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

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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 \(a\), and phosphatase rate constant \(\beta\).

\[
X_n(t) = X_0 e^{-\lambda t} X_n^\text{tot} = X_i + X_j^P
\]

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

\[
\frac{d}{dt} X_i^P = \alpha_i X_j^P - \beta_i X_i^P
\]

Quantitative Measures defined in [1] for

- **Amplification**
  - the Hg model: \(A_0 = \frac{S_n}{S_0}\)
  - the Hw model: \(A_0 = \frac{S_n}{S_0}\)

Optimality criterion: \(O_n = \min (\tau_n \cdot \theta_n)\)

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.

\[X_i + X_j^P \frac{a_i}{d_i} (X_j^P)^{-1} \rightarrow X_i X_j^P \rightarrow X_i^P + X_j^P \]

Each activation/deactivation of proteins follows an enzyme kinetic reaction

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

- act/deact: enzyme kinetics
- \(H_2O, ATP, ... \) are constant
- some conservation laws for proteins

\[
\beta_i = P \frac{k_i}{K_i M} \quad K_i M = d_i + k_i (X_i X_j^P)
\]

Relation of Kinetic Parameters [4]

\[
\alpha_i = \frac{k_i}{K_i M} \quad \beta_i = P \frac{k_i}{K_i M} \quad K_i M = d_i + k_i (X_i X_j^P) \quad V_i = k_i P
\]

Further Information

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References


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