Physics 176/276 - Quantitative Molecular Biology
Problem Set #1
Due: **Tuesday, January 28**
TA Email: `anna.melbinger@gmail.com`

1 Making of the cell

An *E. coli* cell is placed in a tube containing 8 ml sterile growth medium, consisting of 0.5% w/v glucose ($C_6H_{12}O_6$), 6mM ammonium (NH_4Cl), various inorganic ions, and kept shaken (for good aeration) in a 37° C water bath. After a short transient (to be neglected here), it is observed to grow exponentially with 40 min doubling time until it runs out of either the carbon or nitrogen source. Below you are asked to make a number of estimates using only the information provided here (you might check molar masses). Please report your numerical answers as well as the mathematical expressions.

(a) Given that the dry weight of an *E. coli* cell is ~0.3 pg, and that its chemical composition is ~50% carbon and ~14% nitrogen, estimate how many molecules of glucose and ammonium are required to make a new cell. What is the maximum cell density this tube of culture can reach? Express your answer in units of 'OD' (optical density, defined as light absorption through 1 cm of culture at a wavelength of 600nm), with 1 OD~10^9 cells/ml. How long would it take for the tube to reach this density starting from a single cell? from 10^7 cells/ml (the typical starting culture density)? When the culture is saturated, how much volume does each cell have to itself (typical size of an *E. coli* cell with given growth rate is $1\mu m$)? How does this compare to the volume of an *E. coli* cell?

(b) Let us next estimate the energy cost of making the cell. The dominant cost of biosynthesis turns out to be in protein synthesis. It takes 4 ATP molecules to extend a nascent polypeptide chain by one amino acid. Given that about half of the cells dry weight is in proteins, how many ATP does it cost to synthesize all the proteins in a cell? (You may assume that half of the protein mass is in Carbon and that one amino acid contains on average 5 carbon atoms.) Given the ATP hydrolysis energy of ~30 kJ/mol, what is the energy cost (in Joules) to synthesize

1

all the proteins in one cell? In all cells in the tube?

(c) The ATP concentration is maintained at $\sim$4mM in the cell. From your answer to part (b), estimate the rate ATP is being drained to perform protein synthesis. How long would it take to deplete the ATP pool if it is not being supplied? Theoretically, one glucose molecule can maximally generate $\sim$30 ATPs using respiration under aerobic conditions. Estimate the minimal number of glucose molecules needed to supply the energy consumption for protein synthesis. Compare this amount to the need of glucose as building blocks of cell.

(d) It turns out that *E. coli* actually uses glucose very inefficiently even in aerobic conditions, largely fermenting glucose (generating 12 ATP and excreting 2 acetate molecules per glucose) rather than burning up all the carbon into CO_2 as it would occur in respiration. Assuming that glucose is completely fermented, estimate again the minimal number of glucose molecules needed to supply the energy consumption for biosynthesis, and compare this amount to the need of glucose as building blocks of cell. What is the total glucose consumption rate in this case? And what is the rate of acetate accumulation in the medium? Find the acetate concentration in the medium when growth stops. Look up the chemical properties of acetate and express the answer in volume fraction. Compare to table vinegar which tends is $4 \sim 8\%$ of acetate by volume.

2 Scales

In this problem, we will try to get a handle on the magnitude of various sizes and durations for molecules and processes in the cell. Please report your numerical answers as well as the mathematical expressions.

(a) How many pages of a typical novel would it take to spell out the entire genome of *E. coli* ? of the human genome? Assuming the information content of the genome is comprised mostly in the genes, how many pages of a typical novel would the information be comparable to? (You may assume each gene encodes a protein 250 amino acid in length, and the

alphabet size of 20 amino acids for the proteins is comparable to the 26-letter of the English alphabet. Make some reasonable assumptions about page content.)

(b) Suppose a single *E. coli* cell invades into the intestine of a newborn infant and grows at the rate of one doubling every 45 min. How long would it take for the *E. coli* colony to reach the size of 10^{13} cells (the estimated steady-state size of E. coli in adults)? How much would these *E. coli* cells weigh? If the colony continues to grow at this rate, how much more time would it take for the colony to reach a mass of a 150lb person? And how much more time to reach the total biomass of the entire human population?

3 Kinetic proofreading

Consider a chain of reactions as shown in the Figure 1. T are receptors and M^X are ligands to the receptors. Units are chosen so that the concentration of receptors is normalized to unity. The lifetime of the complex receptor-ligand is $1/k_{-1}$. The formation of the complex proceed at a rate k_1 and the C's correspond to multiple phosphorylations of the receptor-ligand complex, i.e. C_i is the complex phosphorylated i times. Note that energy is expended in the phosphorylation process and therefore there is no constraint on the rates due to detailed balance.
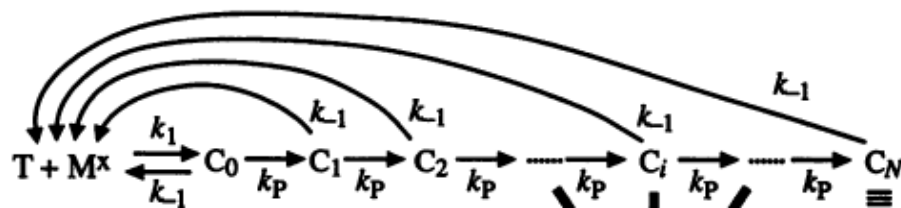

Figure 1: Kinetic proofreading reaction scheme. Receptors T bind ligands M^X and a cascade of phosphorylation reactions is induced.

a) Use chemical kinetics to derive the expression for the steady-state concentration of C_N.

b) Show that in the limit $k_1 \gg k_{-1} \gg k_P$ the concentration $C_N \propto (k_P/k_{-1})^N$, where N is depth of the cascade shown in the figure.

c) Compare the situation for two ligands M^A and M^B differing for their lifetime k_{-1} and conclude that they can be discriminated with a precision $\left(k_{-1}^A/k_{-1}^B\right)^N$, i.e. with a discriminatory power that exponentially amplifies the ratio of their lifetimes.

d) Comment on the conditions that are required for the result in c).

e) Calculate the average time $\langle \tau_{-1} \rangle$ for a particle of ligand (initially dissociated) to reach the N-th level. Show that $\langle \tau_{-1} \rangle \propto 1/\alpha^N$ when $\alpha = k_P/(k_P + k_{-1})$ is small. Hint: it might be useful to introduce the average times $\langle \tau_i \rangle$ for a particle initially in the state C_i to reach the N-th level.