Supplementary Materials for "A Theoretical Framework for Specificity in Cell Signaling", by NL Komarova, X Zou, Q Nie, and L Bardwell

1. Overview

This Supplementary Materials section contains the following items:

1. Overview

2. A detailed walk-through of the equations and solutions of the "basic architecture" network described in the main paper.

3. Equations and solutions for the compartmentalization/scaffolding networks described in the main paper.

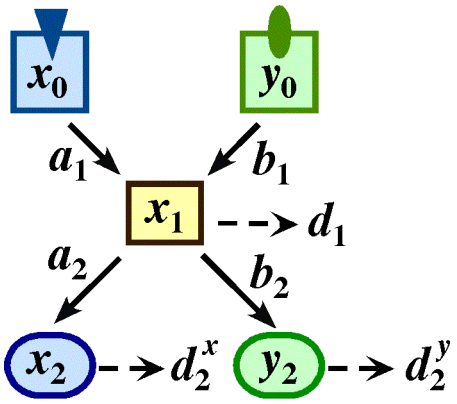
4. References.

2. Equations and solutions of the basic architecture.

2.1 Note on definitions.

Let us denote by $\bar{x}_n = \int_0^\infty x_n(t)\,dt$, the total amount of active component x_n produced when the cell is exposed to a given signal input. Similarly, we define $\bar{x}_n\big|X_{in} = \int_0^\infty x_n(t)dt\Big|_{x_0>0,y_0=0}$ as the total amount of active component x_n produced when the cell is exposed to signal x_0 but not to signal y_0. These two terms are used somewhat interchangeably; that is, if it is understood that we are solving a system for its behavior under the action of signal x_0, then $\bar{x}_n$ is understood to mean $\bar{x}_n\big|X_{in}$. If x_n is the final component of a pathway, then $\bar{x}_n\big|X_{in}$ is the same as $X_{out}\big|X_{in}$.

2.2. Basic Architecture Equations



Basic Architecture

The equations for the basic architecture, given in Table I of the full paper, are:

$$dx_1/dt = a_1 x_0(t) + b_1 y_0(t) - d_1 x_1 \quad \text{(A1)}$$

$$dx_2/dt = a_2 x_1 - d_2^x x_2 \quad \text{(A2)}$$

$$dy_2/dt = b_2 x_1 - d_2^y y_2 \quad \text{(A3)}$$

Here, $x_0(t)$ and $y_0(t)$ are the signal functions. We assume the network only receives one of the two signals at a time. Thus, if $x(t)$ is positive for some duration of time, then $y_0(t)$ is identically zero, and visa versa; either the first or second term of equation (A1) is equal to zero, depending upon which of the two signals the network is receiving. The terms x_1, x_2 and y_2 are concentrations of the active species of these components at a given moment of time. The parameters a_1 and a_2 are activation rate constants for pathway X; a_2 is the rate at which kinase x_1 activates (phosphorylates) target x_2. Similarly, the parameters b_1 and b_2 are activation rate constants for pathway Y; b_2 is the rate at which kinase x_1 activates (phosphorylates) target y_2. Finally, d_1, d_2^x and d_2^y are deactivation rate constants (also called decay rate constants), and can be thought of as representing phosphatase activity, for example. The active species (x_1, x_2) are presumed to be produced from inactive precursors. However, to simplify the mathematics, we assume that the concentrations of the inactive species do not change significantly during the

course of the reaction; that is, we assume that the network is 'weakly activated' (Chaves et al., 2004; Heinrich et al., 2002), and thus can be modeled as a linear system.

Consider equation (A2), which specifies $\frac{dx_2}{dt}$, the rate of change of the concentration of the active species of component x_2 at a particular moment in time. This is equal to the amount of active x_2 being created minus the amount being destroyed at that time. The former is equal to the concentration of active upstream kinase x_1 multiplied by the rate constant a_2; the latter is equal to the concentration of x_2 multiplied by the deactivation rate constant d_2^x.

2.3. Basic Architecture Solutions

The solution to the system (A1-A3) under the action of signal is x_0 obtained as follows: First, set the term $b_1 y_0(t)$ in equation (A1) to zero. Second, integrate both sides of A1-A3 from time zero to infinity (alternatively, assume steady-state conditions apply). This converts the differential equations into algebraic equations in which the left hand sides are zero, and $x_0(t)$, x_1 and x_2 are replaced with $\bar{x}_0$, $\bar{x}_1$ and $\bar{x}_2$, respectively:

$$0 = a_1\bar{x}_0 - d_1\bar{x}_1 \tag{A4}$$

$$0 = a_2\bar{x}_1 - d_2^x\bar{x}_2 \tag{A5}$$

$$0 = b_2\bar{x}_1 - d_2^y\bar{y}_2 \tag{A6}$$

It is then a simple matter to solve equation (A4) for $\bar{x}_1$, and then (A5) for $\bar{x}_2$ and (A6) for $\bar{y}_2$, yielding:

$$\bar{x}_1\big|X_{\text{in}} = \frac{\bar{x}_0 a_1}{d_1}, \quad \bar{x}_2\big|X_{\text{in}} = \frac{\bar{x}_0 a_1 a_2}{d_1 d_2^x}, \quad \bar{y}_2\big|X_{\text{in}} = \frac{\bar{x}_0 a_1 b_2}{d_1 d_2^y}. \tag{A7}$$

