How Quantitative Measures unravel Design Principles in multi-stage Phosphorylation Cascades

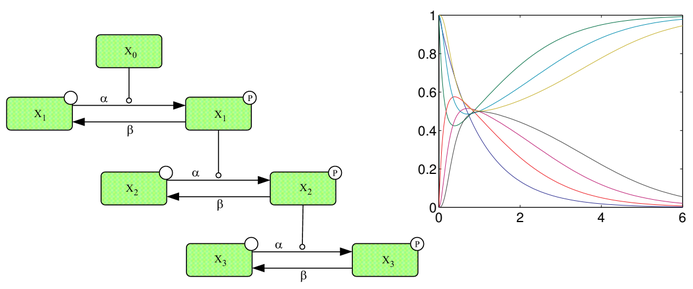
S. Frey[1], Th. Millat[1], S. Hohmann[2], and O. Wolkenhauer[1]

Abstract

- We investigate design principles of linear multi-stage phosphorylation cascades by using quantitative measures for signaling time, signal duration, and signal amplitude.
- We suggest that certain pathway structures are the result of an optimization process aiming for a fast response, defined by the minimum of the product of signaling time and signal duration.
- Several popular models of MAPK cascades form the basis of our study. These models represent different levels of approximation.
- We compare alternative structures of different models and show that certain pathway structures minimize the optimization criterion.
- We show that a model for a weakly activated pathway does not reflect the biological context well, unless it is restricted to certain parameter combinations.

Introduction

The **general model** by **Heinrich *et al.* [1]** (denoted **Hg**) describes a linear cascade with kinase rate constant α, and phosphatase rate contant β.



$$X_0(t) = \mathcal{X}_0\, \mathrm{e}^{-\lambda t} \quad X_i^{\mathrm{tot}} = X_i + X_i^{\mathrm{P}}$$

$$\frac{d}{dt}X_i^P = \alpha_i\, X_{i-1}^P \left\{1 - \frac{X_i^P}{X_i^{\mathrm{tot}}}\right\} - \beta_i X_i^P$$

The **weakly activated model [1]** (denoted **Hw**) describes a linear cascade with *a low* kinase rate constant α, and *a strong* phosphatase rate contant β.

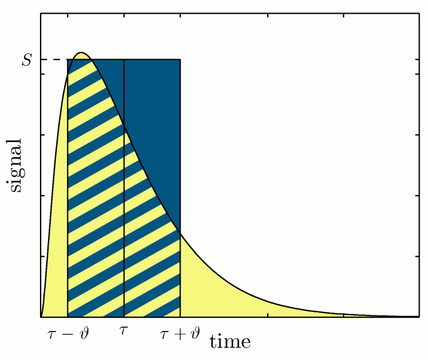
$$\frac{X_i^{\mathrm{P}}}{X_i^{\mathrm{tot}}} \ll 1$$

$$\frac{d}{dt}X_i^P = \alpha_i\, X_{i-1}^P - \beta_i\, X_i^P$$

Quantitative Measures defined in [1] for

Amplification $A_n = \frac{S_n}{S_0}$

	the Hg model	the Hw model
signaling time	$\tau_i = \frac{\int_0^\infty t X_i^{\mathrm{P}}\, dt}{\int_0^\infty X_i^{\mathrm{P}}\, dt}$	$\tau_i = \frac{1}{\lambda} + \sum_{j=1}^{i} \frac{1}{\beta_j}$
signal duration	$\vartheta_i = \sqrt{\frac{\int_0^\infty t^2 X_i^{\mathrm{P}}\, dt}{\int_0^\infty X_i^{\mathrm{P}}\, dt} - \tau_i^2}$	$\vartheta_i = \sqrt{\frac{1}{\lambda^2} + \sum_{j=1}^{i} \frac{1}{\beta_j^2}}$
signal strength	$S_i = \frac{\int_0^\infty X_i^{\mathrm{P}}\, dt}{2\vartheta_i}$	$S_i = \frac{S_0 \prod_{k=1}^{i} \frac{\alpha_k}{\beta_k}}{\sqrt{1+\lambda^2 \sum_{j=1}^{i} \frac{1}{\beta_j^2}}}$



