EXPLORATION OF SIGNALING CYCLES USING DYNAMIC OPTIMIZATION

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Context

Background and Scope

Signal transduction pathways - enable cells to:
- sense changes in their environment
- integrate external or internal signals,

and respond to them by changes in transcriptional activity, metabolism, or other regulatory measures.
These pathways are very important for major developmental and genetic changes in every organism (cell growth, mitogenesis, differentiation, embryo development), and their malfunction is associated with diseases (cancer, asthma, diabetes..).

Signaling Cascade

Simple biochemical network:
- enzyme-catalyzed chemical modification of a protein molecule and
- the reverse reaction catalyzed by a different enzyme (monocyclic cascades)

This basic unit is found repeatedly in multiple configuration, throughout a wide variety of biological pathways, including phosphorylation-dephosphorylation of ***mitogen-activated protein kinase (MAPK) signaling cascades.***

Analysis of MAPK Cascades

$$\frac{dx^*}{d\tau} = \rho^{S/X}\tilde{k}_X\{x:s^*\} + \rho^{P_X/X}(\tilde{d}^*_X\{x^*:p_X\} - \tilde{a}^*_X x^* p_X)$$
$$\frac{d\{x:s^*\}}{d\tau} = \tilde{a}_X x s^* - (\tilde{d}_X + \tilde{k}_X)\{x:s^*\}$$
$$\frac{d\{x^*:p_X\}}{d\tau} = \tilde{a}^*_X x^* p_X - (\tilde{d}^*_X + 1)\{x^*:p_X\}$$
$$0 = 1 - x - x^* - \rho^{S/X}\{x:s^*\} - \rho^{P_X/X}\{x^*:p_X\}$$
$$0 = 1 - s - s^* - \{x:s^*\}$$
$$0 = 1 - p_X - \{x^*:p_X\}$$

Mass balance
+
Mass-Action Kinetics
=
Dimensionless transient model
↕
Differential-algebraic equation system

Key System Parameters

Species: $x, x^*, s, s^*, \{x:s^*\}, p_X, \{x^*:p_X\}$
$y, y^*, \{y:x^*\}, p_Y, \{y^*:p_Y\}$
$z, z^*, \{z:y^*\}, p_Z, \{z^*:p_Z\}$

Parameters: $\tilde{a}_X, \tilde{a}_{X^*}, \tilde{d}_X, \tilde{d}_{X^*}, \tilde{k}_X$ $\quad \tilde{K}_X, \tilde{K}_{X^*}$
$\tilde{a}_Y, \tilde{a}_{Y^*}, \tilde{d}_Y, \tilde{d}_{Y^*}, \tilde{k}_Y, \tilde{k}_{Y^*}$ $\quad \tilde{K}_Y, \tilde{K}_{Y^*}$
$\tilde{a}_Z, \tilde{a}_{Z^*}, \tilde{d}_Z, \tilde{d}_{Z^*}, \tilde{k}_Z, \tilde{k}_{Z^*}$ $\quad \tilde{K}_Z, \tilde{K}_{Z^*}$

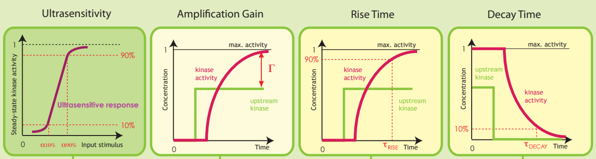
Concentration ratios:
$\varrho^{S/X}, \varrho^{P_X/X}$ $\quad \varrho^{X/Y}, \varrho^{P_Y/Y}$ $\quad \varrho^{Y/Z}, \varrho^{P_Z/Z}$

