Lecture of November 19: Chapter 7 MWC Model; Chapter 8 Polymers

Apichart Linhananta
Department of Physics
Lakehead University

Cooperative Binding of O_2 to hemoglobin

- Earlier we discussed how **hemoglobin** (a protein in red blood cell, RBC) that has **4 sites** for **binding 4 O_2**. They can also bind 4 CO_2.
- The **binding** is **cooperative**, in that binding of **oxygen** increases the **affinity** of **hemoglobin** for more **oxygen**.
- Experiments (read section 4.2, Fig 4.4 and 4.5) found that hemoglobin either bind **no oxygen** of **4 oxygen**. The binding is cooperative, or two state, in that it **all** or **nothing**.
- The **molecular-level** explanation is that the binding of an O_2 causes a conformational change in the hemoglobin protein.

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding

- Section 7.2.4 MWC considers a Dimoglobin that can bind **2 oxygens**.
- The dimoglobin (a protein) can be in two states: **tense** (T) and **relaxed** (R).
- In the absence of ligands the T state has lower energy than R, and T is favored.
- Variable $\sigma_m = 0,1$ for T and R, respectively

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding

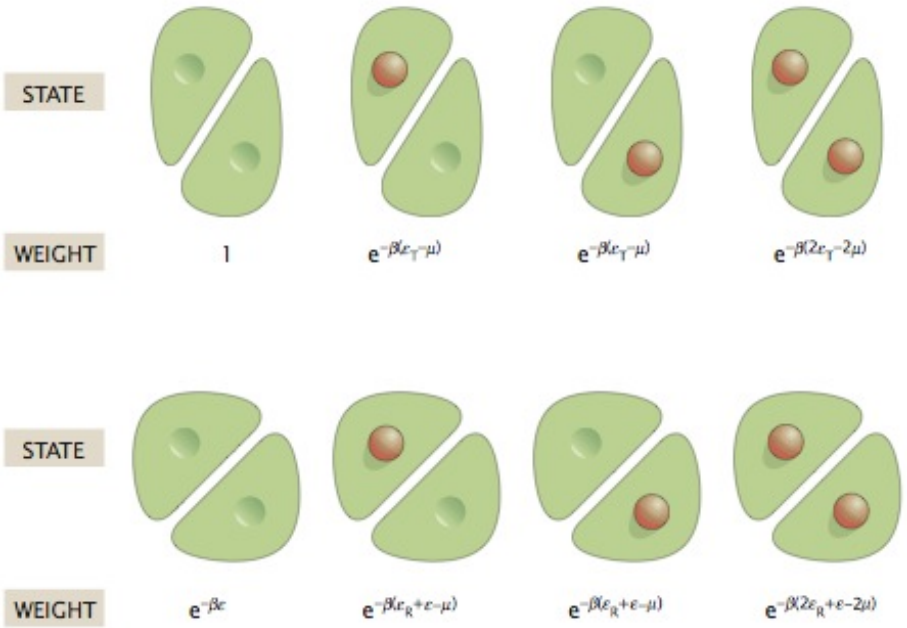
- As before $\sigma_1, \sigma_2 = 0,1$ quantifies whether a site has a bound oxygen
- Energy or Hamiltonian

$$E(\sigma_m, \sigma_i) = (1 - \sigma_m)\varepsilon_T \sum_{i=1}^{2} \sigma_i + \sigma_m \left(\varepsilon + \varepsilon_R \sum_{i=1}^{2} \sigma_i \right)$$

- Partition Function

$$Z = \sum_{\sigma_m = 0.1;, \sigma_i = 0,1} exp - \beta(E(\sigma_m, \sigma_i) - N_s \mu)$$

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding



$$\mathcal{Z} = \underbrace{1 + 2e^{-\beta(\varepsilon_T-\mu)} + e^{-\beta(2\varepsilon_T-2\mu)}}_{\text{T terms}} + \underbrace{e^{-\beta\varepsilon}(1 + 2e^{-\beta(\varepsilon_R-\mu)} + e^{-\beta(2\varepsilon_R-2\mu)})}_{\text{R terms}}. \qquad (7.35)$$

