Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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Introduction

Cell Signaling

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Understanding the functioning of cell signaling is important in many biological areas.

Cell Signaling

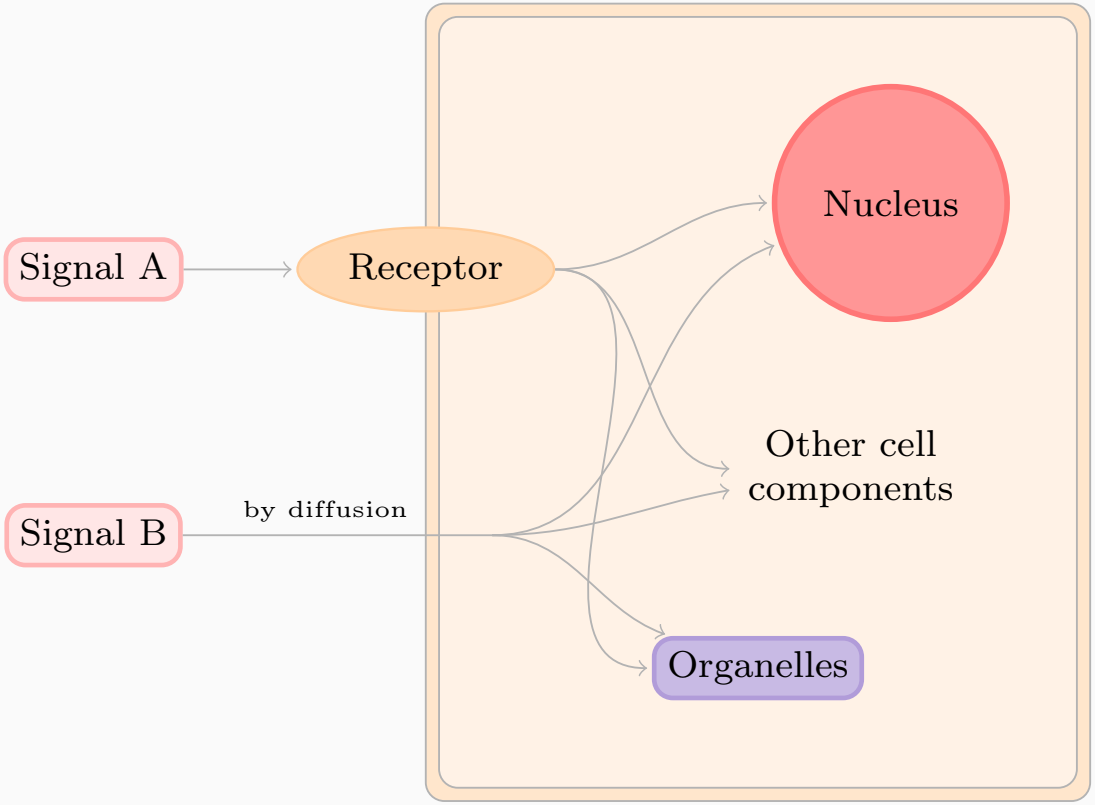

Figura 1: A general cell signaling mechanism.

Cell Signaling Pathways

A cell signaling network can be characterized by a sequence of chemical reactions that allows the presence of a signal to modify the state or behaviour of a cell.

