Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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Introduction

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

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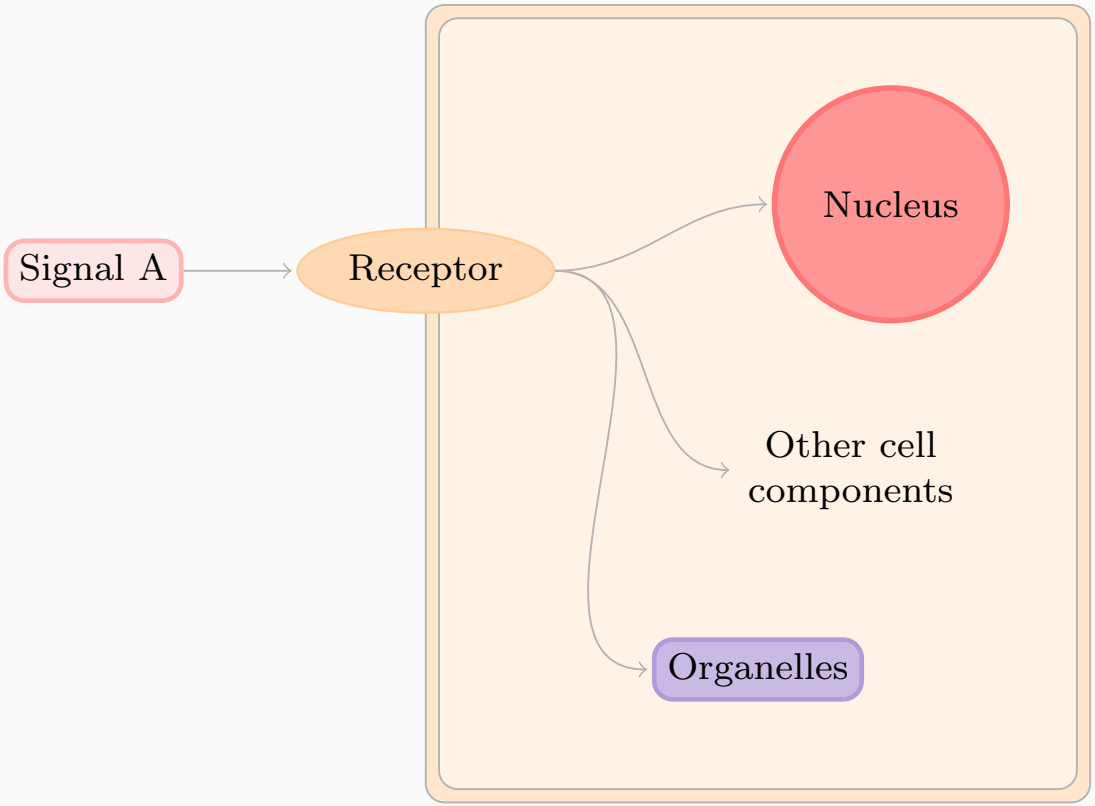

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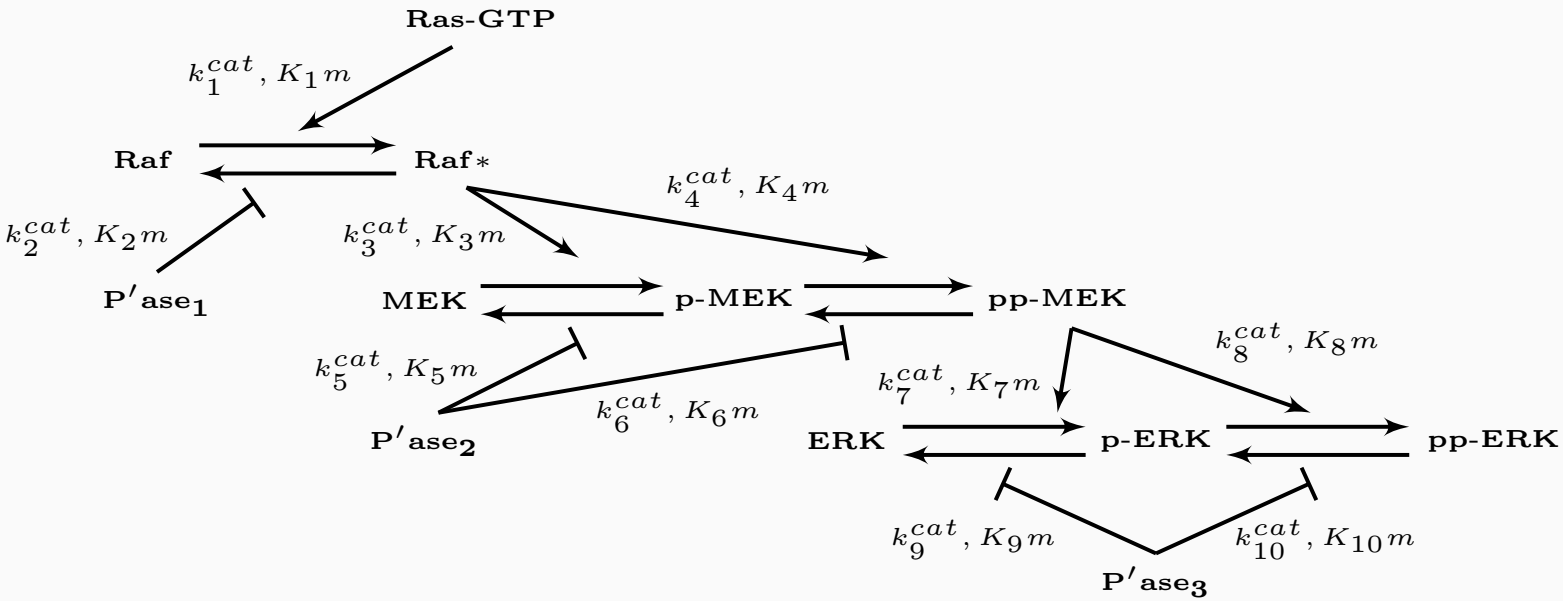
We call the path of a signal a cell signaling pathway.

