Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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May 2019

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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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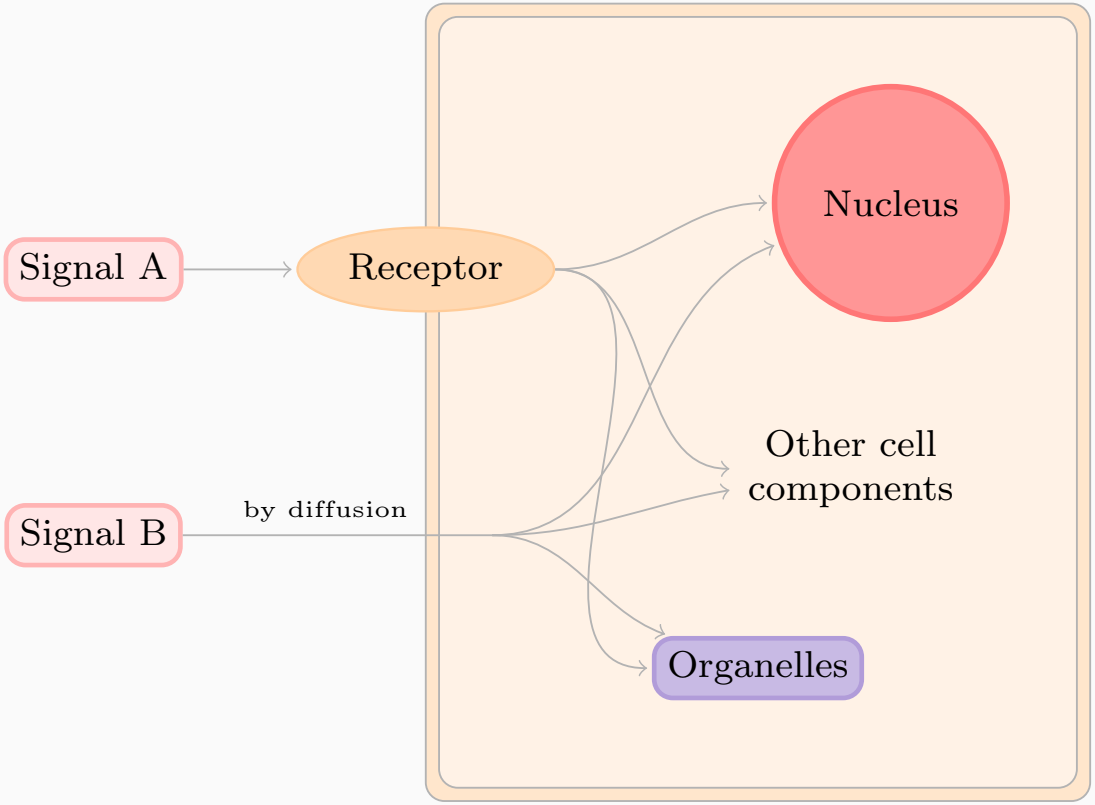

Figura 1: A general cell signaling mechanism.

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.

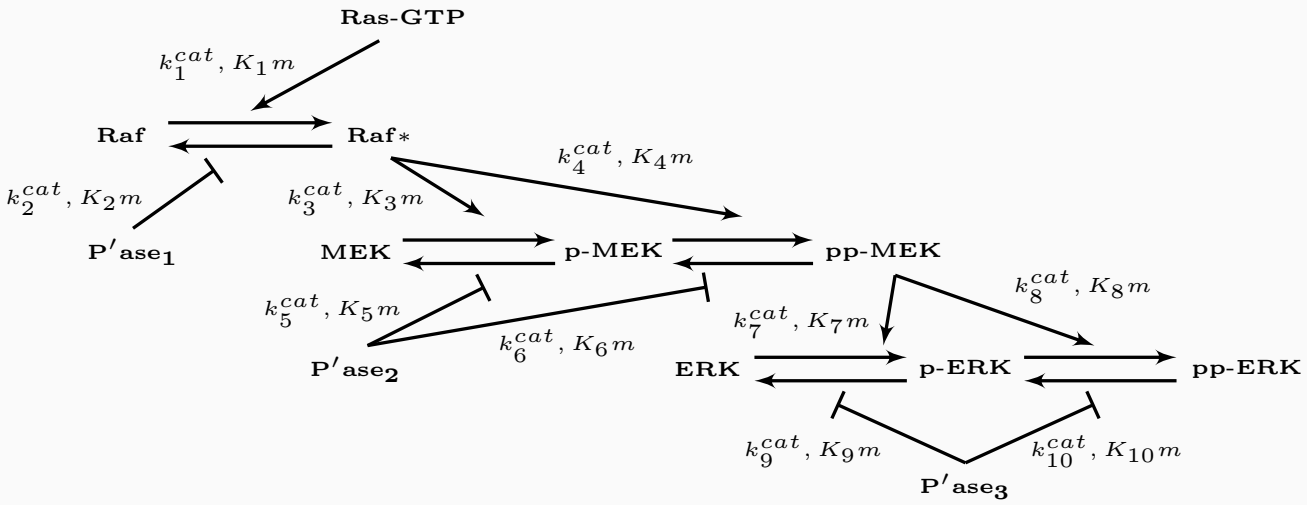

Figura 2: An example of a signaling pathway.

