

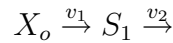
# Linking Genome to Physiome

## Oscillatory Systems: Lab 2

The purpose of this exercise is to explore different kinds of oscillators found in natural systems and to investigate one particular property of cyclic networks.

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Consider the following simple system:



where the rate for the first step  $v_1 = k_1 * X_o + V_{\max} \times X_o \times S_1^n / (15 + S_1^n)$

and the rate for the second step,  $v_2 = k_2 \times S_1$ .

Set  $n = 4$ ,  $k_1$  to a value of 0.01 and  $k_2$  to a value of 0.1.

$X_o$  is assumed to be a boundary species with a value of  $X_o = 1$ .  $V_{\max}$  can be set to 12. Since the second step is irreversible  $X_1$  has been omitted from the pathway diagram (It has no influence).

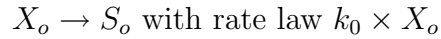
**Question 1.** The first task is to confirm that the above system can show bistable behavior. Attempt to show bistability by varying the starting concentration of  $S_1$  and running simulations. Confirm that you can obtain two different steady states. Supply the necessary plots as evidence.

Jarnac tip:

You can rename a column label in a matrix by using the command `setColumnName()`. For example to set the 3rd column label for a matrix  $m$  to the string "S1(0.01)" use the command:

```
setColumnName (m, 3, "S1(0.01)");
```

**Question 2.** You are now going to build a relaxation oscillator based on the bistable system from question one. This can be very simply done by adding one extra reaction to the bistable model:



Note that the  $X_o$  in the bistable model is now renamed to  $S_o$ . **Make sure** you relabel the species names in the feedback rate law to match this name change.

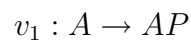
By simulation, locate the range of values where the system oscillates by adjusting the values of the  $k_0$  rate constant. You might find that  $k_0$  has to be on the low side.

The question is how does this oscillator work?

**Question 3.** We will now build a feedback oscillator based on a series of connected genes. The last gene product should inhibit the first gene. All other genes should activate the next in series. You will probably need at least three stages to ensure a sufficient delay (Model will be shown on the overhead projector)

**Stop here**

**Question 4.** Build the following model:



The above reaction steps form a cycle. Species A might represent a protein and AP the phosphorylated form of the protein. Assume that each cycle reaction is catalyzed by a simple irreversible Michaelis-Menten reaction. The table below shows the values for the kinetic constants.

Reaction	Vmax	Km
$v_1$	Vmax1 = 0.1	Km1 = 0.1
$v_2$	Vmax2 = 1	Km2 = 0.1

Initialize A to 1.0 and AP to 0.0.

a) Compute the steady state for this system. If you find that the program complains about being unable to compute the steady state, compute a time course for a short while (eg `p.sim.eval (0, 30, 20, [])`) in order for the steady state command to have a good starting point. Something like this would work:

```
p.sim.eval (0, 30, 20, []);  
p.ss.eval;
```

b) Vary  $V_{\max 1}$  from 0.1 to 2.0 in steps of 0.1 and recompute the steady state at each new  $V_{\max 1}$ . Plot the steady state concentration of AP against the value of  $V_{\max 1}$ .

c) Vary both  $K_m$ 's using the following values:

0.1, 0.2, 0.5, 1.0, 5.0

In each case recompute the curve you generated in b).