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding

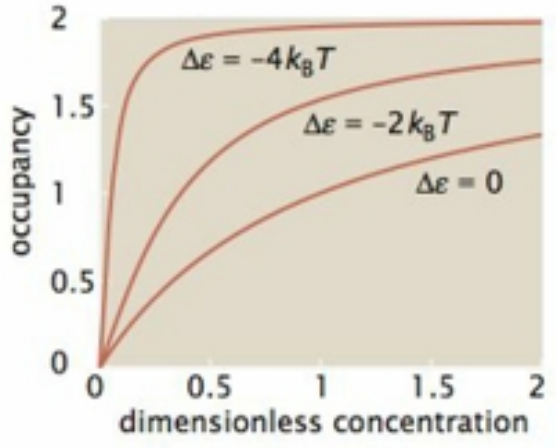
$$\mathcal{Z} = \underbrace{1 + 2e^{-\beta(\varepsilon_T - \mu)} + e^{-\beta(2\varepsilon_T - 2\mu)}}_{\text{T terms}} + \underbrace{e^{-\beta\varepsilon}(1 + 2e^{-\beta(\varepsilon_R - \mu)} + e^{-\beta(2\varepsilon_R - 2\mu)})}_{\text{R terms}}. \quad (7.35)$$

$$\langle N \rangle = \frac{2}{\mathcal{Z}}[x + x^2 + e^{-\beta\varepsilon}(y + y^2)],$$

$$x = (c/c_0)exp\left(-\beta(\varepsilon_T - \mu_0)\right)$$

$$y = (c/c_0)exp\left(-\beta(\varepsilon_R - \mu_0)\right)$$

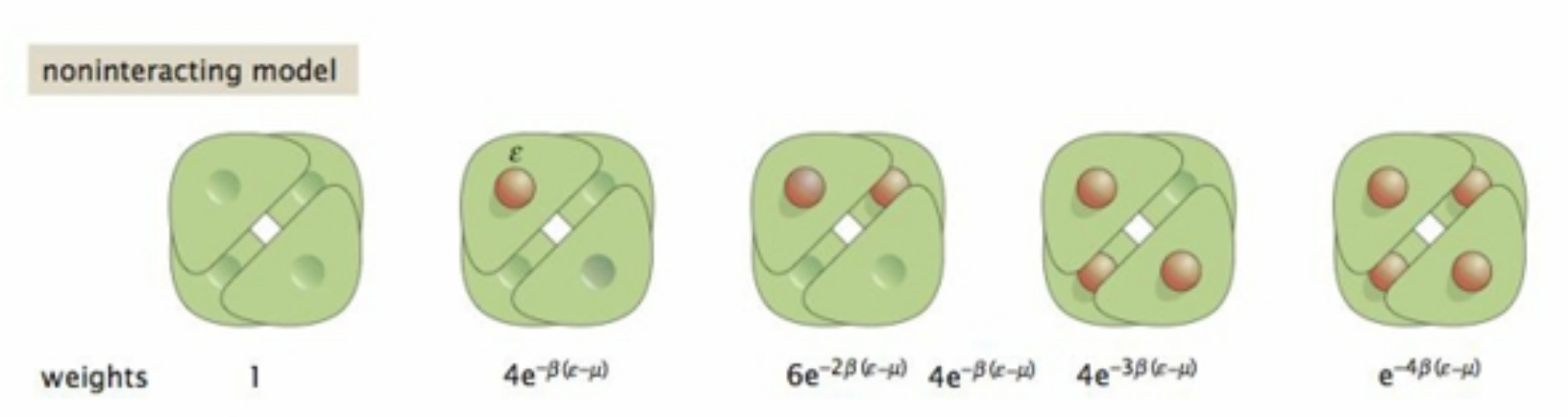
$$\Delta\varepsilon = \varepsilon_R - \varepsilon_L < 0$$