Cell Signaling Pathways

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



Mathematical Models of Signaling Networks

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Using biochemical kinetics, we can model the concentration change of chemical species over time of a 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.

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.

Results of Wu's Methodology

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Wu's Cost Function for Feature Selection

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The cost function is defined as the minimum distance between experimental and simulated data. To find this distance a Simulated Annealing procedure is used.

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Wu's Cost Function for Feature Selection

Complex models were penalized by setting a limit of iterations on the Simulated Annealing algorithm, inducing an arbitrary penalization.

What we Propose on this Project

We proposed to create a methodology that uses a feature selection approach for identification of signaling pathways, tackling the difficulty of penalizing complex models.

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We used Bayesian approaches of model selection that allow us to create estimates of $p(M|\boldsymbol{D})$ or $p(\boldsymbol{D}|M)$.

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- Formulate systematic modifications to a model as the search space of a feature selection model.
- Observe the surface induced by the cost function over the search space.

Fundamental Concepts

Kinetics Modeling of Chemical Reactions

Mathematical Modeling of Reactions

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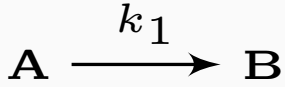
- second order interaction kinetics;
- Michaelis-Menten enzymatic kinetics.

Kinetic Modeling of First Order Iteration

A first order reaction:



Kinetic Modeling of First Order Iteration

A first order reaction:

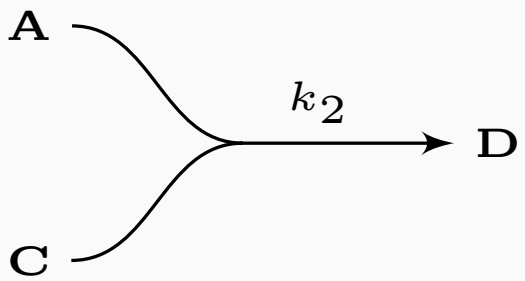
$$\mathbf{A} \xrightarrow{k_1} \mathbf{B}$$

has rate of:

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

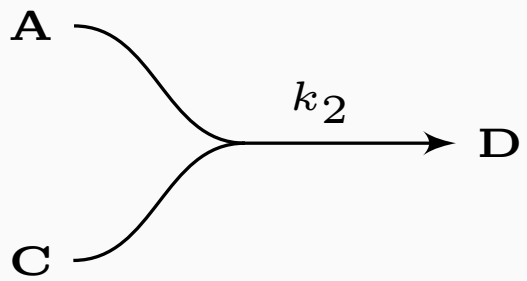
Kinetic Modeling of Second Order Iteration

A second order reaction:



Kinetic Modeling of Second Order Iteration

A second order reaction:



has rate of:

$$k_2[\mathrm{A}][\mathrm{C}].$$

Kinetic Modeling of Enzymatic Reactions

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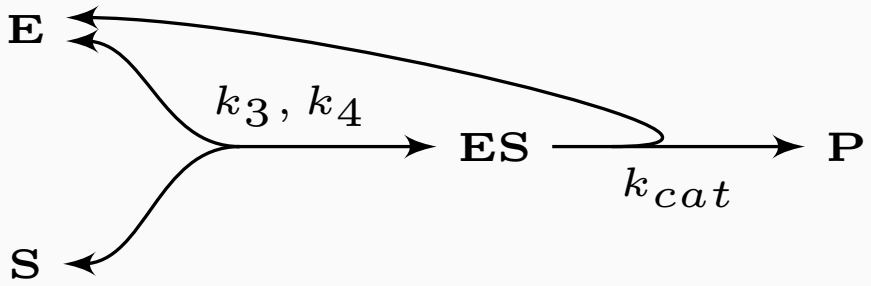

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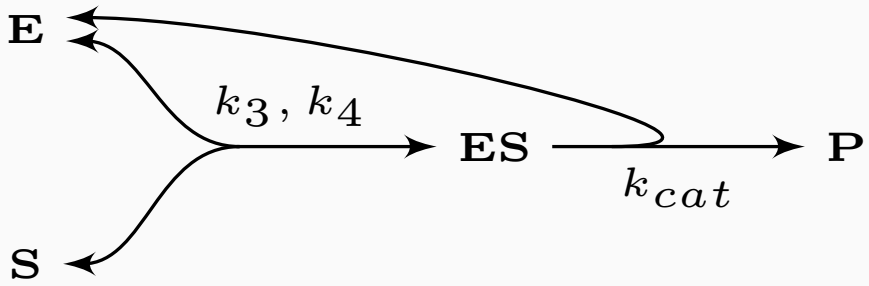

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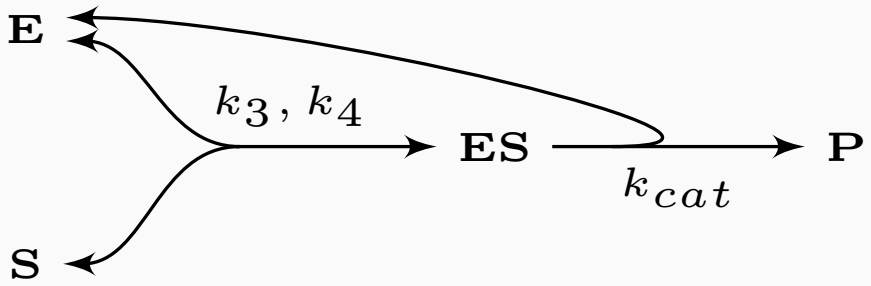
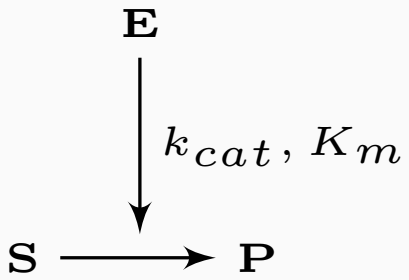


Can be divided in two first order reactions plus a second order reaction. However, with the appropriate assumptions, it is possible to use a Michaelis-Menten simplification of this reaction.

