

Computational Systems Biology
636-0007-00 U, Autumn 2025

Assignment 6

(Issue: 31-Nov-2025)

1 Simulation: Switch Model with positive feedback

The goal of this exercise is to formulate, implement, and analyze a kinetic model of a simple biochemical switch. The actual switch circuit consists only of two elements: a kinase (K_1) that activates itself by autophosphorylation and an opposing phosphatase as shown in Figure 1. These two enzymes catalyze the conversion between the active (phosphorylated) and inactive (unphosphorylated) state of K_1 . The fraction of phosphorylated K_1 , hence, represents the switch output. In addition, the phosphorylation of K_1 can also be catalyzed by the kinase K_2 , which responds to external stimuli. The model we want to consider is based on the work of Lisman (1985).

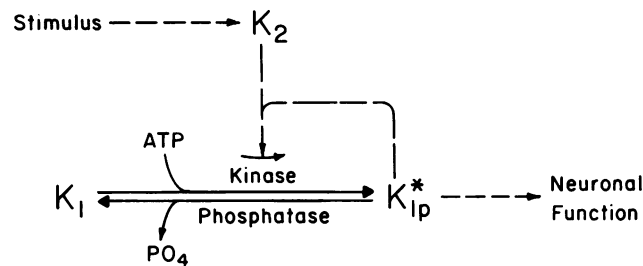


Figure 1: Reaction scheme of the biochemical switch (from Lisman, 1985).

Kinetic rate expressions as well as the associated parameter values of each of the reactions are provided in tables 1 and 2. Neither ATP nor phosphate (PO_4) is explicitly considered as separate species in this model. The total concentration of all model proteins is assumed constant.

Analysis of the Switch Model

Please perform the following tasks:

- Write down the resulting system of balance equations considering only species K_1 and K_{1P}^* and neglect the influence of r_{K_2} .
- Express the kinetic rate laws for r_{K_1} and r_P as function of K_{1P}^* as sole variable using the conservation relation. Plot both rates as function of the K_{1P}^* concentration in MATLAB (or Python).
- Calculate the nullclines

$$\frac{dc_i}{dt} = 0$$

for each single species i of this two-component system. How many steady states are possible in this system and for which concentration of K_{1P}^* do they occur? Could you have also determined them in a graphical way?

- What happens to the steady states if you assume that the phosphatase obeys mass action kinetics

$$r_{P_2} = k_{P_2} \cdot c_P \cdot c_{K_{1P}^*}$$

instead of Michaelis-Menten kinetics?

- e) Simulate and plot the dynamic behavior of the switch for varying pulse input concentrations of K_2 in the range of $0 - 7nM$ (40s intervals, pulse duration 20s followed by 20s of zero input for each pulse). Choose an integrator capable of solving stiff systems in this case (e.g., ode15s, ode23s in MATLAB, in Python you can use `scipy.integrate.solve_ivp` with appropriate solvers - see the methods parameter in the documentation). Perform this simulation for both of the suggested phosphatase rate laws (set $k_{P2} = 0.75 \cdot 10^8 \text{ } 1/M \cdot s$ for mass action kinetics). How would you describe the switch behavior? Does the different phosphatase kinetics cause any difference? What happens if the switch is in *on* state and no input signal is present anymore? When simulating systems with small numerical values, as in this case, it is important to adapt the error tolerance parameters of the ODE solver (or rescale the system). Make sure that the absolute tolerance (often called atol) is $1e-10$.

Some useful MATLAB commands and help entries for this exercise:

`solve`, `eval`, `subs`, `pretty`, `ode23s`, `ode15s`, `function handles (@)`, `nested functions`

Submission:

Please address any questions to

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Table 1: Kinetic rate expressions.

Reaction name	Description	Rate equation
r_{K_1}	Kinase 1	$k_{K_1} \cdot c_{K_{1P}^*} \cdot c_{K_1} / (K_{m_{K_1}} + c_{K_1})$
r_{K_2}	Kinase 2	$k_{K_2} \cdot c_{K_2} \cdot c_{K_1} / (K_{m_{K_2}} + c_{K_1})$
r_P	Phosphatase Michaelis-Menten	$k_P \cdot c_P \cdot c_{K_{1P}^*} / (K_{m_P} + c_{K_{1P}^*})$
r_{P_2}	Phosphatase Mass Action	$k_{P_2} \cdot c_P \cdot c_{K_{1P}^*}$

Table 2: Parameter values.

Parameter name(s)	Parameter value	Unit
k_{K_1}	30	$1/s$
k_{K_2}	30	$1/s$
k_P	3	$1/s$
k_{P_2}	$0.75 \cdot 10^8$	$1/(M \cdot s)$
$K_{m_{K_1}}$	10^{-6}	M
$K_{m_{K_2}}$	10^{-6}	M
K_{m_P}	$2.5 \cdot 10^{-9}$	M
$c_{K_{1tot}}$	$5 \cdot 10^{-8}$	M
c_P	$5 \cdot 10^{-9}$	M

Table 3: Initial concentration values (nM).

Species Name	Value
c_{K_1}	$c_{K_{1tot}}$
$c_{K_{1P}^*}$	0