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Computational Systems Biology
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Assignment 9

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MAP Kinase Signal Transduction: Modular response analysis

The goal of this exercise is to perform a modular response analysis for 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).

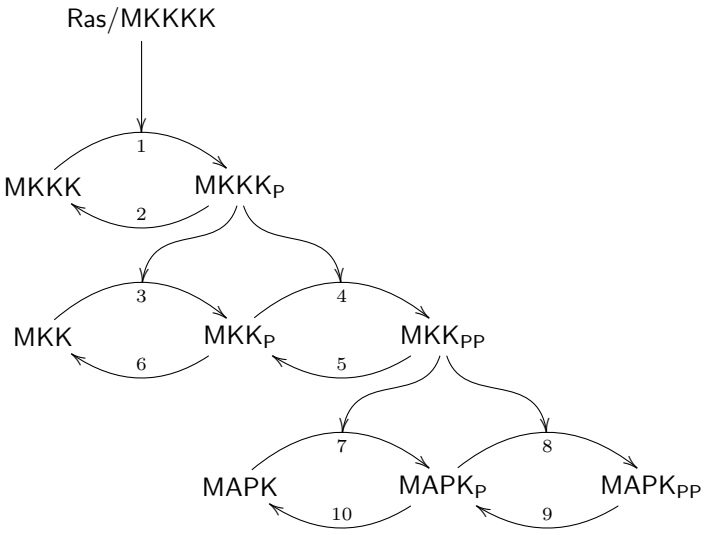

Figure 1: Reaction scheme of the MAPK signaling cascade.

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) Divide the network into 3 modules and choose a communicating intermediate (x_i) for each module i.

b) Compute the global network response to perturbations (R_p). R_p is an $m \times m$ matrix composed of coefficients R_{jp_i}, where m is the number of modules in the network and R_{jp_i} represents the global response coefficient of module j to a perturbation in p_i.

$$R_{jp_i} = (\Delta_i \ln x_j)_{\text{system steady state}} \quad , \quad \forall j, i = 1, .., m$$

The elements R_{jp_i} can be approximated in the following way: e.g. for module 1, use an inhibitor or other perturbation that affects only module 1, and measure the difference in the steady-state levels of communicating intermediates before ($x_j^{(0)}$) and after ($x_j^{(1)}$) the perturbation. Thus,

$$\Delta_1 \ln x_j \approx 2\frac{x_j^{(1)}/x_j^{(0)} - 1}{x_j^{(1)}/x_j^{(0)} + 1}$$

Use as parameter perturbations a 10% decrease in the values of K_1 for module 1, k_3 and k_4 for module 2, respectively k_7 and k_8 for module 3.

c) Compute the local network response to perturbations (r). r is an $m \times m$ matrix, where the coefficient r_{ij} quantifies the sensitivity of module i to module j. A response coefficient r_{ij} less than 1 means that (small) fractional changes in module j output are attenuated in module i, whereas a response greater than 1 means that these fractional changes are amplified by the factor r_{ij}. A response coefficient of 0 means that module j has no direct effect on module i, whereas a negative response coefficient means inhibition. We assign values of -1 to the diagonal elements (r_{ii}) of the matrix r. r can be obtained in the following way:

$$r = -[dg(R_p^{-1})]^{-1} \cdot R_p^{-1}$$

where dg represent the diagonal matrix.

d) Repeat parts b and c, for the following parameter perturbations:

i) 50 % decrease in the values of K_1 for module 1, k_3 and k_4 for module 2, respectively k_7 and k_8 for module 3.

ii) 10% decrease in the values of V_1 for module 1, V_5 and V_6 for module 2, respectively V_9 and V_10 for module 3.

iii) 50% decrease in the values of V_1 for module 1, V_5 and V_6 for module 2, respectively V_9 and V_10 for module 3.

Hints:

Reuse the code from assignment 5.

References:

B.N. Kholodenko et al., Untangling the wires: A strategy to trace functional interactions in signaling and gene networks. Proc. Natl. Acad. Sci. 99: 12841-46 (2002).

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