Michaelis-Menten Kinetics

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



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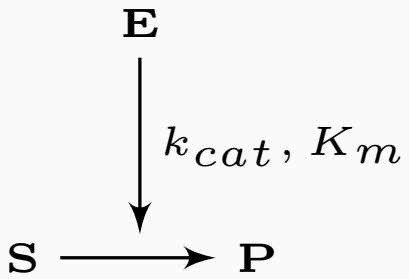
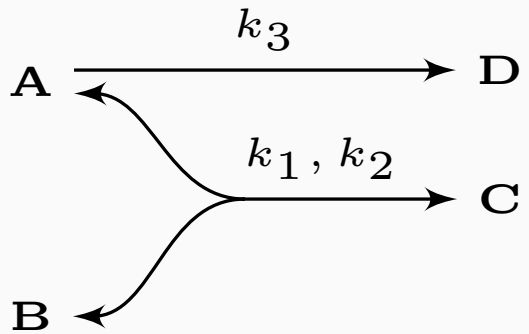


and it has rate of:

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

Kinetics of a System of Reactions

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



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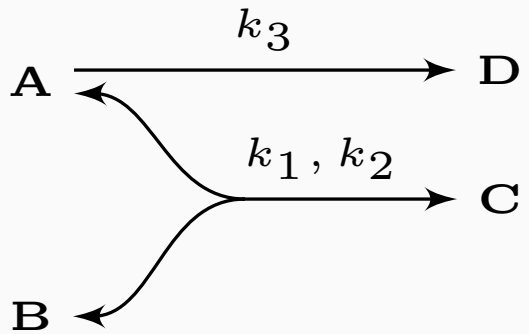

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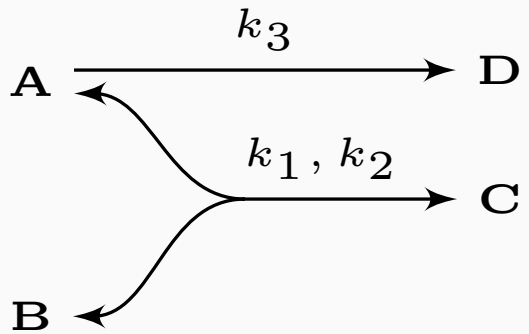

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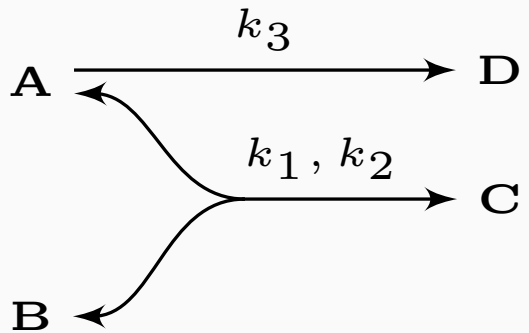

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- $A \longrightarrow D$, with rate $k_3[A]$.

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

Model Selection

Marginal Likelihood Estimation

Likelihood of Data Given Model and Parameters

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Likelihood of Data Given Model and Parameters

If we consider that a model M with parameters $\boldsymbol{\theta}$ correctly represent the signaling pathway and that there is a Gaussian observation error on $\mathbf{D}$. Then, the likelihood of observing experimental data $\mathbf{D}$ is:

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

Where $\phi(M, \boldsymbol{\theta})$ 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:

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

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Note that:

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

The Thermodynamic Integral

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

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

Estimating the Thermodynamic Integral

To produce the estimates of

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

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

Sampling from Power-posteriors

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Sampling from the Power-posteriors

On the second sampling step, called posterior shaped burn-in, we use the covariance of the current sample times some constant as the covariance of the jump distribution.

Sampling from the Power-posteriors

On the third step, we perform the Populational Monte Carlo Markov Chain sampling. This algorithm allows us to mix samples from different power posteriors.

Ranking with Approximate Bayesian Computation

Approximate Bayesian Computation

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4. Repeat until some iteration limit.

Approximate Bayesian Computation

The result of the algorithm is a sample of the distribution

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

ABC Sequential Monte Carlo

ABC Sequential Monte Carlo (`ABC-SMC`) improves a simple ABC algorithm by using a sequence $\epsilon_0 > \ldots > \epsilon_T$ acceptance tolerances.

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

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

Development of SigNetMS

The SigNetMS Software

A software that estimates the marginal likelihood

To choose a cost function, we needed to compare the ABC-SMC and Marginal Likelihood approaches for model selection.

A software that estimates the marginal likelihood

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- `ABC-SysBio` is a software that implements `ABC-SMC`
- `BioBayes` is a software that implements the estimation of the marginal likelihood.

A software that estimates the marginal likelihood

However, the usage of `BioBayes` in our context was cumbersome.

A software that estimates the marginal likelihood

However, the usage of `BioBayes` in our context was cumbersome.
Therefore, we decided to implement SigNetMS.

The SigNetMS software

SigNetMS is a Python package and command line software that estimates the marginal likelihood of data given a model, $p(\boldsymbol{D}|M)$.

The input expected by SigNetMS

The input to SigNetMS includes:

- An SBML file model;
- An XML file with prior distributions of parameters;
- An XML file with experimental data;

The output produced by SigNetMS

SigNetMS produces an estimate of the marginal likelihood, as you may have suspected.