Optimality criterion: $O_n = \min_n (\tau_n \cdot \vartheta_n)$

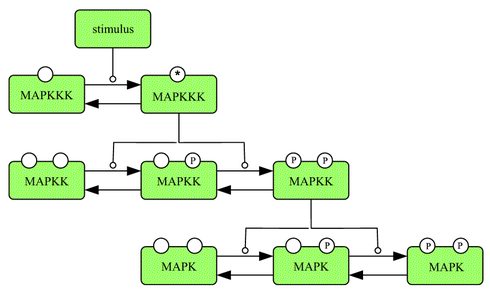
finds the minimum of the product of signaling time and signal duration for different pathway structures. The structures differ in length or number of phosphorylations.

MAPK Models

The MAPK cascade consists of a structure of at least three activation steps and double phosphorylations.

$$\mathrm{X_i} + \mathrm{X_{i-1}^P} \underset{d_i}{\overset{a_i}{\rightleftharpoons}} (\mathrm{X_i\, X_{i-1}^P}) \xrightarrow{k_i} \mathrm{X_i^P} + \mathrm{X_{i-1}^P}$$

Each activation/deactivation of proteins follows an enzyme kinetic reaction



Model by **Huang and Ferrell [2]** (denoted **HF**)

Assumptions:

- act/deact: enzyme kinetics
- H_2O, ATP, … are constant
- some conservation laws for proteins

$$\frac{d}{dt}(X_i\, X_{i-1}^P) = a_i\, (X_i)\ (X_{i-1}^P) - \{d_i + k_i\}\, (X_i\, X_{i-1}^P)$$

Model by **Kholodenko [3]** (denoted **K**)

Assumptions:

- constant phosphatase
- quasi steady state for complexes
- conservation law

$$\frac{d}{dt}X_i^{\mathrm{P}} = \frac{k_i\, X_{i-1}^{\mathrm{P}}\, X_i}{K_{\mathrm{M}} + X_i} - \frac{V_i\, X_i^{\mathrm{P}}}{K_{\mathrm{M}} + X_i^{\mathrm{P}}}$$

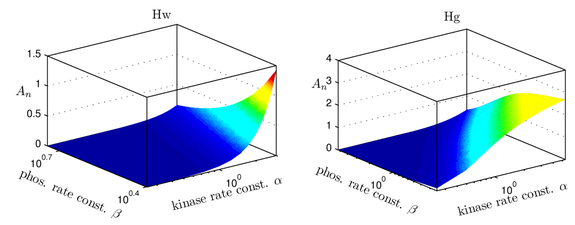
Relation of Kinetic Parameters [4]

$$\alpha_i = \frac{k_i}{K_{\mathrm{M}}^i} \qquad \beta_i = P\frac{k_i}{K_{\mathrm{M}}^i} \qquad K_{\mathrm{M}}^i = \frac{d_i + k_i}{a_i} \qquad V_i = k_i\, P$$

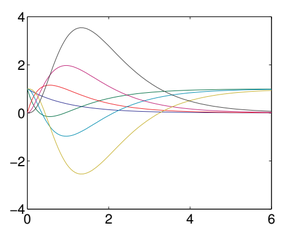
Results

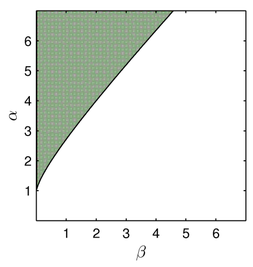
Limitations of a weak activation model

A_n can increase up to infinity but ther is only a finite number of molecules!



S_n is higher than total concentration, or S_n lower than zero. Calculating the minimum of a protein of a cascade of length one, unravels the parameter combinations which fulfill the condition of a weak activation [5].





$$\alpha \leq (\beta - 1)/(\beta^{1/(1-\beta)} - \beta^{\beta/(1-\beta)})$$

Relation of time & duration

With increasing cascade length:
Faster signaling time $\Longrightarrow$
Shorter signal duration!

