

Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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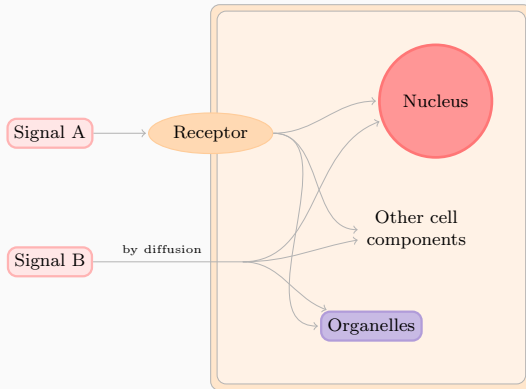
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Understanding the functioning of cell signaling is important in many biological areas.

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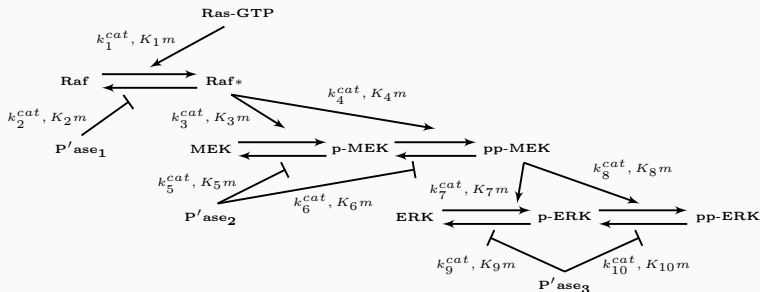
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We call the path of a signal a cell signaling pathway.

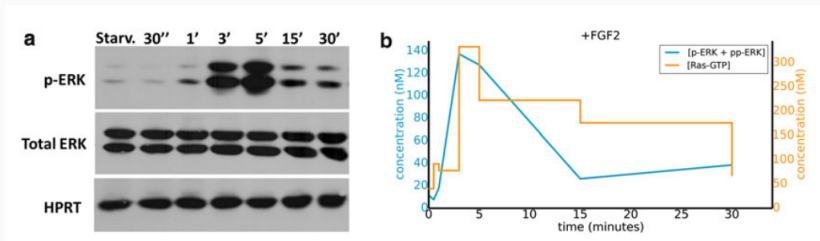
Cell Signaling Pathways

A cell signaling network can be characterized by a sequence of chemical reactions



Dynamic of Cell Signaling Pathways

We can summarize the state of the cell signaling pathway with measurements based on the concentration of some chemical species.



Identification of Cell Signaling Pathways

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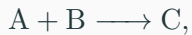
A possible output to the problem is composed by:

- 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.

A Model for Cell Signaling Pathways

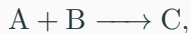
We model cell signaling pathways with a system of ordinary differential equations. These equations represent the dynamic of concentrations of chemical species.

As an example, for the chemical reaction



Mathematical Models of Signaling Networks

As an example, for the chemical reaction



we can write the following equation:

$$\frac{d[C]}{dt} = k[A][B];$$

where k is a reaction rate constant.

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However, that might produce incomplete models, or models with unimportant reactions.

It is then desirable to systematically propose new models.

Identification of Cell Signaling Pathways

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

Feature Selection Problem

The feature selection problem can be defined in the following way:

Given a set of features S and a error function $err()$, find subset $X \subseteq S$, with minimum error $err(X)$.

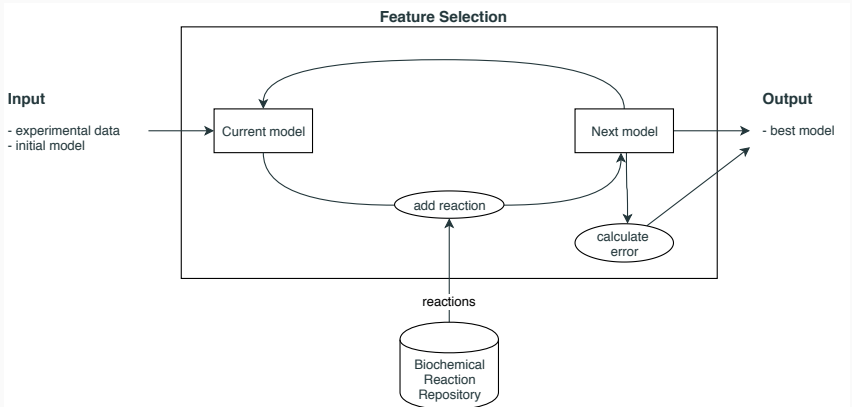
Feature Selection for Identification of Signaling Pathways

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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.