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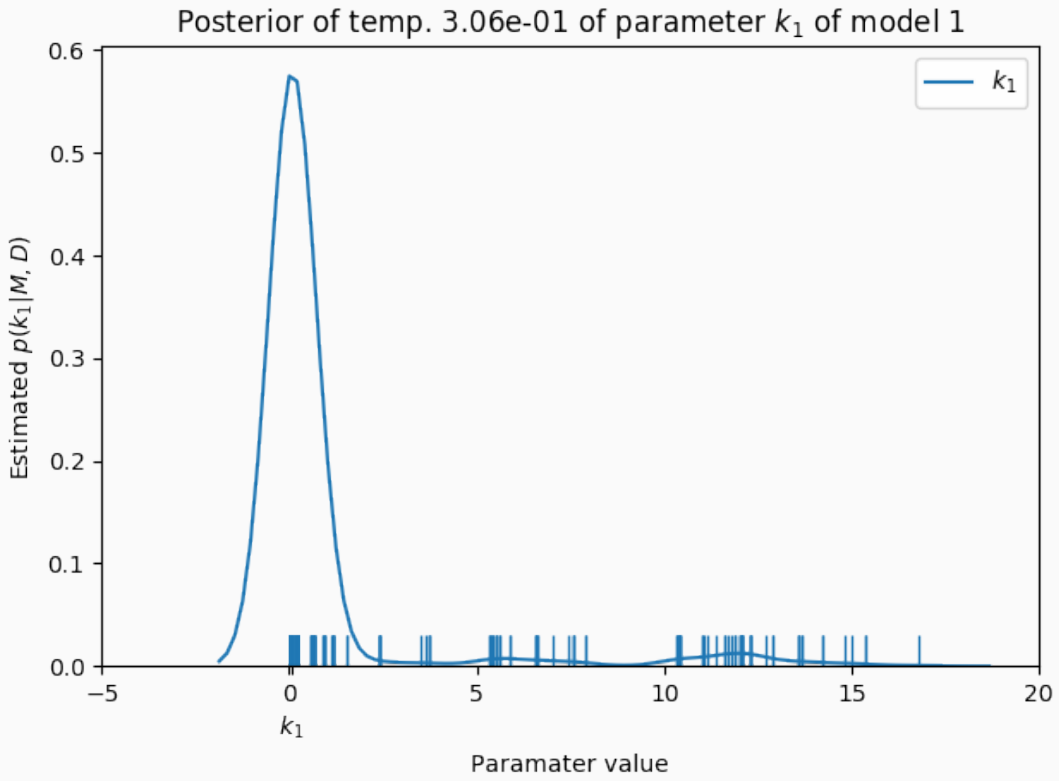

Fast integration and parameter sampling

Problems with efficiency

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The first implementation of SigNetMS did not cope with larger instances of model selection.

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The first implementation of SigNetMS did not cope with larger instances of model selection. We tackled this problem in two ways:

- change the representation of the system of ordinary differential equations;
- implement parallelization.

Changing the representation of the system of ordinary differential equations

In the first implementation of SigNetMS, systems of EDOs were represented as an array of strings.

Changing the representation of the system of ordinary differential equations

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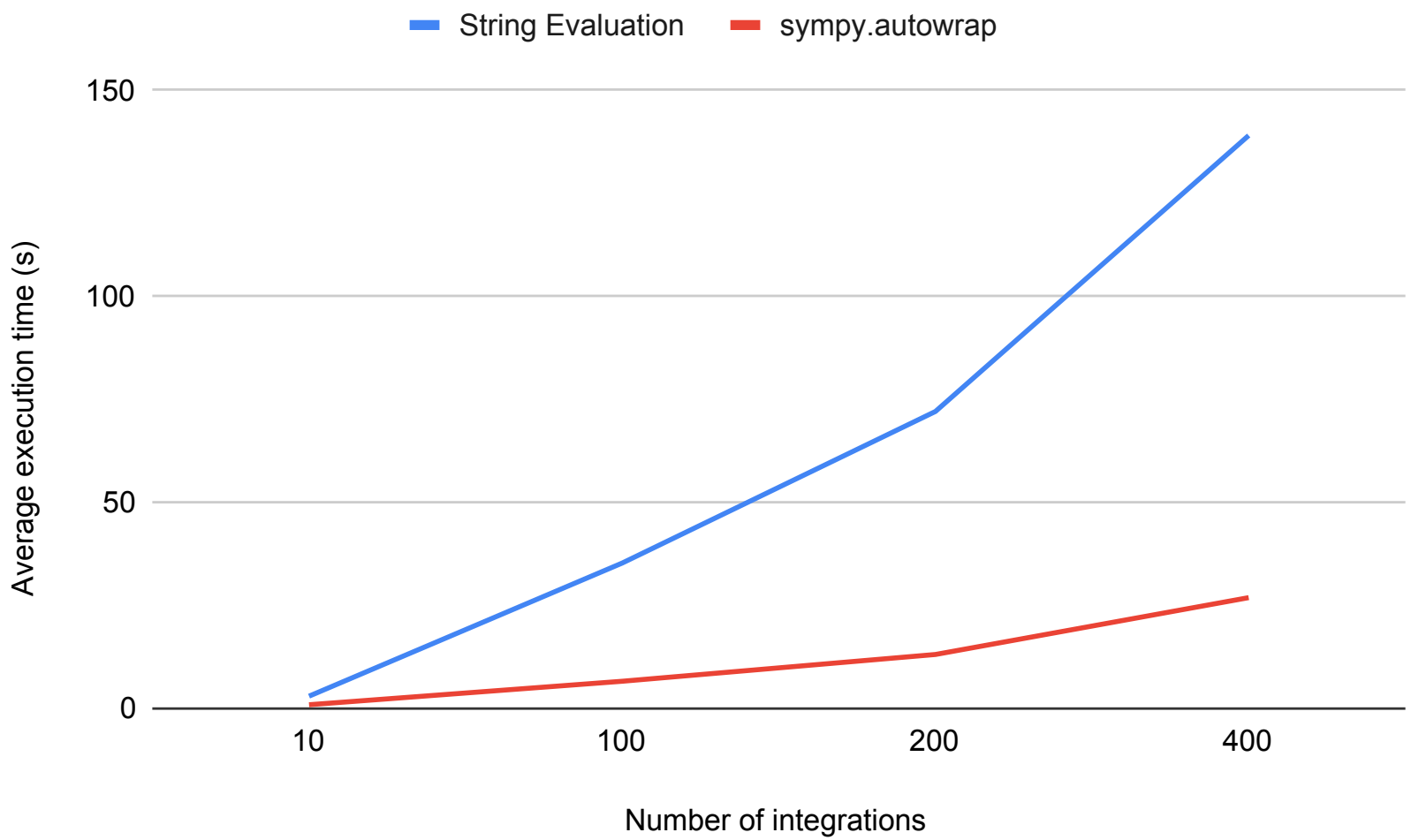
We used SymPy to provide automatically generated code that allowed us to create a C function to represent the system of ODEs.

