Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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Cell Signaling

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

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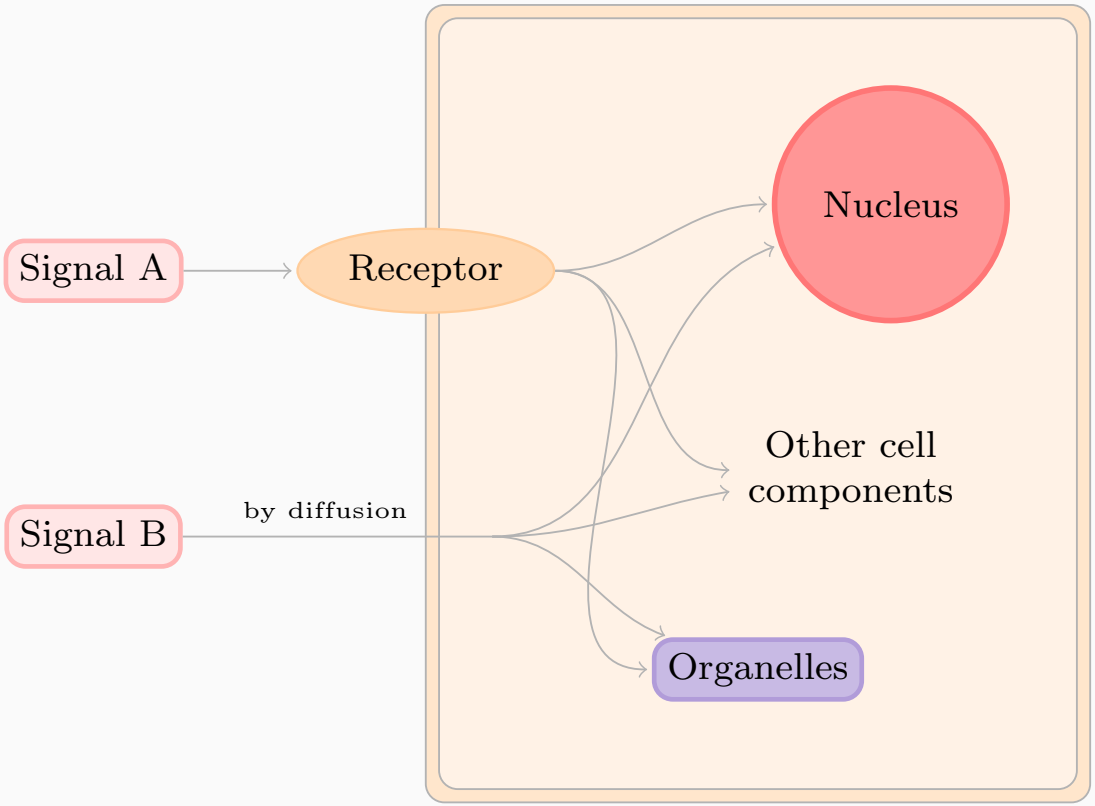

