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Computational Systems Biology
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Assignment 5

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1 MAP Kinase Signal Transduction: Simulation of an ODE model

The goal of this exercise is to formulate and implement a kinetic model of a common eukaryotic signal transduction pathway, a MAP kinase cascade (cf. figure 1). MAPK stands for mitogen-activated protein kinase, which is an important class of regulators involved in transducing proliferation- and differentiation-inducing extracellular signals to the cell interior. The activity of MAP kinase is controlled via a sequence of upstream protein kinases (MKK, MKKK, and MKKKK). Each kinase activates the next one downstream by catalyzing the transfer of a phosphate moiety (denoted by the index P) from ATP to its target kinase. This process is countered by removal of the attached phosphates mediated by so-called protein phosphatases, which brings the respective kinases back to the inactive state. The model we want to consider is based on the work of Kholodenko (2000).

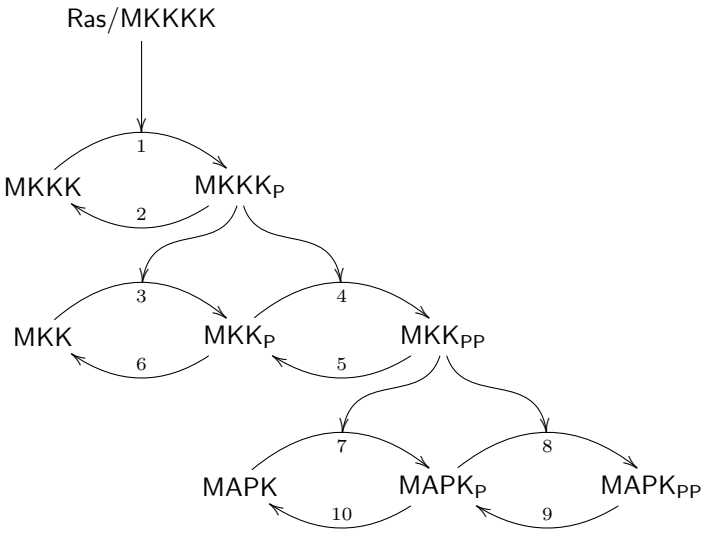

Figure 1: Reaction scheme of the MAPK signaling cascade.

The reaction scheme of the signaling cascade is given in figure 1. Kinetic rate expressions (irreversible Michaelis-Menten-type kinetics) as well as the associated parameter values of each of the reactions are provided in tables 1 and 2. Neither ATP, nor the phosphatases, nor Ras/MKKKK are explicitly considered as separate species in this model. Instead, their effect has been incorporated into the corresponding kinetic rate equations by specifying a maximal rate $V(= V^{max} = k \cdot c_{enzyme})$. MKKK is considered only active in its phosphorylated state, MKK and MAPK only in their doubly-phosphorylated state. Since the concentration of the latter species is time-dependent, this is explicitly considered in the model by substituting V^{max} by $k \cdot c_i$ (i = MKKK$_P$, MKK$_{PP}$) in the reactions they catalyze (3, 4, 7, and 8). The total concentration (sum of phosphorylated and unphosphorylated states) of any of the different proteins (MKKK, MKK, and MAPK) is assumed constant.

Please perform the following tasks:

a) Based on the reaction scheme shown in figure 1, derive the system of balance equations for the species concentrations (c_i) in the form

$$\frac{dc_i}{dt} = \sum_{j=1}^{N} v_{ij} \cdot r_j \quad , \quad \forall i = 1..M$$

where v_{ij} denotes the stoichiometric coefficient of reaction j in the balance of species i (convention: $v_{ij} > 0$ if r_j produces i, $v_{ij} < 0$ if i is consumed in reaction j).

b) Implement the resulting ODE system in MATLAB or Python along with the associated kinetic rate expression for the r_j. Simulate the dynamic behavior of the system for $1000s$ using the ODE solver `ode45` (Runge-Kutta algorithm) for the initial values of species concentrations given in table 3. In Python you may want to use the `odeint` (though it is now deprecated) or `solve_ivp` function from `scipy.integrate`. Plot the simulated concentration trajectories into one graph.
Note: Consider implementing your ODE system as nested function to facilitate parameter passing (cf. MATLAB help entries for `odefile` and for parameterizing ODEs, esp. the van der Pol ODE example `vdpode`). An example routine for a toy system is provided on the homepage (`toymodel_sim.m`).

c) Analyze the steady-state input-output characteristics of the MAPK system. Perform a series of simulations into the steady state for this purpose where you vary the value of V_1 between 0 and $0.5nM/s$. Plot the resulting output activity ($MAPK_{PP}$ concentration) as a function of the input V_1. How would you characterize this signal/response curve?

d) How would you express reaction rate r_1 if you had experimental evidence of a noncompetitive inhibition of MAPKKK phosphorylation from $MAPK_{PP}$ (active MAPK)? What kind of action is that?
Note: If you want to run simulations using the above reaction rate r_1, use $K_I = 9$ and increase the simulation time up to $6000sec$. Do you see any difference in the dynamic response of your system?

Some useful MATLAB commands and help entries for this exercise:

`ode45`, `odeset`, `odefile`, `vdpode`, `function handles (@)`, `find`, `size`, `plot`, `figure`,xlabel, legend, disp, nested functions

Some useful Python commands and help entries for this exercise:

`scipy.integrate` (`odeint`, `solve_ivp`), `matplotlib.pyplot` (`figure`, `xlabel`, `ylabel`, `plot`, `legend`, `show`), `numpy` (`linspace`)

Submission:

Please address any questions to:
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Table 1: Kinetic rate expressions.

Reaction number	*Rate equation*
1	$V_1 \cdot c_{MKKK}/(K_1 + c_{MKKK})$
2	$V_2 \cdot c_{MKKK_P}/(K_2 + c_{MKKK_P})$
3	$k_3 \cdot c_{MKKK_P} \cdot c_{MKK}/(K_3 + c_{MKK})$
4	$k_4 \cdot c_{MKKK_P} \cdot c_{MKK_P}/(K_4 + c_{MKK_P})$
5	$V_5 \cdot c_{MKK_{PP}}/(K_5 + c_{MKK_{PP}})$
6	$V_6 \cdot c_{MKK_P}/(K_6 + c_{MKK_P})$
7	$k_7 \cdot c_{MKK_{PP}} \cdot c_{MAPK}/(K_7 + c_{MAPK})$
8	$k_8 \cdot c_{MKK_{PP}} \cdot c_{MAPK_P}/(K_8 + c_{MAPK_P})$
9	$V_9 \cdot c_{MAPK_{PP}}/(K_9 + c_{MAPK_{PP}})$
10	$V_{10} \cdot c_{MAPK_P}/(K_{10} + c_{MAPK_P})$

Table 2: Parameter values.

Parameter name(s)	*Parameter value*	*Unit*
V_1	2.5	nM/s
V_2	0.25	nM/s
V_5, V_6	0.75	nM/s
V_9, V_{10}	0.5	nM/s
k_3, k_4, k_7, k_8	0.025	s^{-1}
K_1	10	nM
K_2	8	nM
$K_3 - K_{10}$	15	nM

Table 3: Initial concentration values (nM).

Species Name	*Value*
MKKK	100
$MKKK_P$	0
MKK	300
MKK_P	0
MKK_{PP}	0
MAPK	300
$MAPK_P$	0
$MAPK_{PP}$	0