Comparing the representation of the system of ordinary differential equations



Parallelizing the sampling of multiple power posteriors

The first two phases of the sampling procedure occurs independently between different power posteriors.

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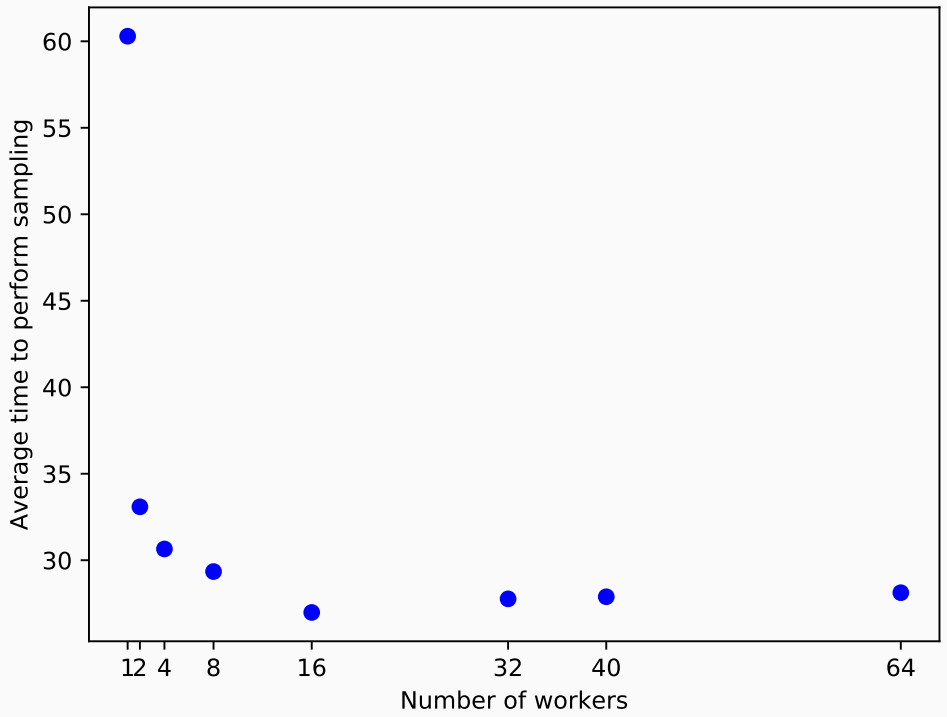

Experiments and Results

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We prepared two experiments in this work:

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- Comparison between ABC-SysBio and SigNetMS
- Solving model selection as a feature selection instance

Comparison between ABC-SySBio and SigNetMS

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ABC-SysBio and SigNetMS use different Bayesian approaches for model selection. The first creates an estimate of $p(M|\boldsymbol{D})$, and the second creates an estimate of $p(\boldsymbol{D}|M)$ (the marginal likelihood).

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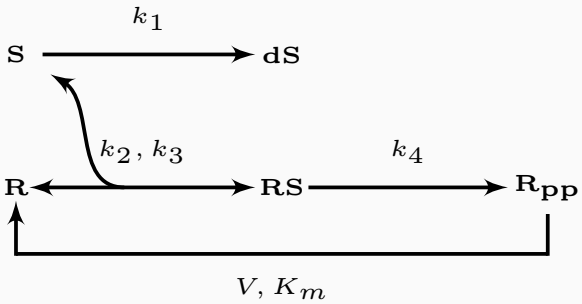
- Neglect chosen parameter values and define prior distributions for every parameter.
- Rank the four models.

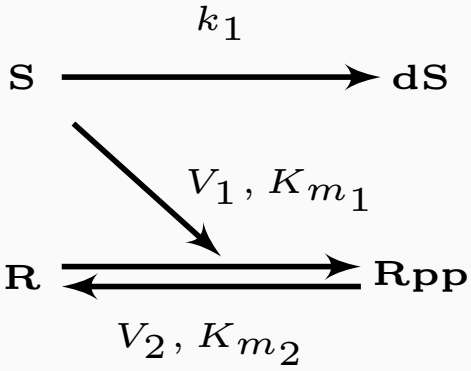
The instance

This instance is originally from Vyshemirsky and Girolami (2007), in which they present results of Annealing Melting Integration.

