# Quantitative Understanding in Biology

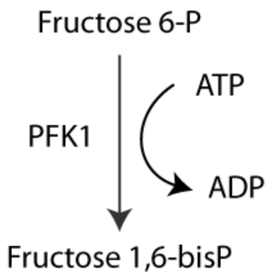
# Module IV: Differential Equations

# Computer Laboratory

## The Sel’kov Model of Glycolysis

*Reference: Keener and Sneyd (Chapt. 1)*

One step in the glycolytic pathway is the phosphorylation of fructose 6-phosphate to fructose 1,6 bisphosphate, which it catalyzed by the enzyme phosphofructokinase (PFK1). This reaction transforms a molecule of ATP to a molecule of ADP; this is the source of the phosphate that is added to the fructose. This process is drawn as…



The enzyme involved, PFK1, exhibits properties of allosteric regulation which are quite complex and which we will not cover here (see your favorite biochemistry text for the gory details). A simplified model of this allosteric regulation, proposed by Sel’kov, is to view PFK1 as being activated by some number, $\gamma$, molecules of ADP.

$$PFK1_{inactive} + \gamma ADP \leftrightarrow PFK1_{active}$$

The fact the phosphorylation reaction produces a product that actives the enzyme that catalyzes the reaction can lead to some interesting dynamics, which we will investigate here.

When we have modeled chemical reactions before, we have considered the system to be closed; that is we modeled the system with some amount of starting material and investigated how the concentrations of those materials would evolve over time, but we never added or took away material during the simulation. In this case, we will model an open system. We will provide our simulated system with a steady supply of ATP, and we will continuously remove ADP at a rate proportional to its concentration. You can think about these two steps as a very, very gross model of many other reactions that might be going on in the cell to regulate the concentrations of ATP and ADP.

This system can be modeled by the following set of chemical reactions, as proposed by Sel'kov:

$$\xrightarrow{v_1} ATP$$

$$\gamma ADP + PFK1_{inactive} \xleftrightarrow{k_3, k_{-3}} PFK1_{active}$$

$$ATP + PFK1_{active} \xleftrightarrow{k_1, k_{-1}} PFK1_{complex} \xrightarrow{k_2} PFK1_{active} + ADP$$

$$ADP \xrightarrow{v_2}$$

Note that the 3rd equation does not include the fructose reactant or product!

**Apply the law of mass action to write a system of differential equations that can be used to simulate this system.**

Take the constants in the model to be:

$\gamma$=2.0
$v_1 = 0.003$
$v_2 = 2.5 \cdot v_1$
$k_1 = 0.1$
$k_{-1} = 0.2$
$k_2 = 0.1$
$k_3 = 0.2$
$k_{-3} = 0.2$

**Find any steady states for this system, and investigate stability.**

*Hint: Matlab's symbolic math tools can be your friend. See the `solve` function.*

Consider an initial condition where only ATP, ADP, and inactive enzyme are present in the following amounts.

[ATP] = 1.0

[ADP] = 2.0

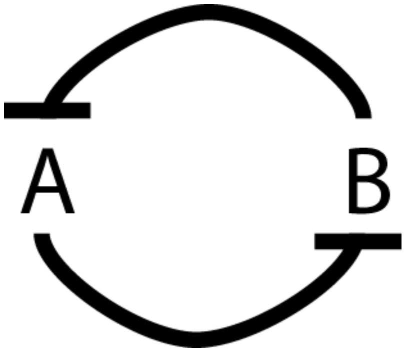
$[PFK1_{inactive}] = 1.4$

**Simulate the system numerically. Prepare appropriate plots, and compare your results to your steady-state analysis.**

## Dynamic Systems and Bifurcation

*Reference: (Gardner, Cantor and Collins, Nature, 2000).*

Consider the genetic switch model we worked on in class…

| | |
|---|---|
|  | $\frac{dx}{dt} = -x + \frac{\alpha}{1+y^n}$<br>$\frac{dy}{dt} = -y + \frac{\alpha}{1+x^n}$ |

We saw that when the Hill parameter, n, is 2 and basal production, α, is three, we find two stable steady states and one unstable steady state.

**Show that for (n, α) = (3, 1), there is only one equilibrium point. Find it, and investigate its stability.**

**Keeping n fixed at 2, find the value of α at which the number of equilibrium points changes.**

This point in parameter space, that is (n, α) space, is called a bifurcation point.

**Prepare a plot showing how the steady-state points move as α varies while n is held fixed at n=2.**

*Hint: This kind of bifurcation is called a 'pitchfork' bifurcation.*

Challenge (optional): **Prepare a map showing where in (n, α) space the system has one equilibrium point and where it has three equilibrium points. If you were trying to engineer a biological switch, where would you want to be in this space?**