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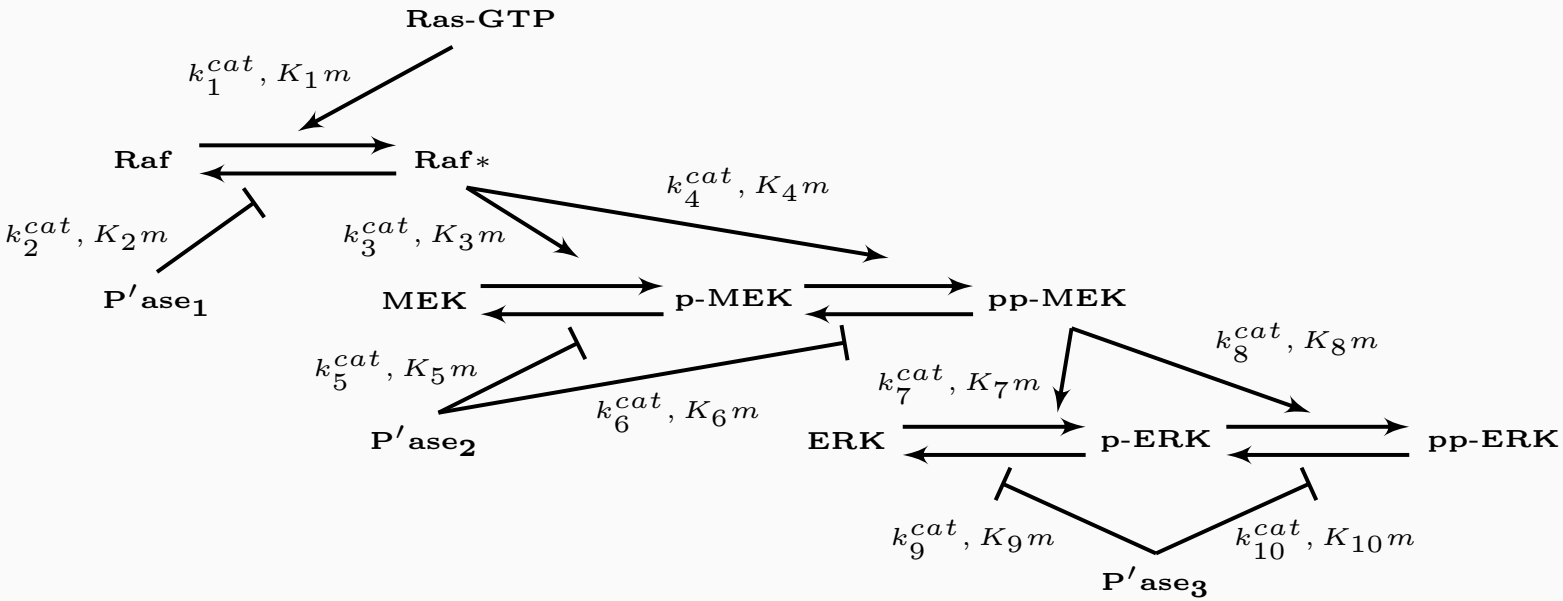
We call the path of a signal a cell signaling pathway.

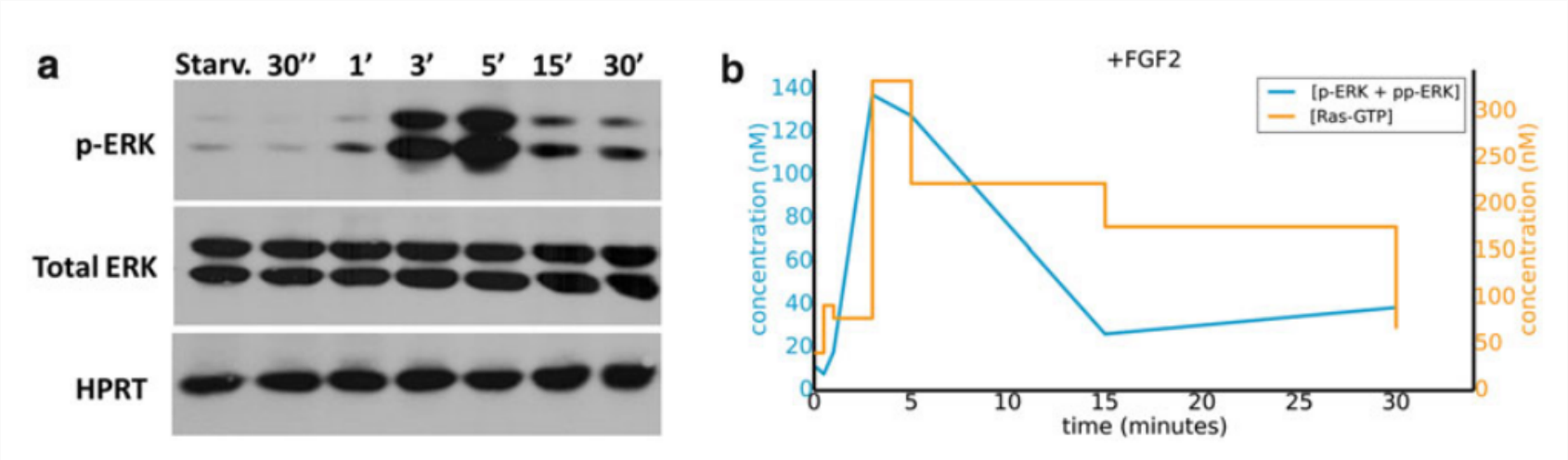
Cell Signaling Pathways

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.