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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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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Lulu Wu (2015) presented in her master dissertation a methodology that proposes to systematically modify models of signaling network in order to better represent experiments.

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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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Feature Selection for Identification of Signaling Pathways

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The methodology proposed by Wu defines the set of features as a set of chemical reactions that can be added to a starting model.This set of chemical reactions is fetched from KEGG and stored in a database of interactions.

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

Wu defines the cost function as the minimum distance between experimental and simulated data.

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Results of Wu's Methodology

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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,

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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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- Test the methodology on known signaling pathways.
- Apply the methodology on a real case.

Fundamental Concepts

Kinetics Modeling of Chemical Reactions

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- Michaelis-Menten enzymatic kinetics.

Kinetic Modeling of First Order Iteration

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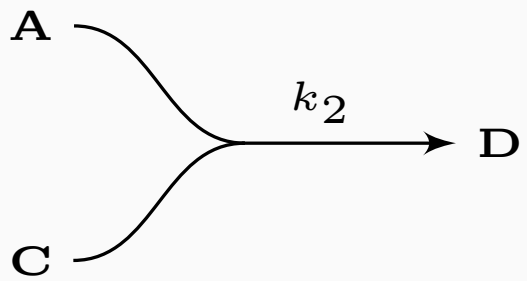
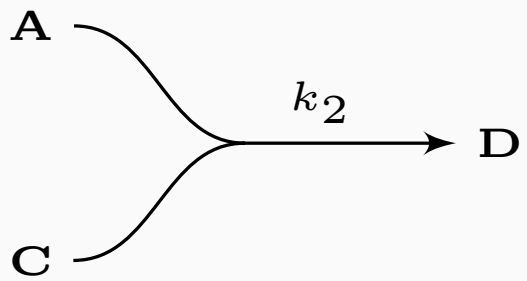


Kinetic Modeling of Second Order Iteration

A second order reaction:



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Kinetic Modeling of Enzymatic Reactions

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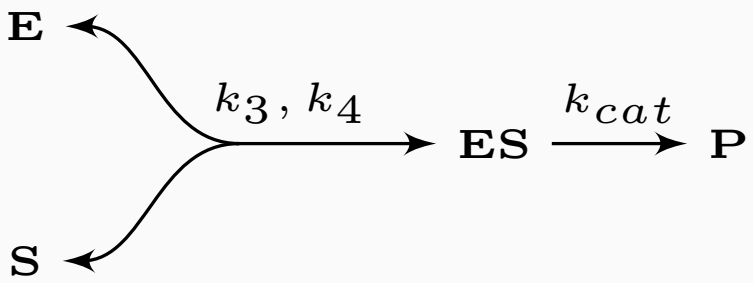

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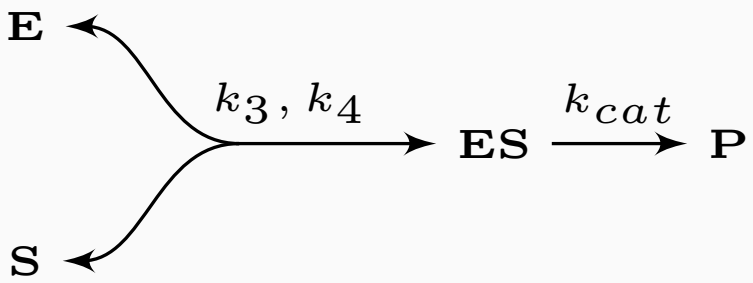

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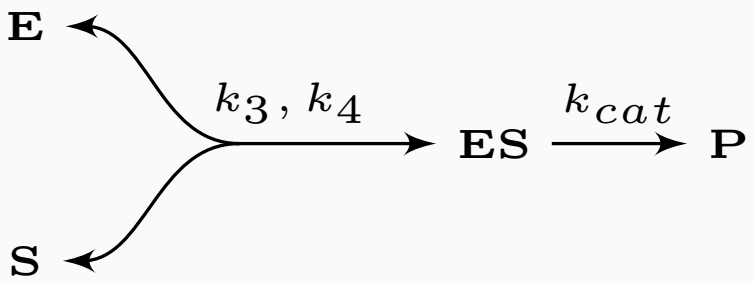
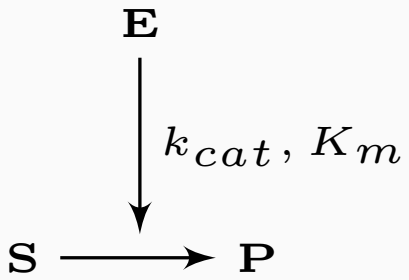


Can be divided in two first order reactions plus a second order reaction. However, with the appropriate assumptions, it is possible to use a Michaelis-Menten simplification of this reaction.

