Problem Set 2
BIOE5060: Biomolecular Dynamics and Control
February 16, 2015
Due: February 27 (by email)

Problem 1. **Modeling receptor-ligand trafficking**. Receptors (R_s), ligands (L_s) and complexes (C_s) on the surface of a cell undergo endocytosis or internalization. The internalized receptors (R_i) and ligands (L_i) continue to bind and unbind, albeit with different kinetics due to the pH difference between endocytic vesicles and the extracellular milieu. Internalized species (R_i, L_i, C_i) are then sorted to either recycle back to the surface ($1 - f_j$) or degrade in lysosomal compartments (f_j where j refers to receptor, ligand or R/L complexes). Through this process of receptor-ligand trafficking, ligand is depleted over time, and receptor expression attains a steady-state level that balances lysosomal degradation and de novo receptor synthesis.

(a) Develop a mass-action kinetic model of receptor-ligand trafficking by performing the following steps:

   i. write the elementary reactions in the system. Please do not sketch a schematic of the cell. Write the reactions in standard form (e.g., $X \rightarrow Y$, $X + Y \rightleftharpoons Z$ or $X \rightarrow \emptyset$ where $\emptyset$). represents degraded species).
   ii. identify the time-dependent state variables,
   iii. write the conservation equations (mass balances) (*Careful!*Ask yourself which species are conserved.), and
   iv. write the rate equations.

(b) Consider a situation where 5x10^5 cells are seeded in 3 mL of medium. There is no EGF in the medium. Predict the distribution of receptors in the system at steady-state.

(c) Consider now the situation when the medium is replaced with medium containing 1 nM EGF. Predict the time evolution of L_s, C_s and $L_i^{\#}$ following EGF addition. Recall that $L_i^{\#}$ is the amount of internal ligand, both in its free form and bound to receptor.

   You may use the following values for rate constants: $k_f = 7.2\text{x}10^7$ M^{-1}/min, $k_r = 0.3$ min^{-1}, $k_{eC} = 0.3$ min^{-1}, $k_{eR} = 0.03$ min^{-1}, $k_{rec} = 0.06$ min^{-1}, $k_{deg} = 0.002$ min^{-1}, $f_R = f_L = 0.2$, $f_C = 0.5$. We assume $k_{eL} = 0$. Typical receptor synthesis rate is 100 receptors/min.

Problem 2. Enzyme kinetics. Under the assumption that complex (C) formation is at quasi-steady state, we derived that the rate of product formation is given by

$$\frac{dP}{dt} = \frac{k_2 E_o S}{K_m + S} \tag{1}$$

(a) It was noted that the rate of product formation is greatest at initial time (i.e. $t = 0$). Explain why this is the case.

(b) Now, consider the initial rate of product formation, often referred to as the velocity, V, given by

$$V = \frac{dP}{dt}_{t=0} = \frac{k_2 E_o S_o}{K_m + S_o} \tag{2}$$

where S_o refers to the initial substrate concentration. Under what conditions of substrate concentration does the velocity reach its maximum value?