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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

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we can write the following equation:

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

where k is a reaction rate constant.

Identification of Cell Signaling Pathways

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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 cost function c, find subset $X \in \mathcal{P}(S)$, with minimum cost $c(X)$.

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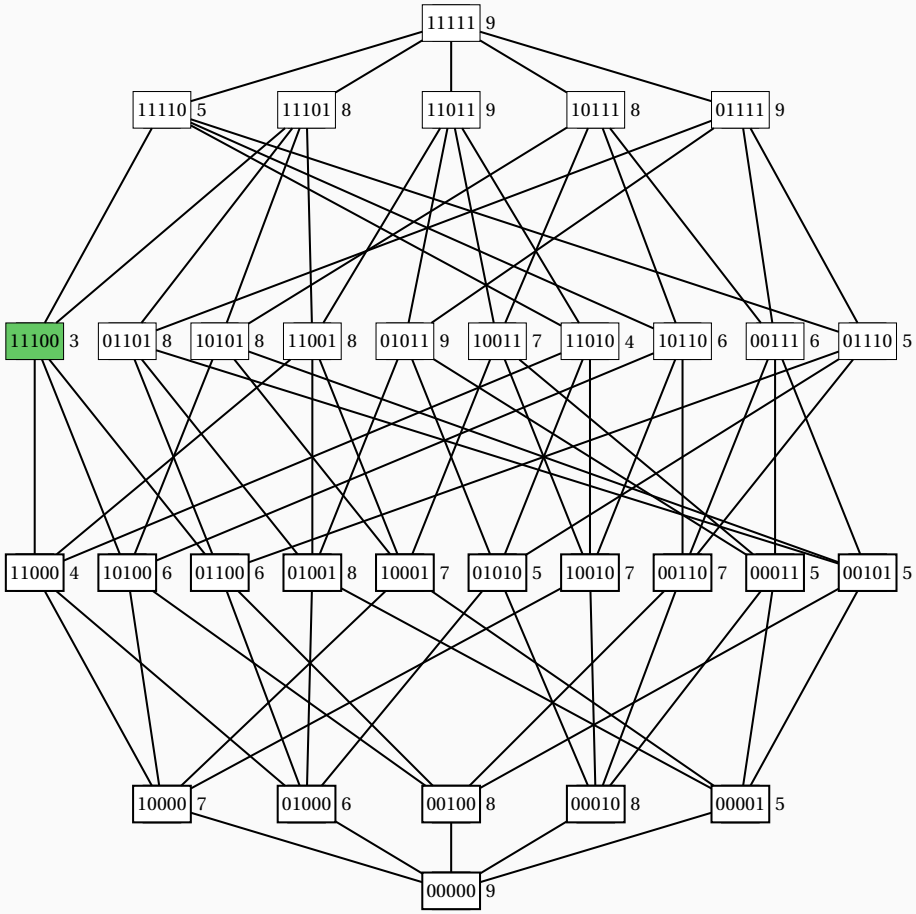

Feature Selection for Identification of Signaling Pathways

The methodology proposed by Wu defines the set of features as a set of chemical reactions that can be added to a starting model.

