

Take the limit N large $\Rightarrow \langle \theta \rangle = \frac{1}{2} + \frac{\sinh \alpha}{2\sqrt{\sinh^2 \alpha + e^{-4\gamma}}}$

The transition from coil dominates ($\alpha < 0$) to helix dominates ($\alpha > 0$) occurs at $T = T_m = \Delta E / \Delta S$ ($\alpha = 0$)



Experimentally, helix-coil transition sharp if N large:

$$\left.\frac{d\theta}{dT}\right|_{T\approx T_m} \text{ large}$$

$$\alpha \approx 0 \quad \Rightarrow \quad \theta \approx \frac{1}{2} + \frac{\alpha e^{2\gamma}}{2}$$

$$\alpha = -\frac{\Delta G}{2k_B T} = -\frac{\Delta E - T\Delta S}{2k_B T} = \left\{ T_m = \frac{\Delta E}{\Delta S} \right\}$$

$$= -\frac{\Delta E - \frac{T}{T_m}\Delta E}{2k_B T} = -\frac{\Delta E}{2k_B}\left(\frac{1}{T} - \frac{1}{T_m}\right)$$

$$= \frac{\Delta E}{2k_B} \, \frac{T - T_m}{T T_m} = \{ T \approx T_m \} = \frac{\Delta E}{2k_B T_m^2} (T - T_m)$$

The slope of $\theta(T)$ at $T \approx T_m$: $\frac{1}{2} e^{2\gamma} \frac{\Delta E}{2k_B T_m^2}$

The large slope could be due to:

1) $\gamma > 0$
2) ΔE is large

It turns out that it is difficult to distinguish between the two possibilities based on large-N data alone. See Fig. 9.9a, pg 371.

BUT:

ΔE large, $\gamma = 0 \Rightarrow$ no N dependence

$\gamma > 0 \Rightarrow N$ dependence

The N dependence turns out to be strong, showing that $\gamma \neq 0$. See Fig. 9.7, pg. 365.

More generally, size dependence is a hallmark of cooperative transitions.