Conclusion:

- Without O_2 T state is at a higher energy of ε than the R state
- Bound Ligands make T state energetically favorable

Non-Interacting Model

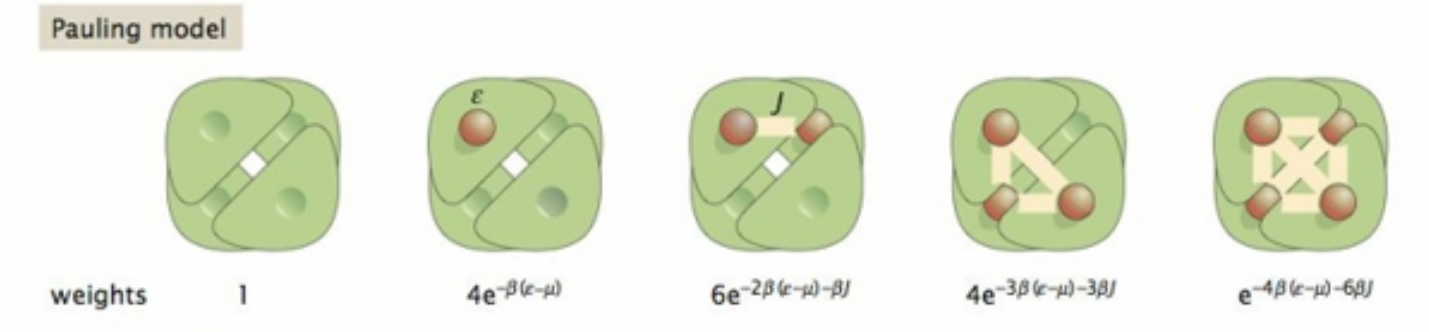


$$E = \varepsilon \sum_{\alpha=1}^{4} \sigma_\alpha ,$$

$$\mathcal{Z} = \sum_{\sigma_1=0}^{1} \sum_{\sigma_2=0}^{1} \sum_{\sigma_3=0}^{1} \sum_{\sigma_4=0}^{1} e^{-\beta(\varepsilon-\mu)\sum_{\alpha=1}^{4}\sigma_\alpha} .$$

$$\langle N \rangle = 4 \frac{(c/c_0)e^{-\beta(\varepsilon-\mu_0)}}{1+(c/c_0)e^{-\beta(\varepsilon-\mu_0)}} . \qquad (7.42)$$