Dynamic of Cell Signaling Pathways



Results of Wu's Methodology

However, the methodology worked satisfactorily only when the Kernel model was similar to a correct model.

Difficulties of Wu's Methodology

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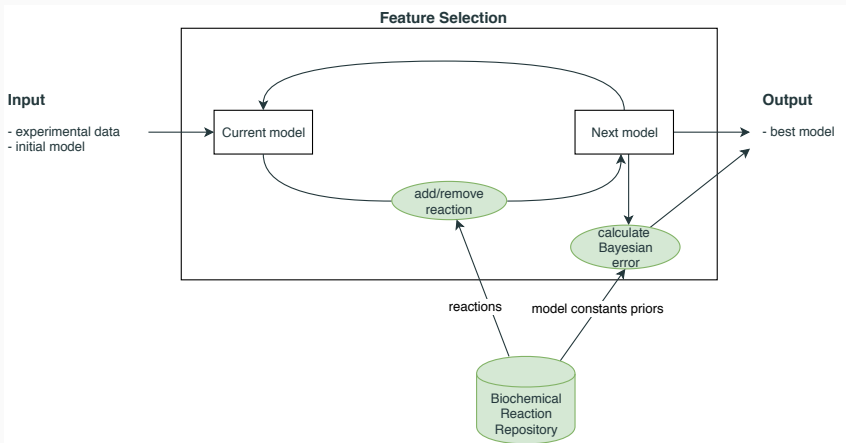
We can point three aspects of Wu's work that could explain its limitations.

- 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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- Create a cost function for models of signaling pathways.
- Formulate systematic modifications to a model as the search space of a feature selection model.
- Test the methodology on known signaling pathways and also on pathways of interest in our lab.

Bayesian Ranking of Models

To perform model ranking, we created a Python package called SigNetMS.

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Given a experimental data, a model and its constants priors, the software can calculate an estimative of $p(D|M)$. This value is called the marginal likelihood.

SigNetMS is an open source software and it is available at:

<https://github.com/gustavoem/SigNetMS>

Experiments on Model Selection

Model Ranking Experiment

We tested SigNetMS on the ranking of models.

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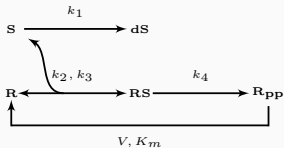
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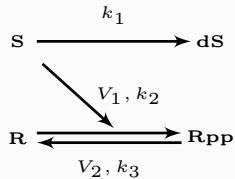
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- Neglect chosen parameter values and define prior distributions for every parameter.
- Rank the four models.

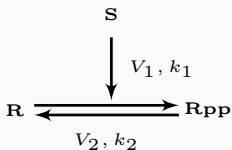
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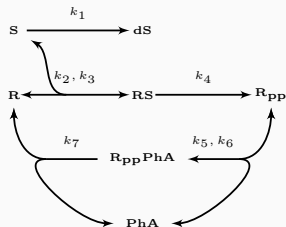
Model 1



Model 2



Model 3



Model 4

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Note that:

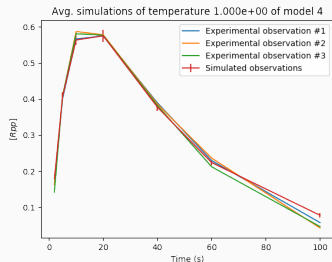
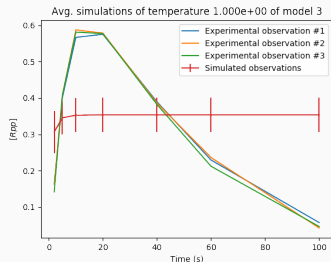
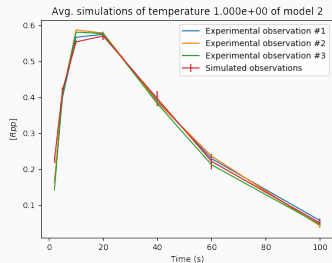
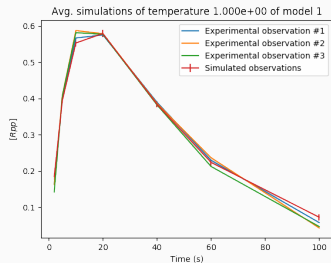
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Note that:

- the correct model is ranked first;
- overly complex models are ranked worse than simpler models.

Results on SigNetMS



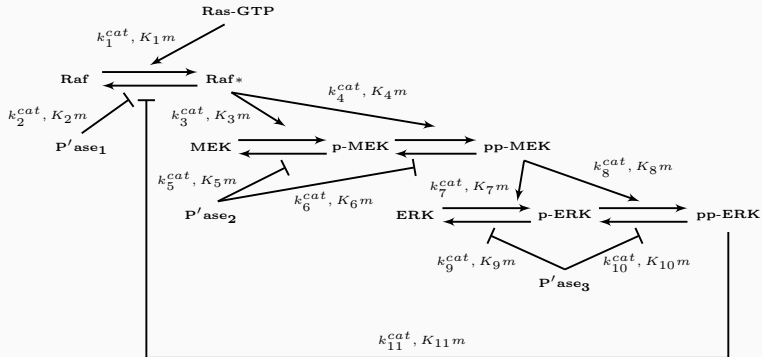
Surface Walk Experiment

We also designed an experiment to walk on search space of models. The experiment consists in starting with a base model and then iteratively add reactions to it randomly, calculating their scores.

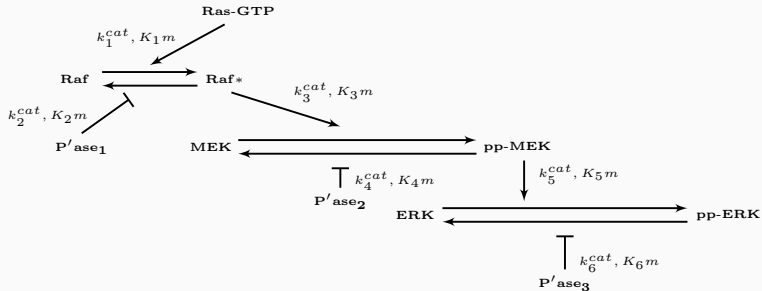
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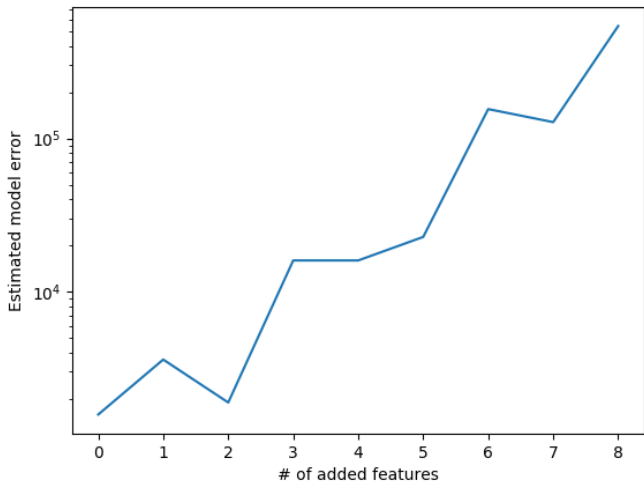
Surface Walk Experiment



Surface Walk Experiment



Surface Walk Experiment



Future Work

More activities are expected to be completed in this project, mainly the follow:

- Creation of a relational database of chemical interactions focused on our further applications.

- Apply the method in ERK signaling pathways of tumor cell lines Y1 and HEK293.

Thank you!