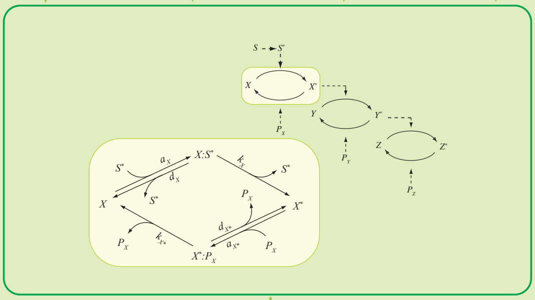
Acitivity coefficient:
$$\alpha_X = \tilde{k}_X \frac{\varrho^{S/X}}{\varrho^{P_X/X}}$$

Methodology

Dynamic Optimization Problem

variation in functional behavior





optimization techniques

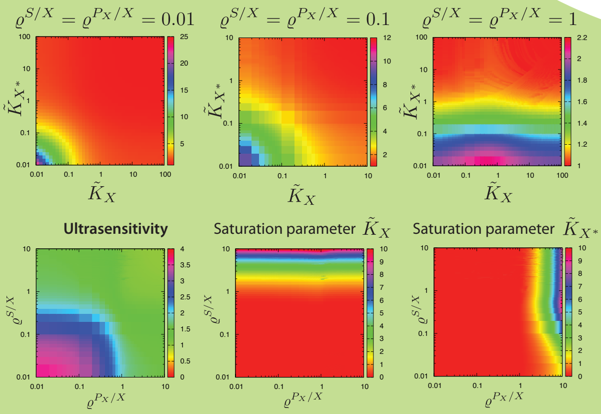
required parameter values

Optimal Design for Maximal Ultrasensitivity

Dimensionless Michaelis-Menten constants:

$$\tilde{K}_X = \frac{\tilde{d}_X + \tilde{k}_X}{\tilde{a}_X} \qquad \tilde{K}_{X^*} = \frac{\tilde{d}_{X^*} + 1}{\tilde{a}_{X^*}}$$

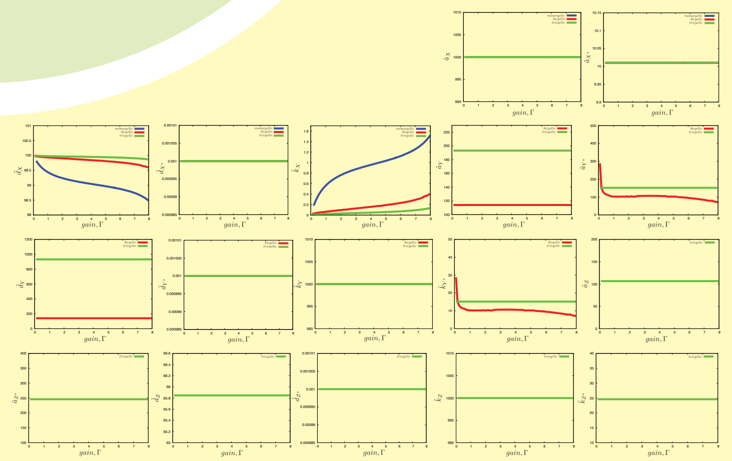
Concentration ratios: $\varrho^{S/X} = \frac{[S]_T}{[X]_T}$ $\quad \varrho^{P_X/X} = \frac{[P_X]_T}{[X]_T}$

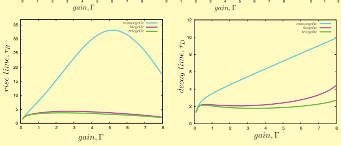


- Ultrasensitivity can always be achieved when both the signaling-enzyme-to--substrate and phosphatase-to-substrate ratios are small.
- However, this condition alone is not sufficient to allow ultrasensitivity. It is also required that both the activation and deactivation reactions operate at enzyme saturation.

Optimal Design for Minimal Signal Propagation Time

- Given amplification gain
- Given maximal ultrasensitivity
- Optimization of the sum of two signal propagation times





Monocylic: Promotes longer signaling times than a multicyclic, even under lower ultrasensitivity constraints.
Multicyclic: Similar trend for the kinetic parameters for bi- and tricyclic cascade.

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