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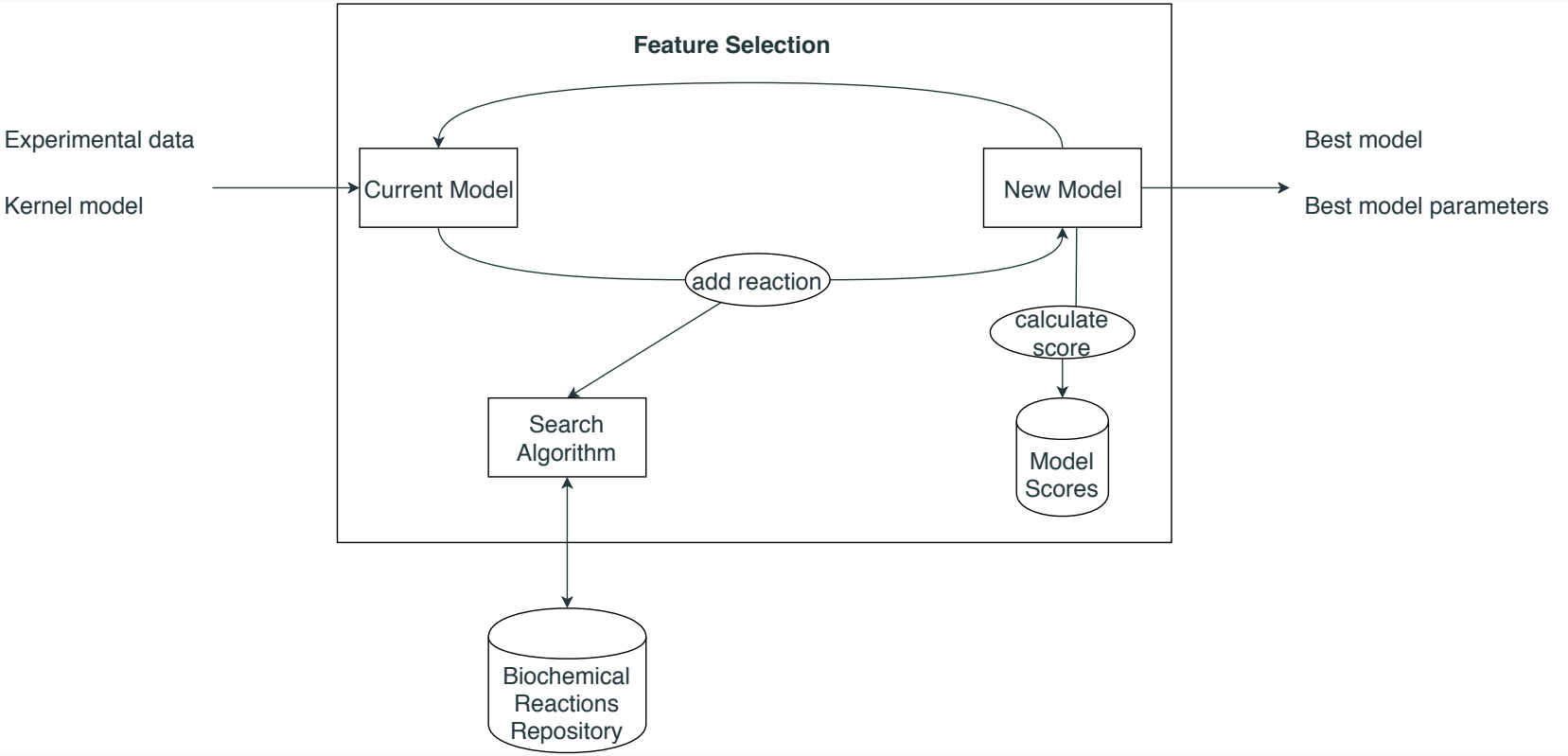
The methodology proposed by Wu defines the set of features as a set of chemical reactions that can be added to a starting model.This set of chemical reactions is fetched from KEGG and stored in a database of interactions.