Pauling Model

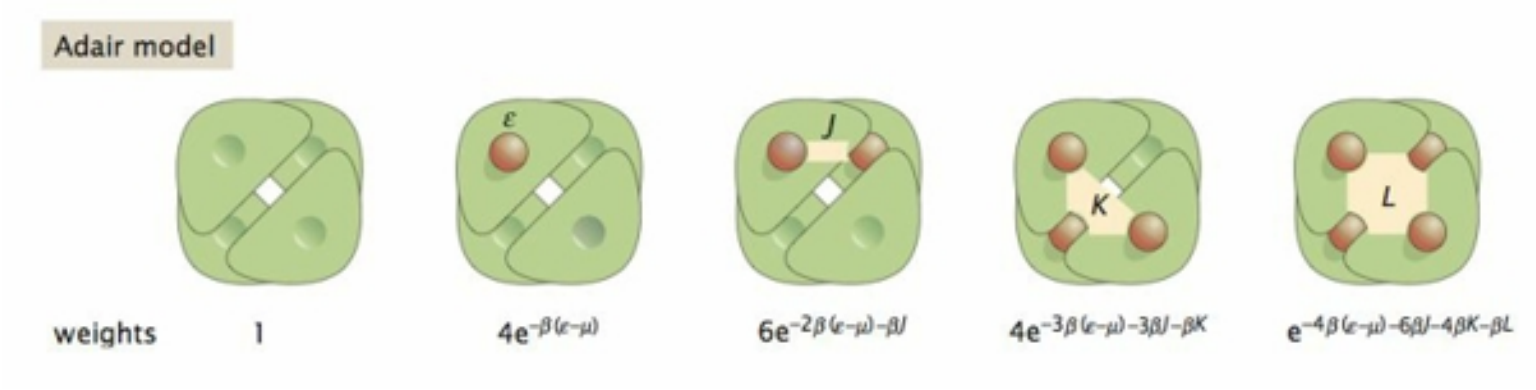


$$E = \varepsilon \sum_{\alpha=1}^{4} \sigma_\alpha + \frac{J}{2} \sum_{(\alpha,\gamma)}{}' \sigma_\alpha \sigma_\gamma, \qquad \mathcal{Z} = \sum_{\sigma_1=0}^{1} \sum_{\sigma_2=0}^{1} \sum_{\sigma_3=0}^{1} \sum_{\sigma_4=0}^{1} e^{-\beta(\varepsilon-\mu)\sum_{\alpha=1}^{4}\sigma_\alpha - \beta(J/2)\sum_{\alpha,\gamma}{}'\sigma_\alpha\sigma_\gamma},$$

$$\mathcal{Z} = \underbrace{1}_{\text{0 bound}} + \underbrace{4e^{-\beta(\varepsilon-\mu)}}_{\text{1 bound}} + \underbrace{6e^{-2\beta(\varepsilon-\mu)-\beta J}}_{\text{2 bound}} + \underbrace{4e^{-3\beta(\varepsilon-\mu)-3\beta J}}_{\text{3 bound}} + \underbrace{e^{-4\beta(\varepsilon-\mu)-6\beta J}}_{\text{4 bound}}.$$

$$\langle N \rangle = \frac{4e^{-\beta(\varepsilon-\mu)} + 12e^{-\beta(\varepsilon-\mu)-\beta J} + 12e^{-3\beta(\varepsilon-\mu)-3\beta J} + 4e^{-4\beta(\varepsilon-\mu)-6\beta J}}{1 + 4e^{-\beta(\varepsilon-\mu)} + 6e^{-2\beta(\varepsilon-\mu)-\beta J} + 4e^{-3\beta(\varepsilon-\mu)-3\beta J} + e^{-4\beta(\varepsilon-\mu)-6\beta J}}.$$