Michaelis-Menten Kinetics

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



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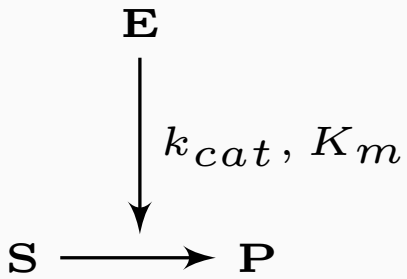
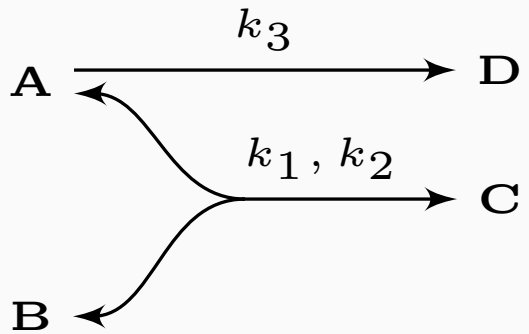


and it has rate of:

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

Kinetics of a System of Reactions

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



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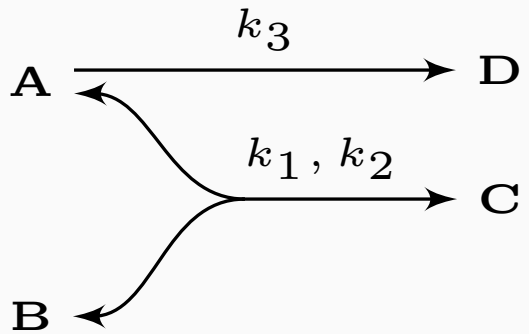

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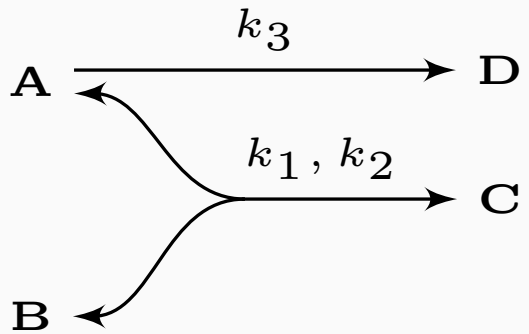

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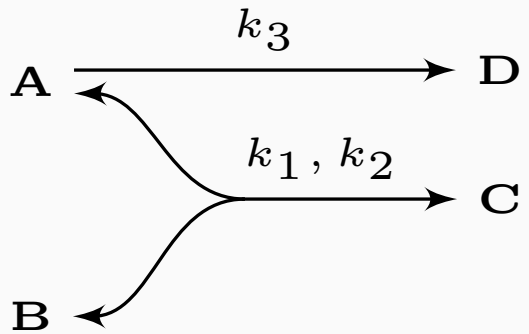

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- $A \longrightarrow D$, with rate $k_3[A]$.

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

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

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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4. Set $\lambda_t = \lambda^*$ with probability $\min(1, r)$ and $\lambda_t = \lambda_{t-1}$ otherwise;
5. Increase t by one and repeat from Step 2 if not reached iteration limit.

Model Selection

Ranking with Marginal Likelihood Estimation

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$$p(D|M,\theta) = p_{\mathcal{N}_{(\vec{0},\Sigma)}}(\phi(M,\theta) - D).$$

Where $\phi(M,\theta)$ is the simulated observation.

Marginal Likelihood of Data

We can marginalize the likelihood to obtain:

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Calculating this integral is hard, therefore we resort to estimating another integral.

Power-posterior distributions

We define a power-posterior distribution as:

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$$p_{\beta=1}(\theta) = \frac{p(D, \theta|M)}{\int_\Theta p(D, \theta|M) d\theta} = \frac{p(\theta|D, M)p(D|M)}{p(D|M)} = p(\theta|D, M).$$

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$$\ln p(D|M) = \int_0^1 \mathbb{E}_{p_\beta(\theta)}[\ln p(D|\theta, M)] d\beta.$$

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$$\sum_{t=0}^{T-1} (\beta_{t+1} - \beta_t) \frac{\mathbb{E}_{p_{\beta_{t+1}}(\theta)}[\log p(D|M,\theta)] + \mathbb{E}_{p_{\beta_t}(\theta)}[\log p(D|M,\theta)]}{2}$$

Estimating the Thermodynamic Integral

To produce the estimates of

$$\mathbb{E}_{p_{\beta_t}(\theta)}[\log p(D|M,\theta)] \text{ for } t \in \{0,\ldots,T\}$$

we need to produce samples of the power-posteriors $p_{\beta_t}(\theta)$.

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On the second and third step, the covariance matrix of the jump distributed is estimated with the current sample of the posterior.

Sampling from the Power-posteriors

On the third step a Populational Monte Carlo Markov Chain is performed. This algorithm allows us to mix samples from different temperatures.

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4. Repeat until some iteration limit.

Approximate Bayesian Computation

The result of the algorithm is a sample of the distribution

$$p(\theta, M | d(\phi(M, \theta), D) \leq \epsilon).$$

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We can use the accepted parameters of tolerance ϵ and model M to estimate

$$p(M|d(\phi(M, \theta)) < \epsilon, D).$$

Experiments on Model Selection

Next Steps