Dynamic of Cell Signaling Pathways



Results of Wu's Methodology

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

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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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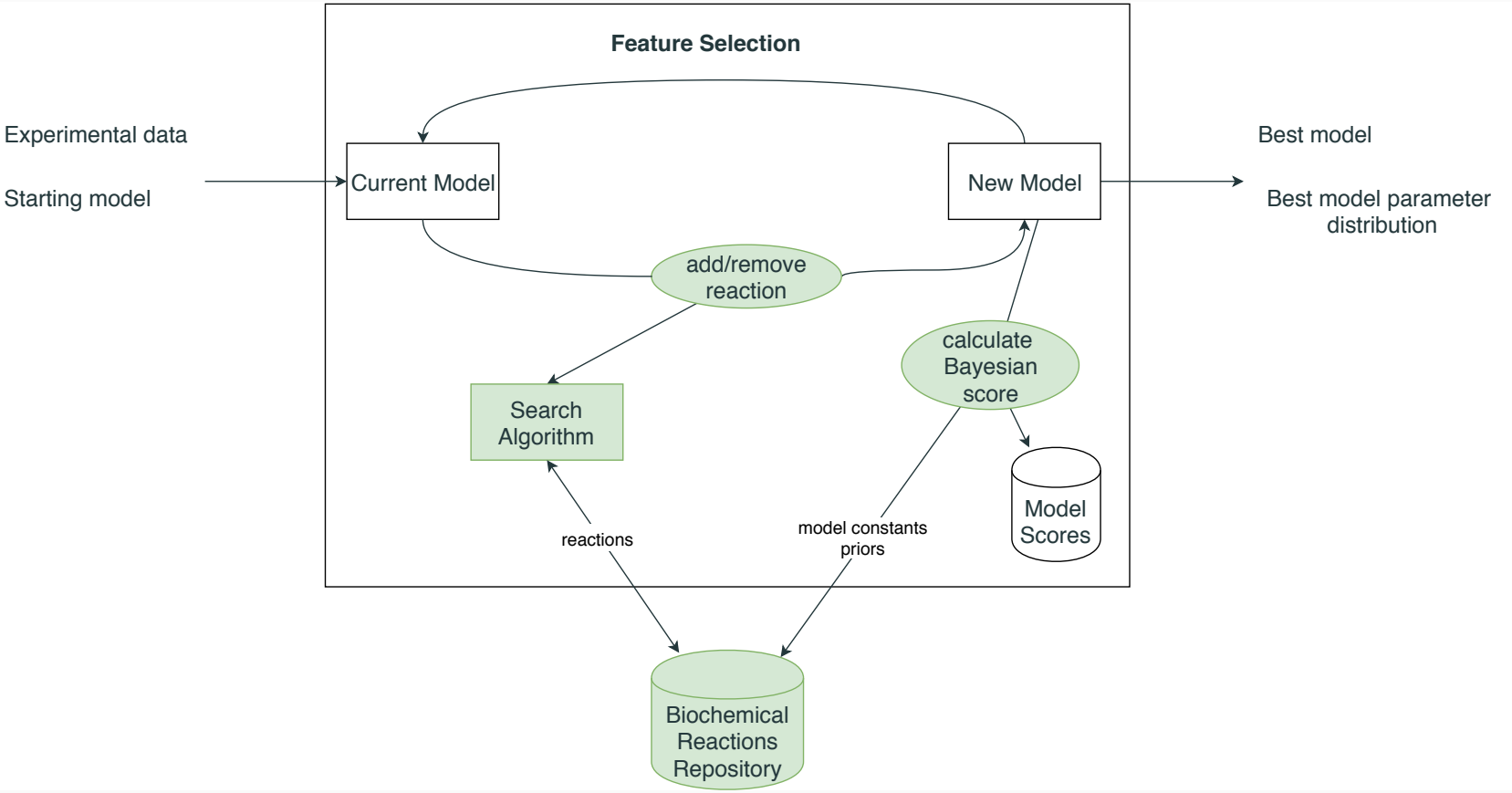

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To use new search algorithms, we intend to use more general algorithms that can also remove interactions.

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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 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

SigNetMS

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

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.