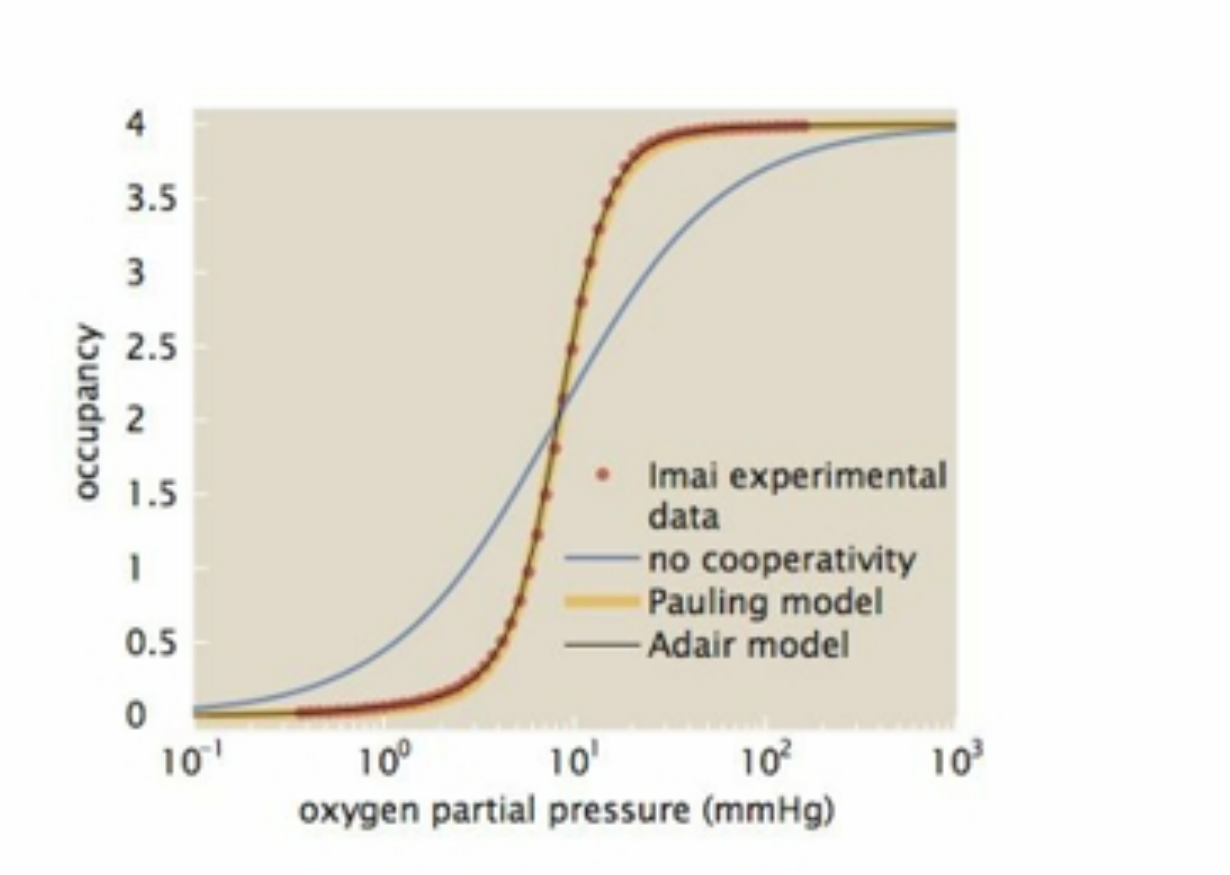
Adair Model



$$E = \varepsilon \sum_{\alpha=1}^{4} \sigma_\alpha + \frac{J}{2} \sum_{\alpha,\gamma}{}' \sigma_\alpha \sigma_\gamma + \frac{K}{3!} \sum_{\alpha,\beta,\gamma}{}' \sigma_\alpha \sigma_\beta \sigma_\gamma + \frac{L}{4!} \sum_{\alpha,\beta,\gamma,\delta}{}' \sigma_\alpha \sigma_\beta \sigma_\gamma \sigma_\delta,$$

$$\mathcal{Z} = \underbrace{1}_{\text{0 bound}} + \underbrace{4e^{-\beta(\varepsilon-\mu)}}_{\text{1 bound}} + \underbrace{6e^{-2\beta(\varepsilon-\mu)-\beta J}}_{\text{2 bound}} + \underbrace{4e^{-3\beta(\varepsilon-\mu)-3\beta J-\beta K}}_{\text{3 bound}} + \underbrace{e^{-4\beta(\varepsilon-\mu)-6\beta J-4\beta K-\beta L}}_{\text{4 bound}}.$$