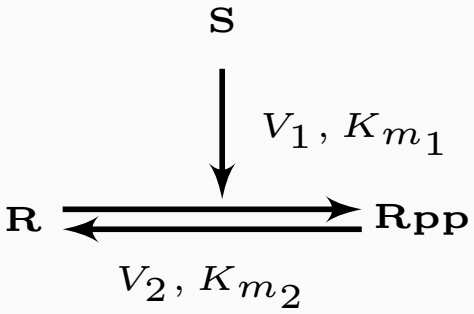
The instance



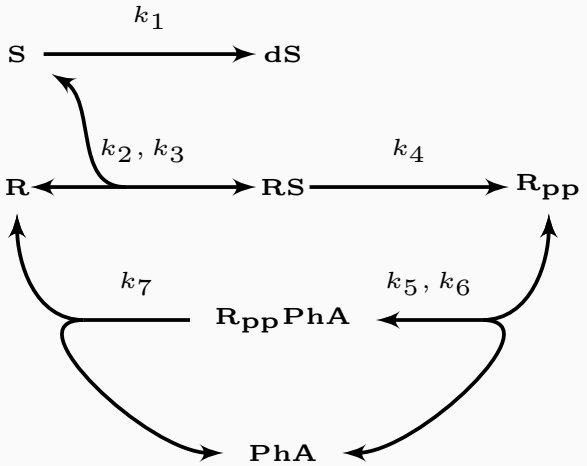
The "correct" model



The simplification model

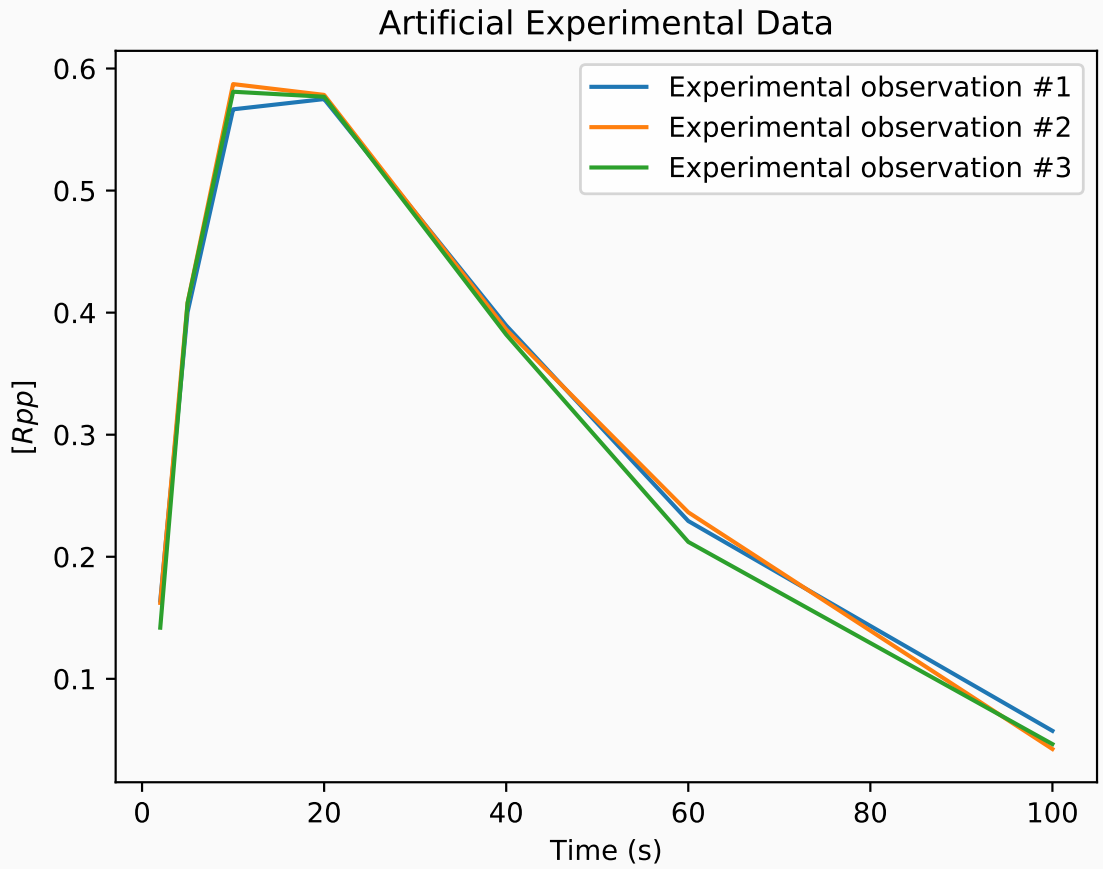


The incorrect model



The generalization model

The instance



Results on ABC-SysBio

The ABC-SysBio software returned the following ranking of models:

Results on ABC-SysBio

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1. incorrect model

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The ABC-SysBio software returned the following ranking of models:

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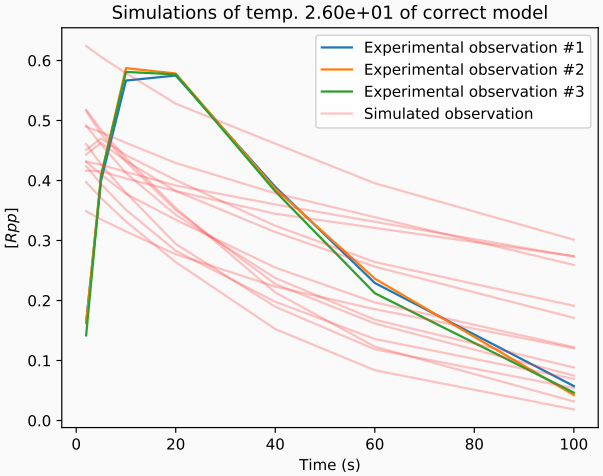
Results on ABC-SysBio

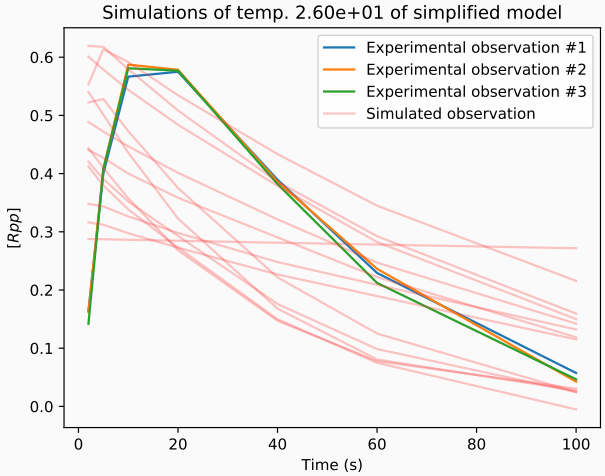
The ABC-SysBio software returned the following ranking of models:

1. incorrect model
2. simplification model
3. generalization model
4. correct model

