Home Assignment 1: Enzyme Dynamics

November 3, 2014

Preparation: Go through the exercises in Chap. 1,2 and 3 of the exercise manual.

The glycolysis is the first step, of three, of the fundamental glucose metabolic pathway of the human cell. The glycolysis consists of 10 different steps of converting glucose into pyrovate, which is the input to the citric acid (Krebs) cycle. Here, we will study the third step of the glycolysis, which is considered to be the rate-limiting step of the glycolysis and also an important contributor to possible ATP oscillations. This step is the phosphorylation of fructose 6-phosphate to fructose 1,6-bisphosphate, and also includes hydrolysis of ATP to ADP, catalyzed by the enzyme phosphofructokinase (PFK1). In the active state, the enzyme catalyzes the production of ADP from ATP as fructose 6-phosphate is phosphyralated. A simplified model of the enzyme reactions are given by the following stochiometry. PFK1 (E) is activated or deactivated by binding or unbinding with γ molecules of ADP (S_2)

$$\gamma S_2 + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_1 \tag{1}$$

and ATP (S_1) can bind with the activated form of the enzyme (C_1) to produce a complex (C_2). There is a steady supply rate of S_1, and likewise S_2 is removed at a rate proportional to the concentration of S_2.

$$\underset{v_1}{\rightharpoonup} S_1 \tag{2}$$

$$S_1 + C_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_2 \tag{3}$$

$$C_2 \overset{k_2}{\rightharpoonup} C_1 + S_2 \tag{4}$$

$$S_2 \underset{v_2}{\rightharpoonup} \tag{5}$$

1. Derive expressions for the differential equations of the substrates and complex products using the law of mass action with $s_1 = [S_1], s_2 = [S_2], e = [E], x_1 = [C_1]$ and $x_2 = [C_2]$, subject to $e + x_1 + x_2 = e_0$.

2. You may skip this problem. Introduce the dimensionless concentrations

$$\sigma_1 = \frac{k_1}{k_2 + k_{-1}} s_1 \qquad \sigma_2 = (\frac{k_3}{k_{-3}})^{1/\gamma} s_2$$
$$u_1 = x_1/e_0 \qquad u_2 = x_2/e_0$$

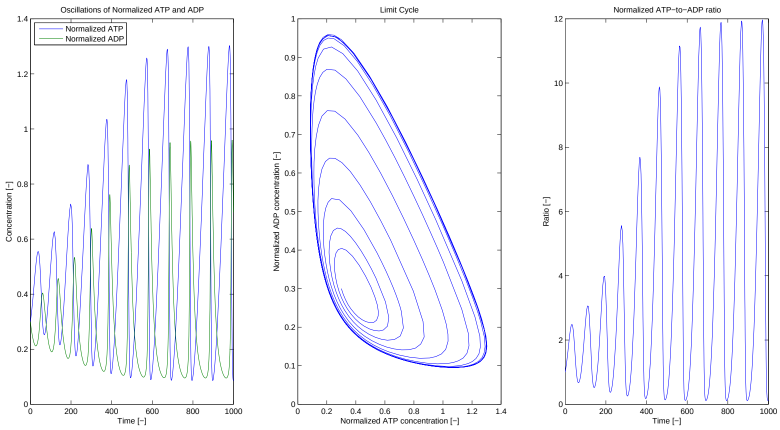

Figure 1 Simulation plots of the normalized ATP and ADP excursions.

and the new time scale

$$\tau = \frac{e_0 k_1 k_2}{k_2 + k_{-1}} t$$

and assume quasi-steady-state assumptions ($du_i/dt = 0$) for the normalized complex products u_1 and u_2 (compare to the derivation of Michaelis-Menten relationships). Derive the first ($d\sigma_1/d\tau$) of the following expressions for the normalized substrate differential equations:

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2) \tag{6}$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2 \tag{7}$$

where the steady-state solution:

$$u_2 = f(\sigma_1, \sigma_2) = \frac{\sigma_1 \sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1} \tag{8}$$

and $\nu = v_1/k_2 e_0$ and $\alpha = (k_2 + k_{-1})/k_1 (k_3/k_{-3})^{-1/\gamma}$ and $\eta = v_2(k_2 + k_{-1})/k_1 k_2 e_0$.

3. Fill in the missing code in the file `enzymeskeleton.m` provided on the course home page. Simulate the system in Matlab for 1000 steps using the `glureg.m` file and the `function_handle @(x)f(x)` and the `ode45` commands with the following sets of parameter values: $\nu = 0.0285, \alpha = 1.0, \eta = 0.1$ and $\gamma = 2$. Assume initial values of $\sigma_1 = \sigma_2 = 0.3$. Produce the plots in Fig. 1. Glycolytic oscillations have been observed in vitro in human cell extracts and in yeast cells, and is hypothesizied to play a key role in, e.g., pulsatile pancreatic insulin secretion.

4. Linearize the dynamics around the (unique) point $d\sigma_1/d\tau = 0, d\sigma_2/d\tau = 0$. Is the system stable in this point?