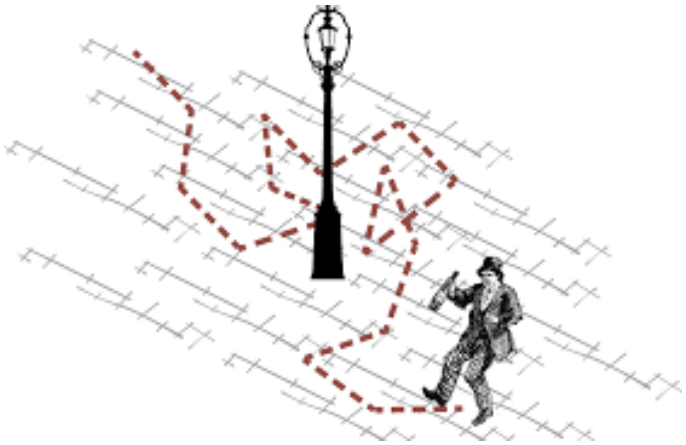
Hierarchical Hemoglobin Models

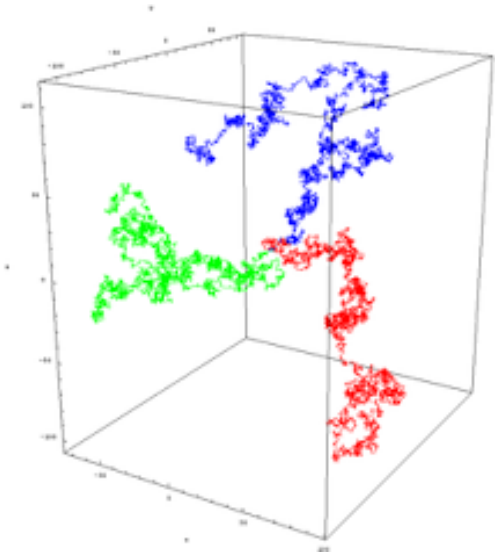


Random Walk

- Stochastic means having a probability distribution that may be analyzed statistically, but cannot be predicted precisely.
- A Random Walk is a Stochastic Path determined by steps whose length and direction is determined by a probability distribution.
- For large number steps the distribution is Gaussian. This is the central limit theorem.

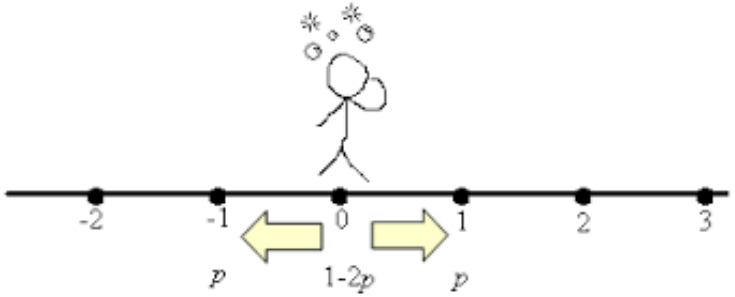
Random Walk





- On average, after a large number of steps, the random walker position will be, $\langle x \rangle = 0$ (1D), $\langle \vec{r} \rangle = 0$ (3D)
- After a large number of steps, N, the random walker will end up far away from where he started: $\langle x^2 \rangle = NL^2$ (1D), $\langle R^2 \rangle = 2NL^2$ (3D), where L is the average step size.