Experiment description

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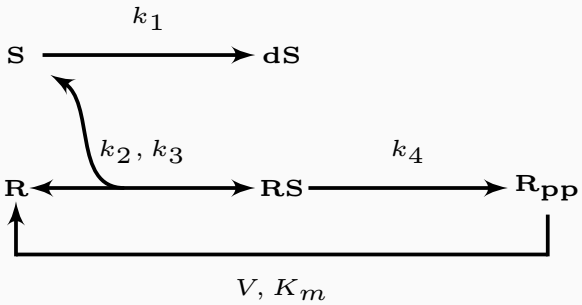
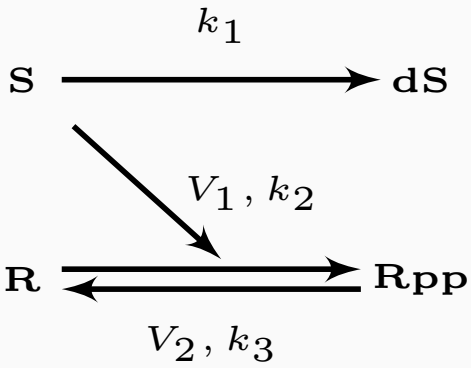
- Rank the four models.

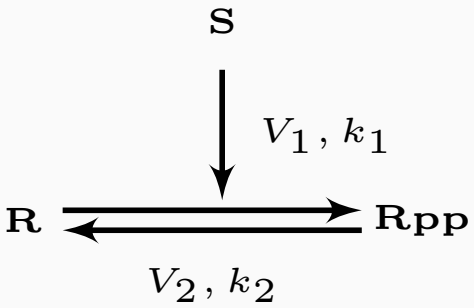
Model Ranking Experiment



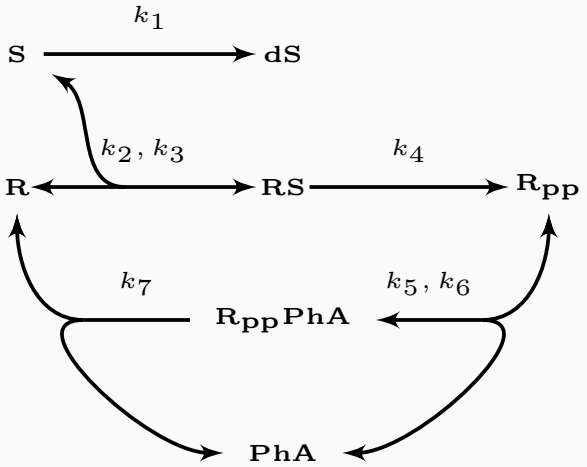
Model 1



Model 2



Model 3



Model 4

Results on SigNetMS

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Note that:

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

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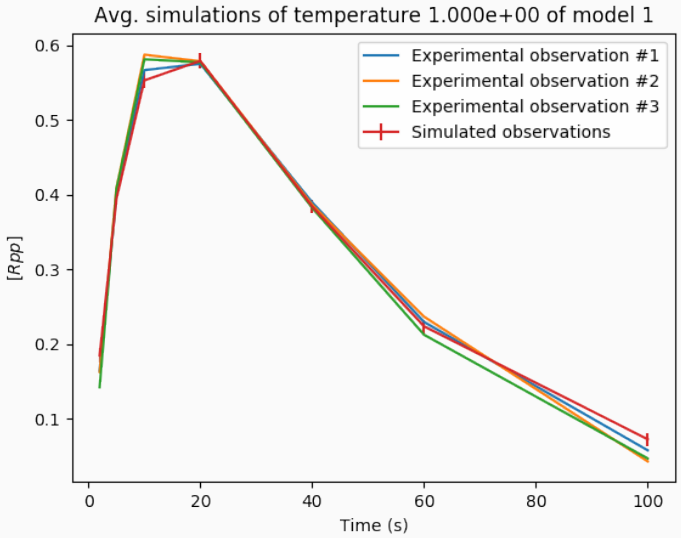

