Lecture March 10, 2020

Adapted Levinthal's paradox

Modified Levinthal's Paradox

Proteins: Amino Acid (AA) Sequence



Amino Acid (AA) Conformations



- Amino Acid (AA) either in correct
 (C) or incorrect (I) conformation.
- c conformation is associated with N state
- I conformation associated with U state.

C conformation is

 $P_c = \alpha = A \exp(-E_c / RT)$, where A is a constant, E_c the internal energy of aa in the c conformation.

I conformation is

 $P_i = 1 - \alpha = A \exp(-E_i / RT)$, where A is a constant, E_i the internal energy of aa in the i conformation.

Application to RNASE A



N = 124 AA

Folding time $t_{fold} \sim 1s$

$$\Delta H = H_U - H_N = 484 \frac{kJ}{mol} \text{ and } \Delta S = S_U - S_N = 1.46 \frac{kJ}{K \cdot mol}$$

- Assume that τ is the average time that an amino acid (AA) convert between the $I \leftrightarrow C$ conformation.
- On average every τ the probability that a protein with N AA is in a folded native (N) state is α^N .
- On average every τ , the probability of protein with N AA is in an unfolded (U) state is $(1 \alpha^N)$
- What about after a longer period of time $t \gg \tau$?
- In this case the number of τ intervals is $n = \frac{t}{\tau}$
- The probability after time t that the protein is in an unfolded state is $P_U(t) = (1 \alpha^N)^n = (1 \alpha^N)^{\frac{t}{\tau}}$

- The folding time t_{fold} is the time when the protein has equal probability of being in the Native (N) or the unfolded (U) state, or $P_U(t_{fold}) = 0.5 = (1 \alpha^N)^{\frac{t_{fold}}{\tau}}$
- Solving, $t_{fold} = \tau \frac{-0.693}{ln(1-\alpha^N)}$
- Rearranging we have $ln(1 \alpha^N) = \frac{\tau}{t_{fold}}(-0.693)$
- For RNASE A, N = 124 and experiment found $t_{fold}{\sim}1s$, and assuming $\tau = 10^{-12}s$
- $ln(1 \alpha^N) = -6.93 \times 10^{-13}$

- Since $\alpha < 1$, for RNASE A, $\alpha^N = \alpha^{124} \ll 1$
- Use Taylor expansion, $ln(1+x) = x \frac{x^2}{2} + \frac{x^3}{3} \frac{x^4}{4} + \cdots$, or if we use $x \to -x$, $ln(1-x) = -x \frac{x^2}{2} \frac{x^3}{3} \frac{x^4}{4} + \cdots$.
- If $x \ll 1$, $ln(1-x) \sim -x$
- For RNASE, $ln(1 \alpha^N) = -6.93 \times 10^{-13} \rightarrow \alpha^{124} = 6.93 \times 10^{-13}$
- Take the log base 10 of both side, 124log10 = log(6.93) 13

•
$$log\alpha = \frac{log(6.93) - 13}{124} = -0.09806 \rightarrow \alpha = 10^{-0.09806} = 0.7978844$$

- $P_c = \alpha = Aexp(-E_c / RT)$, where A is a constant, E_c the internal energy of aa in the c conformation.
- $P_i = 1 \alpha = Aexp(-E_i / RT)$, where A is a constant, E_i the internal energy of aa in the i conformation.

•
$$\frac{P_c}{P_I} = \frac{\alpha}{1-\alpha} = e^{-\frac{\Delta E_{ci}}{RT}}$$
, with $\Delta E_{ci} = E_c - E_i$

- Use $\alpha = 0.7978844$, and T = 300 K, $\Delta E_{ci} = -3.7 \frac{kJ}{mol}$
- $\Delta E_{ci} < 0$ makes sense since the energy of the correct (c) should be lower than that of the incorrect (I) conformation.