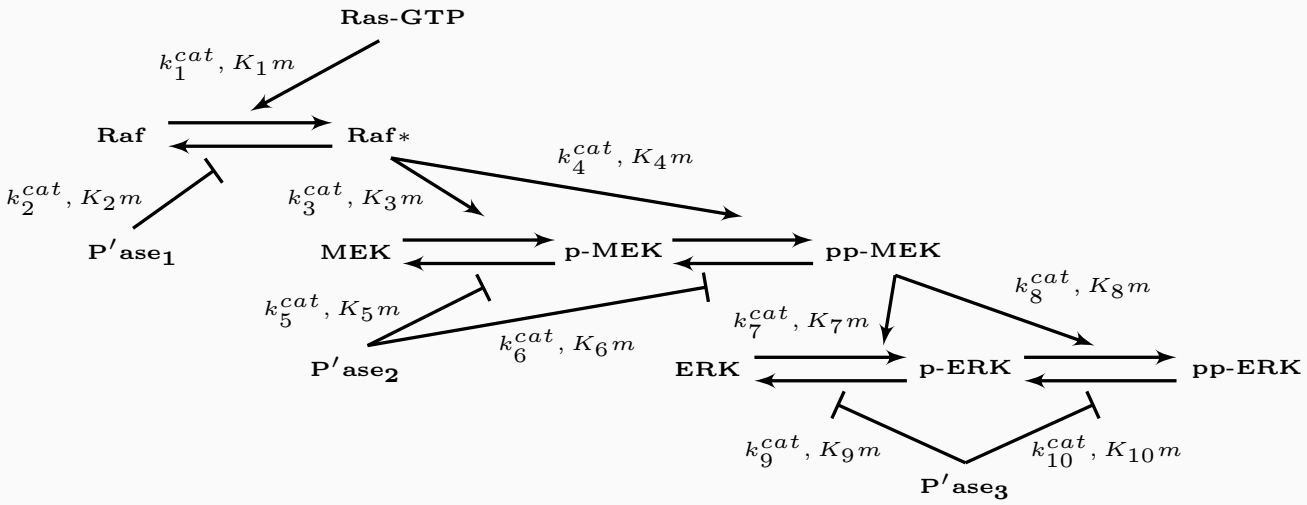

Figura 2: An example of a signaling pathway.

Mathematical Models of Signaling Networks

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Using biochemical and enzymatic kinetics, we can write equations that represent the rate of change of concentration for a chemical species.

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Repeating this procedure for all reactions of a pathway allows us to derive a system of ordinary differential equations that can model the signaling pathway.

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- a model composed by a set of chemical reactions that are relevant for the biological experiment;
- information about the reaction rate constants of the model.

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Hence, it is desirable to construct a method that can systematically modify these models and choose the one that better represents the experiment.

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On her work, the problem of identification of cell signaling pathways is treated as a feature selection problem.

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> Given a set of features S and a cost function c, find subset $X \in \mathcal{P}(S)$, with minimum cost $c(X)$.

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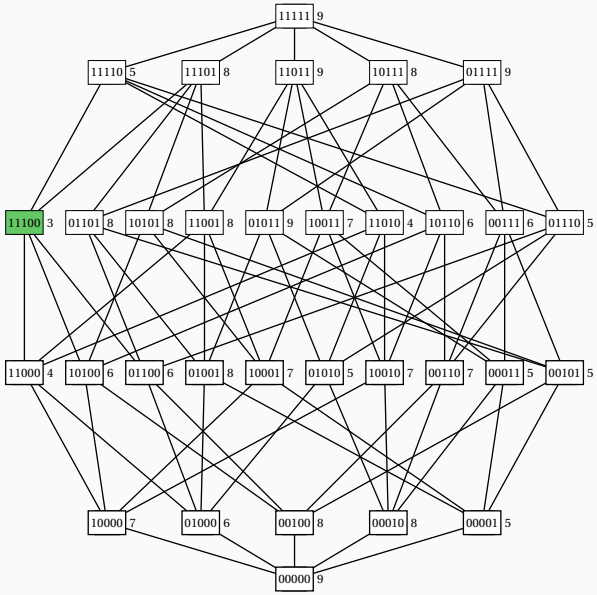

Figura 3: An example of feature selection search space with 5 features.

Feature Selection for Identification of Signaling Pathways

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Wu's Search Algorithm for Feature Selection

The search algorithm used by Wu is the Sequential Forward Selection (SFS).

Wu's Cost Function for Feature Selection

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where $R(M)$ is a regularization function.

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Results of Wu's Methodology

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We can point three aspects of Wu's work that could explain its limitation.

- the database of interactions used could be more nearly complete;
- the search algorithm could also consider removing interactions;
- the cost function could implement a proper penalization of models;

What we Propose on this Project

We propose to create a methodology that uses a feature selection approach for identification of signaling pathways, tackling the difficulties encountered by Wu.

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To create new search algorithms, we intend to use more general algorithms that can also remove interactions.

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To define new cost functions, we intend to use Bayesian approaches of model selection that allow us to create estimates of probabilities such as $p(M|D)$ or $p(D|M)$.

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- Create search algorithms for the feature selection problem.
- Test the methodology on known signaling pathways.
- Apply the methodology on a real case.

Fundamental Concepts

Mathematical Modeling of Enzymatic Reactions

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- Michaelis-Menten enzymatic kinetics.

Kinetic Model of First Order Iteration

A first order reaction:

$$\mathrm{R} \xrightarrow{k_1} \mathrm{P},$$

Kinetic Model of First Order Iteration

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has rate of:

$$k_1[R]$$

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A first order reaction:

$$\mathrm{R}_1 + \mathrm{R}_2 \xrightarrow{k_1} \mathrm{P},$$

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has rate of:

$$k_1[R_1][R_2]$$

Model Selection

Experiments on Model Selection

Next Steps