# Problems/Suggested reading ICTS 2016

December 26, 2016

1. Suggested reading 1: Physical limits to biochemical signaling, Bialek and Sethasyagar, PNAS, 10040: 10045, July 19, 2005 vol. 102. Work thorough the fluctuation dissipation bound for the system with many receptors see Fig 3.

2. Suggested reading 2 /problem: What happens if the systems in Suggested reading 1 are driven out of equilibrium. Work through the model in Energetic costs of cellular computation, Metha and Schwab, PNAS, 17978: 17982, vol. 109. Specifically, explain the trends in Fig 3.

3. Suggested reading 3: Cellular Signaling Networks Function as Generalized Wiener-Kolmogorov Filters to Suppress Noise, Hinczewski and Thirumalai, PRX, 4, 041017 (2014). Do the limits in this paper agree with those in Suggested reading 1.

4. Error correction in DNA replication. Biological systems strive to maintain high fidelity

$$\mathtt{E}(A \equiv G) - \mathtt{E}(A \equiv T) = \Delta$$
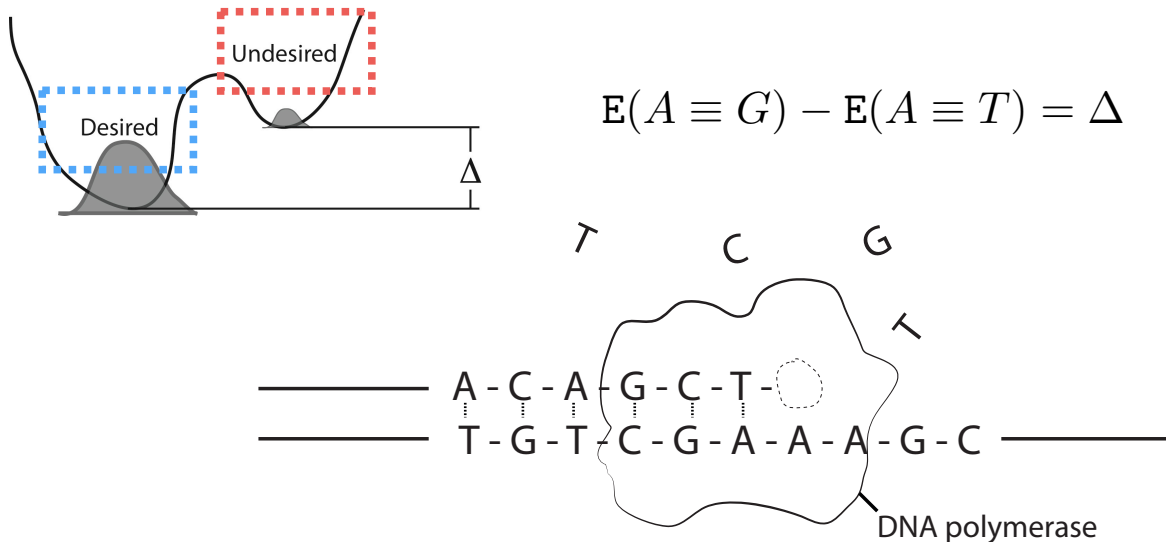
in processes such as DNA replication. In this problem, we will consider the biophysics

of accurate DNA replication. The figure above has a sketch of DNA replication catalyzed by a DNA polymerase enzyme. In order for replication to be accurate, every A residue in the bottom template strand has to associated with a T residue in the complimentary strand (and vice versa). Similarly, every G residue in the template strand has to be associated with a T residue in the complimentary replicated strand. Thermodynamically, the energy of binding between incompatible (undesired) pairs is higher that the energy of binding between compatible (desired) pairs. The energy difference is denoted by Δ. Assuming a temperature T (sorry for the confusing notation, use T for temperature in all the algebraic sub parts below).

(a) Assuming that the concentration of the four residues in solution around the polymerase is equal and is given by c, work out a formula for the error rate, or probability of formation of an incorrect bond, in the replicated strand. You may have to make a few simple physical assumptions along the way to work this out. For instance, you can ignore any catalytic role played by the polymerase enzyme in this calculation and assume that errors are uncorrelated.

(b) Using p_{error}^{eq} to denote the probability of an incorrect bond in the previous part, work out an expression for the Shannon entropy of the replicated system. Again, you may need to make physically justifiable assumptions.

(c) The error rate observed in biology is much lower than that predicted by the thermodynamic result in part (a). It has been posited (and experimentally demonstrated) that the lower error rate is achieved at the cost of energy consumption (the DNA polymerase consumes energy rich ATP molecules to facilitate DNA replication). This energy flow can be regarded as a heat flux into the system. Again, making physically justifiable assumptions, provide an estimate for the energy flux required to reduce the error probability to p_{error}^{ATP}.

(d) The errors in DNA replication typically have some spatialy correlation. We model this process by introducing two new energy scales Δ_1 and Δ_2. In addition to the binding energy described in part (a), Δ_1 denotes the energetic cost of adding an in correctly paired residue or an undesired bond next to a correctly paired residue (or a desired bond) and vice versa. Similarly, Δ_2 denotes the cost of adding an undesired bond next to an undesired bond or a desired bond next to a desired bond. In order to compute the probability of errors/undesired bonds in this problem, it is easiest to map the current problem onto that of a 1 D Ising model with a nearest neighbor coupling constant J and an external field h. Show that this mapping is possible and work our the values of J and h.

(e) The (per spin) free energy of an Ising chain with a nearest neighbor coupling constant J and an external field h is given by

$$f = -\frac{1}{\beta} \ln \left(e^{\beta J} \cosh \beta h + \sqrt{e^{2\beta J}(\sinh \beta J)^2 + e^{-2\beta J}} \right) \qquad (1)$$

Using this expression, compute the probability or undesired bonds in the DNA replication problem.

(f) Using the results of the previous parts, provide an estimate for the minimum work that needs to be performed by the DNA polymerase (think of the DNA polymerase as a machine that can consume ATP to do work) to reduce the error rate to p_{error}^{ATP}. The calculations in this part can get really messy. Full credit will be given for qualitative reasoning.