Equations (A7) indicate that $\bar{x}_1$ (the total amount of active kinase x_1 produced in response to the signal) is directly proportional to the total amount of signal applied ($\bar{x}_0$) and to the rate constant (a_1) for the production of x_1 from x_0, and is inversely proportional to its deactivation constant (d_1). Likewise, $\bar{x}_2$ is directly proportional to the signal and to the forward rate constants for pathway X (a_1 and a_2), and is inversely proportional to the deactivation constants for pathway X.

A similar procedure can be used to solve the system under the assumption that the signal/receptor for pathway Y is 'on', and X is 'off' (that is, $y_0(t) > 0$ and $x_0(t) = 0$):

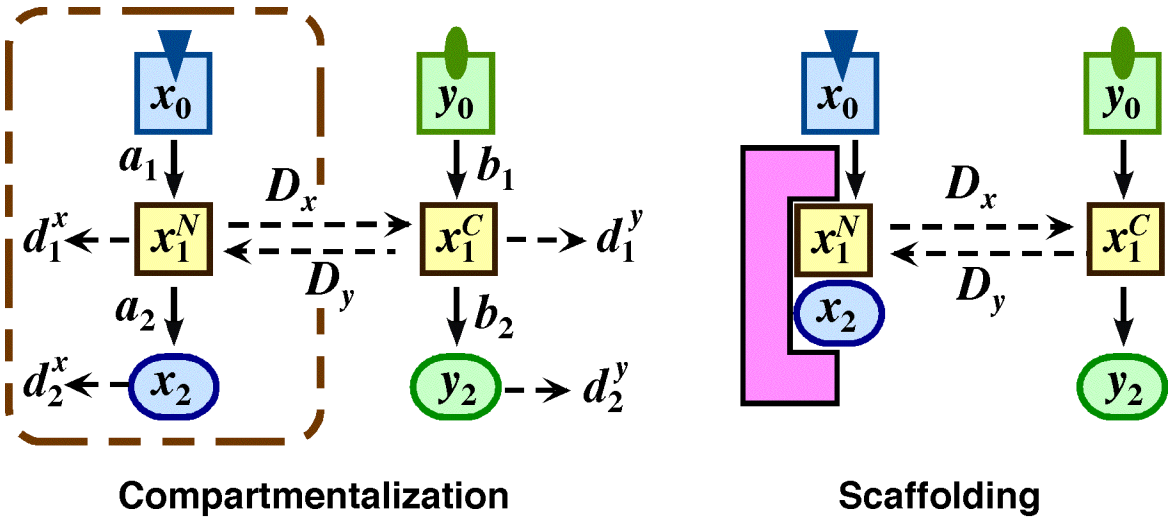
$$\bar{x}_1 | Y_{in} = \frac{\bar{y}_0 b_1}{d_1}, \quad \bar{x}_2 | Y_{in} = \frac{\bar{y}_0 b_1 a_2}{d_1 d_2^x}, \quad \bar{y}_2 | Y_{in} = \frac{\bar{y}_0 b_1 b_2}{d_1 d_2^y}. \tag{A8}$$

From expressions (A7) and (A8) we can calculate that

$$S_X = \frac{a_2 d_2^y}{b_2 d_2^x}, S_Y = \frac{b_2 d_2^x}{a_2 d_2^y}, F_X = \frac{\bar{x}_0 a_1}{\bar{y}_0 b_1}, F_Y = \frac{\bar{y}_0 b_1}{\bar{x}_0 a_1}. \tag{A9}$$

Hence, $S_{network} = F_{network} = 1$.

3. Compartmentalization and scaffolding equations and solutions.



The equations for this system are as follows:

$$dx_1^N/dt = a_1 x_0(t) - D_x x_1^N + D_y x_1^C - d_1^x x_1^N \tag{A10}$$

$$dx_1^C/dt = b_1 y_0(t) + D_x x_1^N - D_y x_1^C - d_1^y x_1^C \tag{A11}$$

$$dx_2/dt = a_2 x_1^N - d_2^x x_2 \tag{A12}$$

$$dy_2/dt = b_2 x_1^C - d_2^y y_2 \tag{A13}$$

For compartmentalization, x_1^N represents the Nuclear pool of x_1, and x_1^C the Cytosolic pool. For scaffolding, x_1^N (aNchored x_1) represents kinase x_1 bound to the scaffold and x_1^C is unbound

x_1, free in solution in the cytosol. D_x is the coefficient for the rate at which x_1 exits the nucleus (or dissociates from the scaffold) and enters the cytosol, and D_y is the rate constant for x_1 leaving the cytosol and entering the nucleus (or binding to the scaffold). D_x and D_y can be considered as pseudo-diffusion rate constants, or exchange rate constants. The parameters d_1^x and d_1^y are the deactivation constants for x_1 in the nucleus/on the scaffold and in the cytosol, respectively.