1D Random Walk: Step Size a; N steps



$$\langle R \rangle = \left\langle \sum_{i=1}^{N} x_i \right\rangle,$$

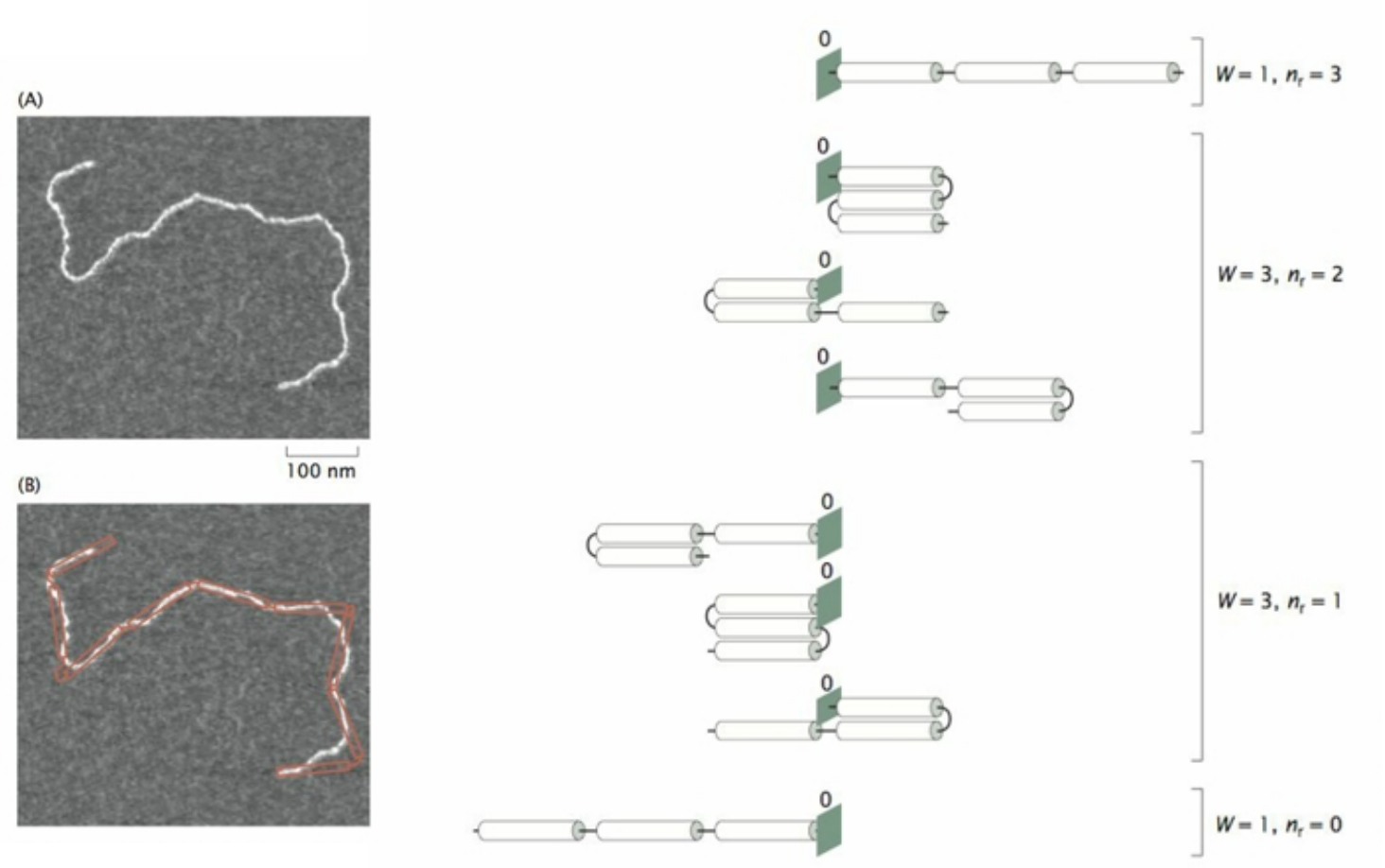
$$\langle R^2 \rangle = Na^2.$$

See Class Notes for Detail

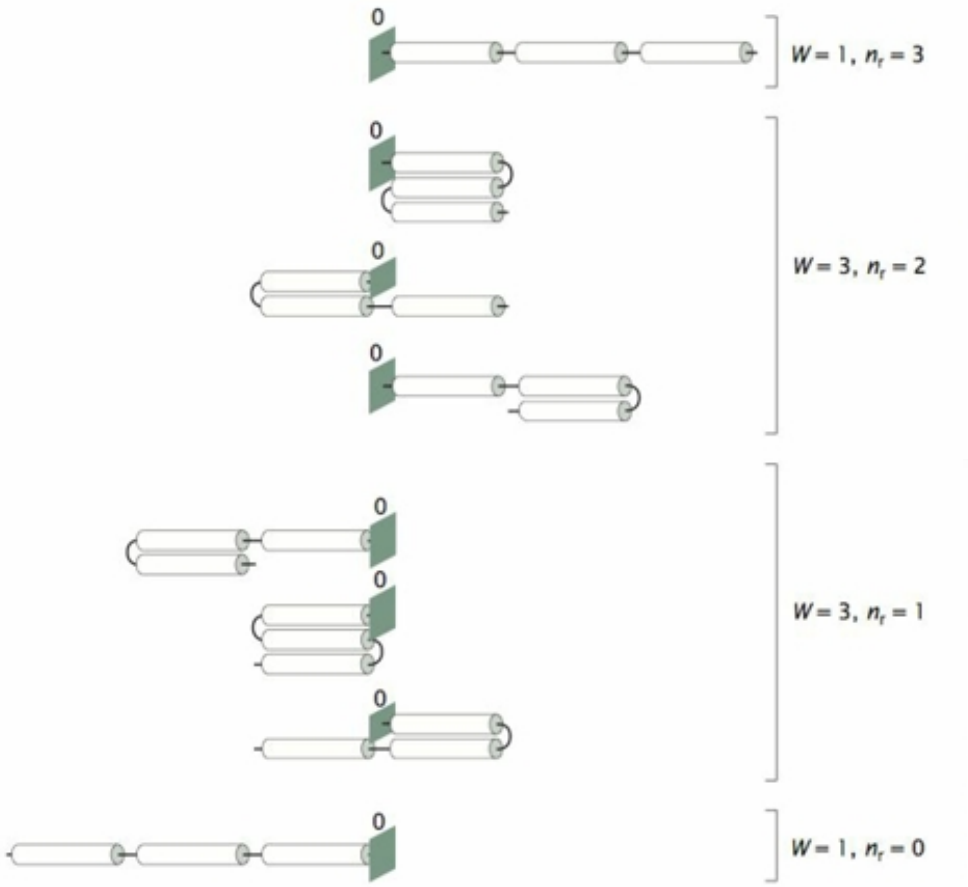
DNA, RNA and Proteins as a Random Walk

- Long molecules made of repeating units are called polymers.
- Homopolymers are polymers made up of one type of unit. An example is polyethylene (plastic)
- DNA, RNA and proteins are heteropolymers since they are made up of type of units (i.e. nucleotides, amino acids

DNA conformations as a random walk