For the same outcome S of a cascade of length *n* and a cascade of length *n-j* ($n,j \in \{1,2,3,\ldots\}$ and $n > j$), the signaling time τ is faster for the longer cascade if:

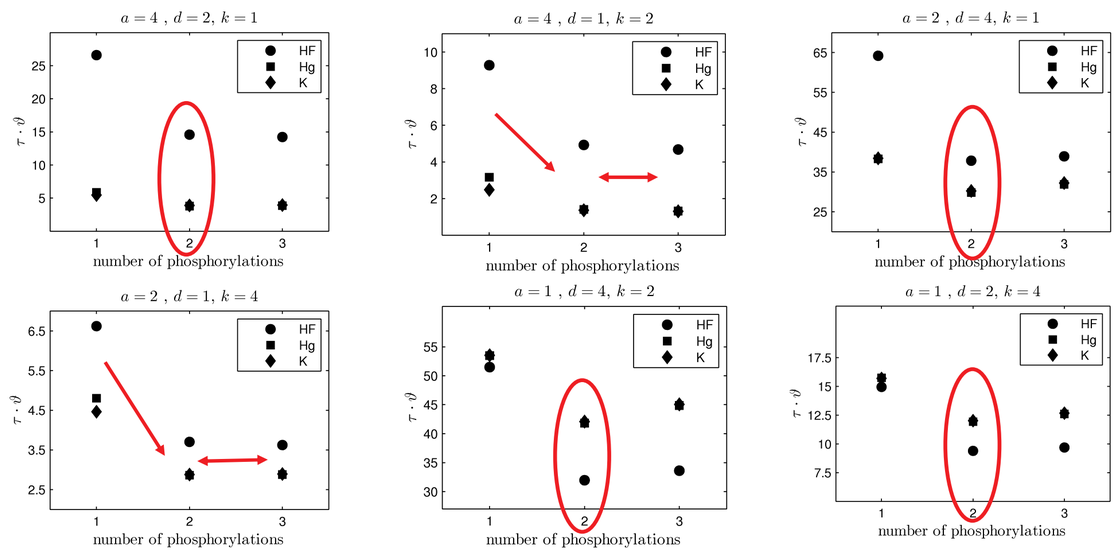
$$\frac{1}{\lambda} + \frac{n}{\widehat{\beta}_n} < \frac{1}{\lambda} + \frac{n-j}{\beta_{n-j}}$$
$$\Leftrightarrow \frac{n}{\widehat{\beta}_n} < \frac{n-j}{\beta_{n-j}}$$
$$\Leftrightarrow \frac{\beta_{n-j}}{\widehat{\beta}_n} < \frac{n-j}{n}$$

and the signal duration υ is shorter for the longer cascade if:

$$\frac{\beta_{n-j}}{\widehat{\beta}_n} < \sqrt{\frac{n-j}{n}}$$

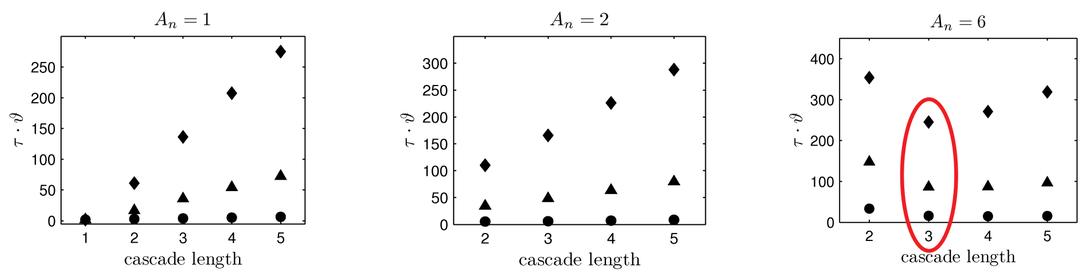
where β is the phosphatase rate constant of the shorter cascade and $\hat{\beta}$ of the longer one.

Comparison of different model approximations



The quantitative measures of the Hg and K model lie close together, reflecting the similar assumptions made. Our optimality criterion is minimal for a pathway structure with double phosphorylation [5].

Comparison of a model of different cascade lengths



Our optimality criterion becomes minimal for an amplification of six at a cascade length of three [5] which represents the structure of the MAPK cascade.

Further Information

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