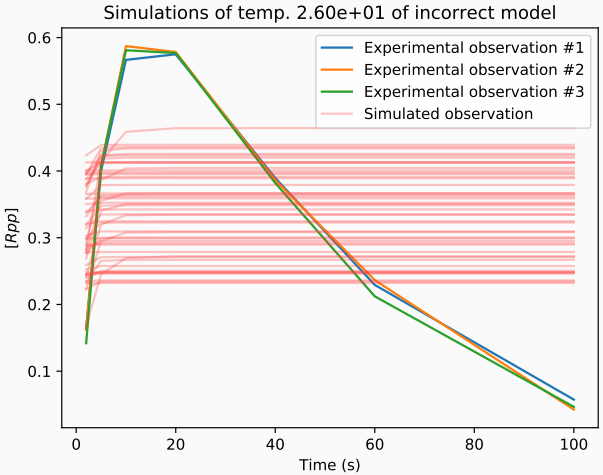
Results on ABC-SysBio



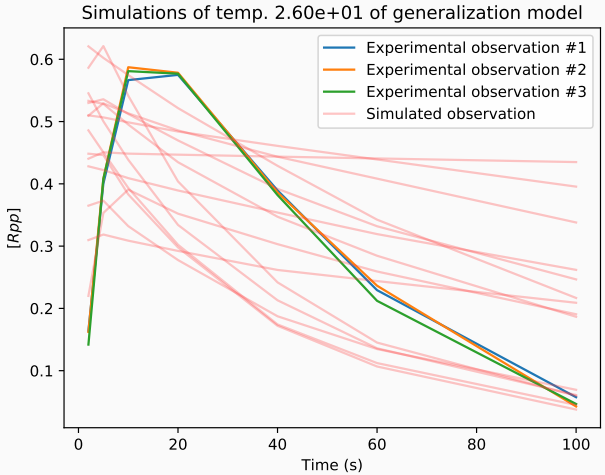
correct model



simplified model



incorrect model



generalization model

Results on SigNetMS

The ranking returned by SigNetMS on the first experiment is:

1. correct model

Results on SigNetMS

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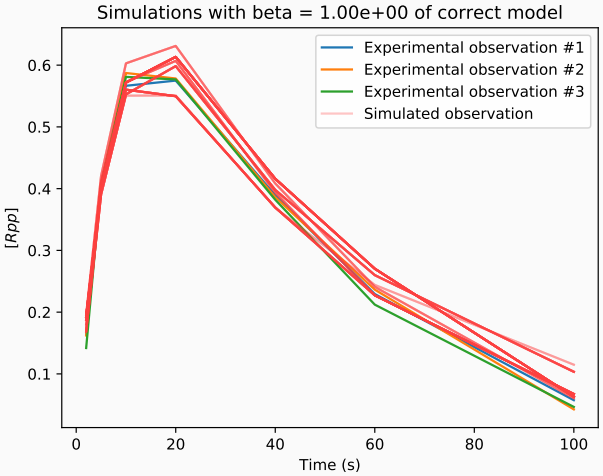
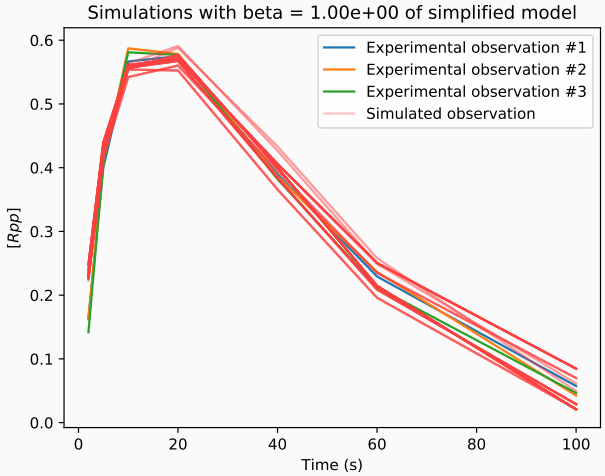
Results on SigNetMS



correct model



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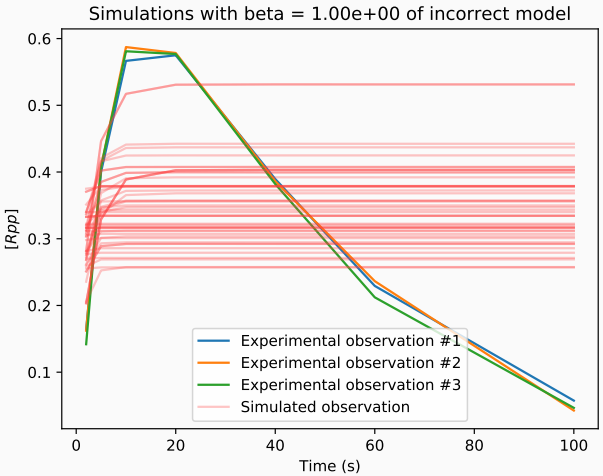
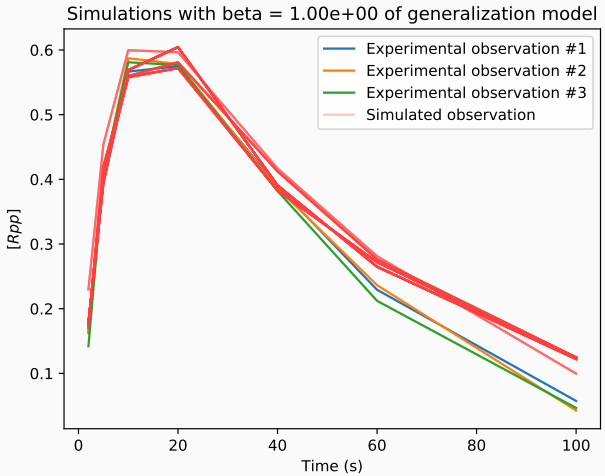


incorrect model



generalization model

Simulations generated by the correct model

Model selection as a feature selection problem

Model selection as a feature selection problem

After defining that SigNetMS is our software choice for a cost function, we are able to experiment the approach of solving a model selection instance as a feature selection problem.

The model selection instance

We proposed a Ras switch pathway to experiment on.