DNA conformations as a random walk



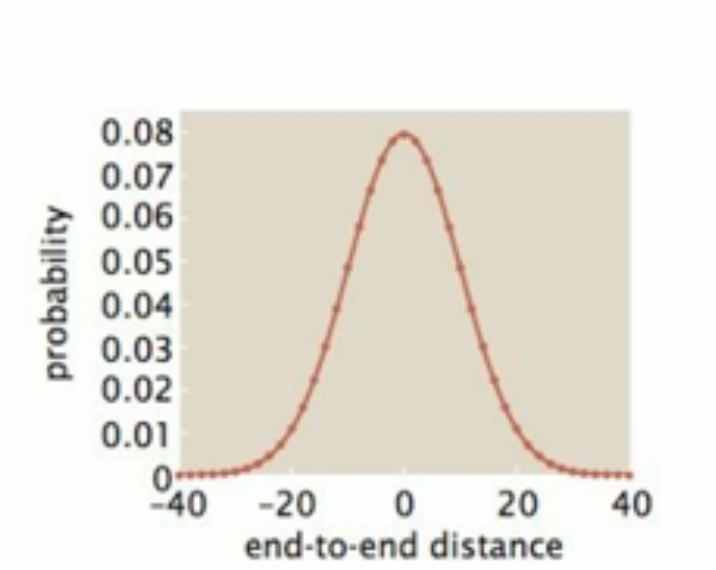
$$W(n_r; N) = \frac{N!}{n_r!(N - n_r)!}, \tag{8.5}$$

$$p(n_r; N) = \frac{N!}{n_r!(N - n_r)!}\left(\frac{1}{2}\right)^N.$$

DNA end-to-end distance is a Gaussian Distribution

$$\sum_{n_r=0}^{N} \frac{N!}{n_r!(N-n_r)!} = 2^N.$$

$$p(R;N) = \frac{N!}{\left(\frac{N}{2}+\frac{R}{2a}\right)!\left(\frac{N}{2}-\frac{R}{2a}\right)!}\left(\frac{1}{2}\right)^N,$$



$$p(R;N) = \frac{2}{\sqrt{2\pi N}} e^{-R^2/2Na^2}.$$

1D Discrete probability

$$P(R;N) = \frac{1}{\sqrt{2\pi Na^2}} e^{-R^2/2Na^2},$$

1D continuous probability per unit length