Consider equation (A10), for dx_1^N/dt. For compartmentalization, the first term indicates that the activation of kinase x_1 by signal x_0 occurs only in the nucleus, the second and third terms represent the leaking of x_1 out of and into the nucleus, respectively, and the final term is the deactivation of x_1 by nuclear phosphatases. For scaffolding, the first term indicates that the activation of kinase x_1 by signal x_0 occurs only on the scaffold, the second term is the dissocation of active x_1 from the scaffold, the third term the binding of x_1 activated in the cytosol to the scaffold, and the final term is the deactivation of x_1 while on the scaffold. Now consider Equation (A12) for dx_2/dt. The first term indicates that the activation of target x_2 by kinase x_1 also occurs only in the nucleus (or on the scaffold); the second term is the deactivation of x_2 by nuclear phosphatases.

To solve system A10-A13, we follow a similar procedure as was used to solve the basic architecture. Under the action of signal x_0,

$$\bar{x}_1^N = \frac{\bar{x}_0 a_1 + D_y \bar{x}_1^C}{d_1^x + D_x} \tag{A14}$$

$$\bar{x}_1^N = \bar{x}_1^N \frac{D_x}{d_1^y + D_y} \tag{A15}$$

To solve for $\bar{x}_1^N \big| X_{\text{in}}$, substitute (A15) into (A14):

$$\bar{x}_1^N = \frac{\bar{x}_0 a_1}{d_1^x + D_x} + \frac{D_x D_y \bar{x}_1^N}{(d_1^x + D_x)(d_1^y + D_y)} \quad \rightarrow$$

$$\bar{x}_1^N \left(1 - \frac{D_x D_y}{(d_1^x + D_x)(d_1^y + D_y)} \right) = \frac{\bar{x}_0 a_1}{d_1^x + D_x} \quad \rightarrow$$

$$\bar{x}_1^N = \frac{\bar{x}_0 a_1}{\delta\left(d_1^x + D_x\right)} \tag{A16}$$

where

$$\delta = \left(1 - \frac{D_x D_y}{(d_1^x + D_x)(d_1^y + D_y)}\right), \quad 0 \le \delta \le 1 \tag{A17}$$

Note: δ approaches 1 as exchange rates (D_x, D_y) shrink and deactivation rates increase.

Similarly, to solve for $\bar{x}_1^C \,|X_{in}$, substitute (A16) into (A15):

$$\bar{x}_1^C = \bar{x}_1^N \frac{D_x}{\left(d_1^y + D_y\right)} \quad = \frac{\bar{x}_0 a_1}{\delta\left(d_1^x + D_x\right)} \frac{D_x}{\left(d_1^y + D_y\right)} \tag{A18}$$

From (A12) and (A13):

$$\bar{x}_2 \,|X_{in} = \frac{a_2 \bar{x}_1^N}{d_2^x}, \quad \bar{y}_2 \,|X_{in} = \frac{b_2 \bar{x}_1^C}{d_2^y} \tag{A19}$$

Thus,

$$S_X = \frac{\bar{x}_2 \,|X_{in}}{\bar{y}_2 \,|X_{in}} \quad = \frac{a_2 d_2^y}{b_2 d_2^x} \frac{\bar{x}_1^N}{\bar{x}_1^C} \quad = \frac{a_2 d_2^y}{b_2 d_2^x} \frac{(d_1^y + D_y)}{D_x} \tag{A20}$$

Using a similar procedure, or just applying considerations of symmetry, we can solve for $\bar{x}_2 \,|Y_{in}$ and $\bar{y}_2 \,|Y_{in}$, and thus calculate the remaining metrics:

$$S_Y = \frac{b_2 d_2^x}{a_2 d_2^y} \frac{(d_1^x + D_x)}{D_y} \tag{A21}$$

$$F_X = \frac{\bar{x}_0 a_1}{\bar{y}_0 b_1} \frac{(d_1^y + D_y)}{D_y}, \; F_Y = \frac{\bar{y}_0 b_1}{\bar{x}_0 a_1} \frac{(d_1^x + D_x)}{D_x} \tag{A22}$$

$$S_{network} = \frac{(d_1^y + D_y)(d_1^x + D_x)}{D_y D_x} \tag{A23}$$

4. References.

Chaves M, Sontag ED, Dinerstein RJ (2004) Optimal length and signal amplification in weakly activated signal transduction cascades. J Phys Chem B 108: 15311-15320

Heinrich R, Neel BG, Rapoport TA (2002) Mathematical models of protein kinase signal transduction. Mol Cell 9: 957-970