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.

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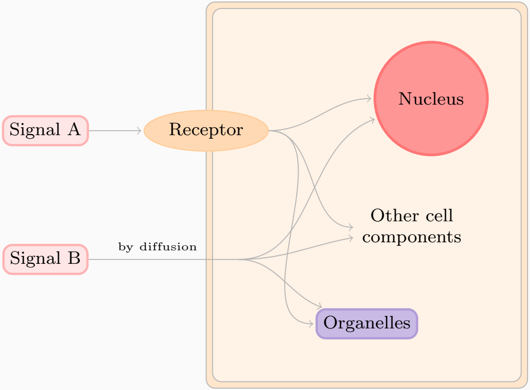

Figura 1: A general cell signaling mechanism.

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.

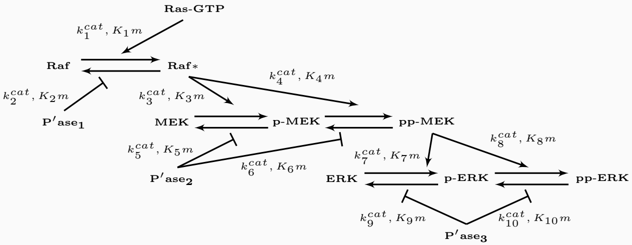

Figura 2: An example of a signaling pathway.

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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One can search for the set of chemical reactions relevant for a biological experiment in repositories like the Kyoto Encyclopedia of Genes and Genomes (KEGG). However, the pathway maps from KEGG may be incomplete or have impertinent reactions for the biological experiment of interest.

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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The feature selection problem is a combinatorial optimization problem:

> 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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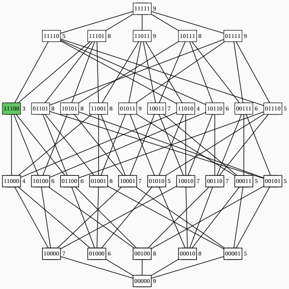

Figura 3: An example of feature selection search space with 5 features.

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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- 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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- Apply the methodology on a real case.

Fundamental Concepts

Kinetics Modeling of Chemical Reactions

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- second order interaction kinetics;
- Michaelis-Menten enzymatic kinetics.

Kinetic Modeling of First Order Iteration

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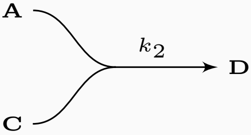
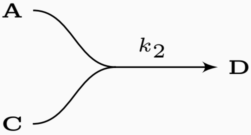
Kinetic Modeling of Second Order Iteration

A second order reaction:



Kinetic Modeling of Second Order Iteration

A second order reaction:

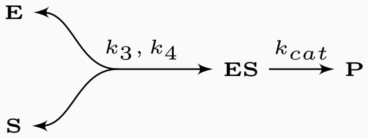


has rate of:

$$k_1[\mathrm{A}][\mathrm{C}].$$

Kinetic Modeling of Enzymatic Reactions

An enzymatic reaction:



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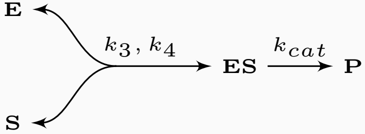

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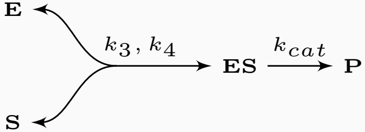

Can be divided in two first order reactions plus a second order reaction. However, with the appropriate assumptions, it is possible to use a Michaelis-Menten simplification of this reaction.

Michaelis-Menten Kinetics

We denote Michaelis-Menten simplification of the last enzymatic reaction as

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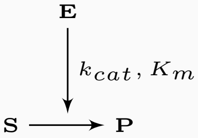
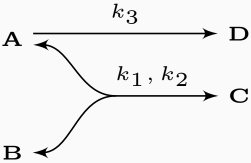


and it has rate of:

$$k_{cat}\frac{[\mathrm{E}][\mathrm{S}]}{K_M + [\mathrm{S}]}.$$

Kinetics of a System of Reactions

Suppose we want to model the kinetics of A on these reactions:



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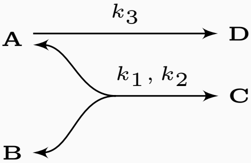

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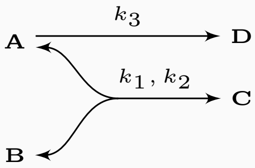

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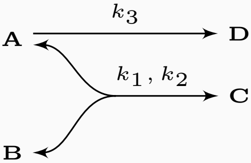

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- $A + B \longrightarrow C$, with rate $k_1[A][B]$,
- $C \longrightarrow A + B$, with rate $k_2[C]$,
- $A \longrightarrow D$, with rate $k_3[A]$.

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Then, the differential equation that models the concentration change of A is:

$$\frac{d[\mathrm{A}]}{dt} = -k_1[\mathrm{A}][\mathrm{B}] + k_2[\mathrm{C}] - k_3[\mathrm{D}].$$

Bayesian Methods for Biochemical Model Selection

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For both methods, we resort to Metropolis-Hastings algorithm to generate samples of distributions.

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5. Increase t by one and repeat from Step 2 if not reached iteration limit.

Model Selection

Experiments on Model Selection

Next Steps