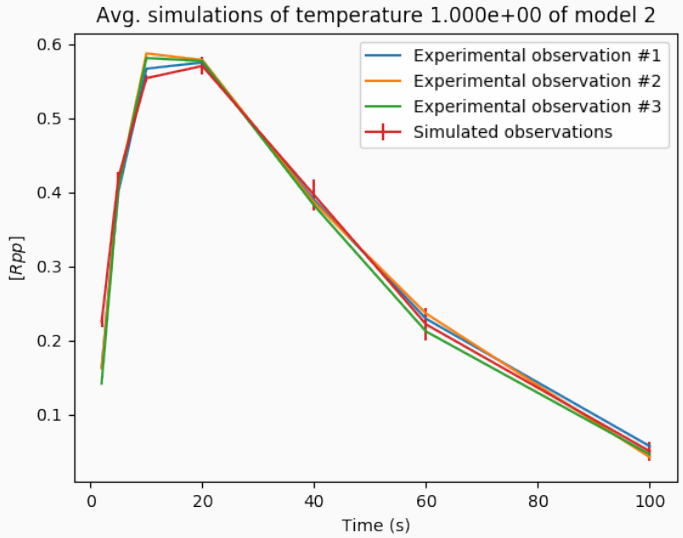

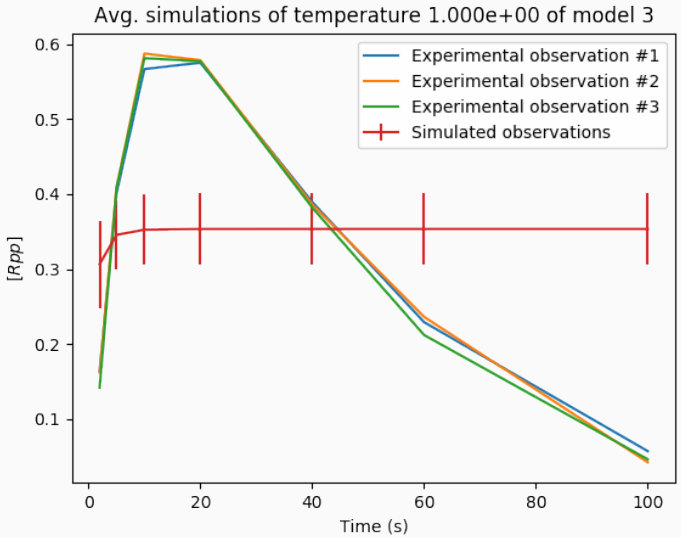

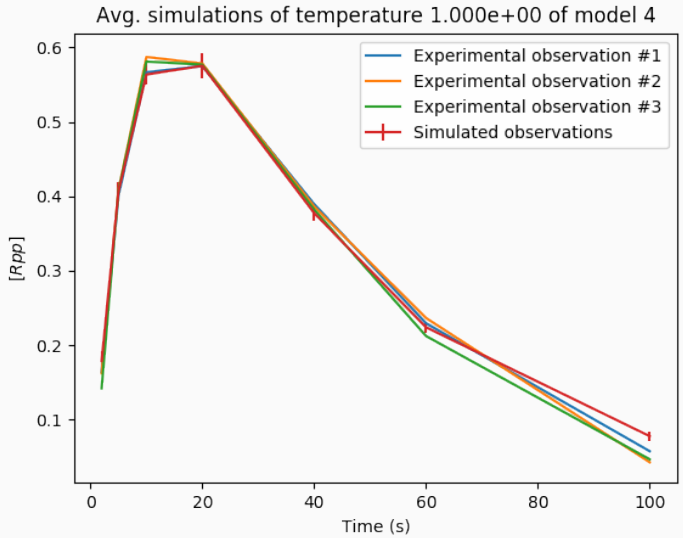

Surface Walk Experiment

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The scores are calculated in respect to experimental data generated by a model that is present in the search space.

Surface Walk Experiment

the starting model

Surface Walk Experiment

the base model

Surface Walk Experiment

gráfico com valores calculados na cadeia percorrida
*provavelmente um comentário sobre a penalização dos modelos, e sobre o fato de que a cadeia percorrida não passa pelo modelo correto, o que fez os custos apenas subissem. *

Future Work

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

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- Embedding SigNetMS as a cost function for featsel, a framework for feature selection.
- Creation of a relational database of chemical interactions focused on our further applications.

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- Choice of a feature selection search algorithm.

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

Thank you!