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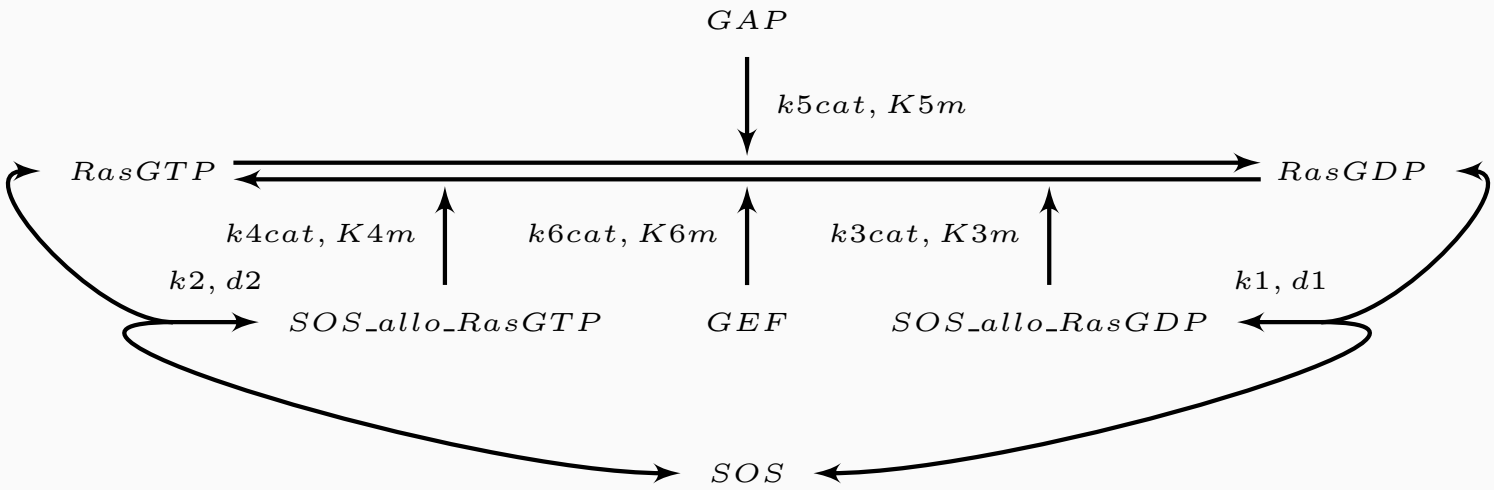

The model selection instance

The concentration of activated Ras was measured at the time steps of 30, 60, 90, 120, 150, 180, 210, and 240 seconds.

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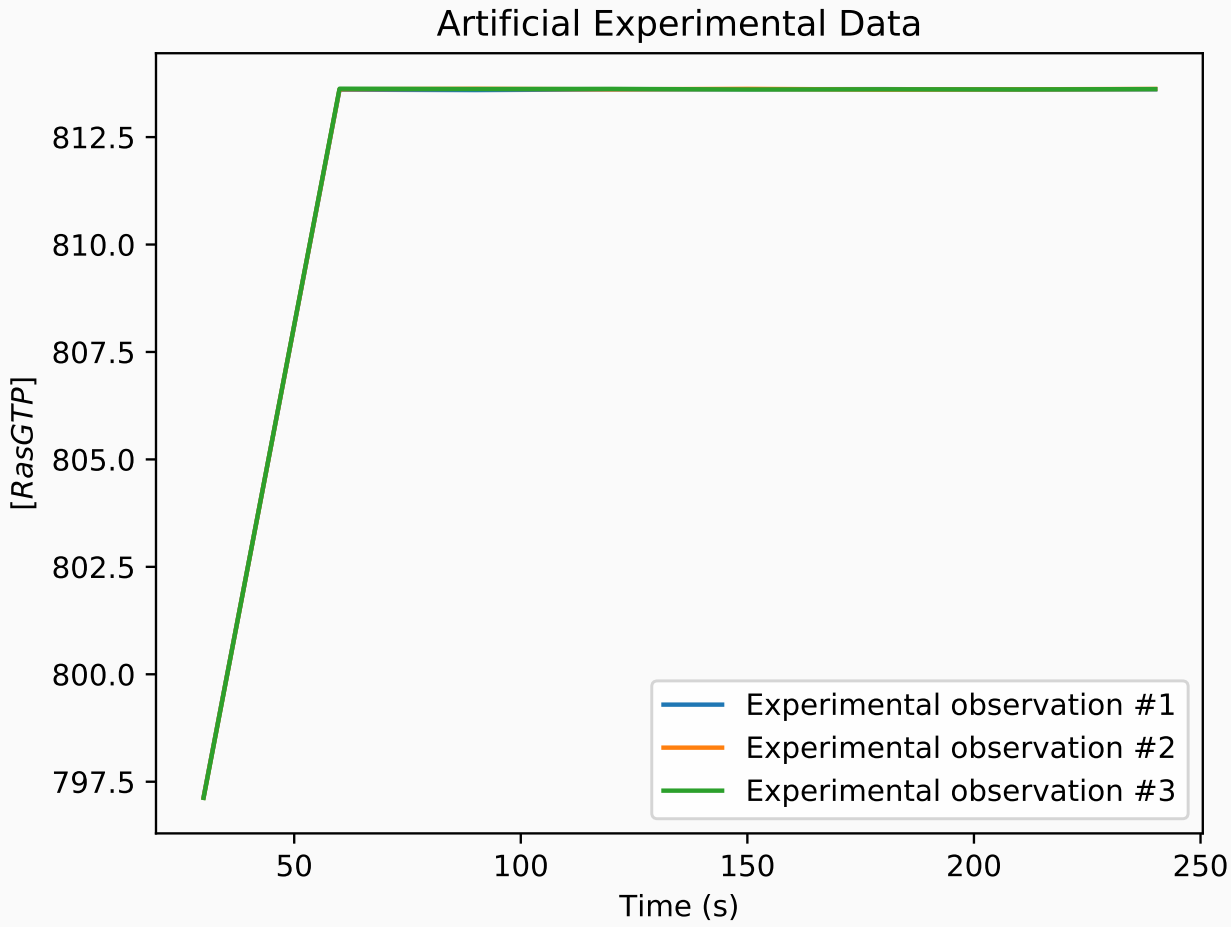

Model selection as a feature selection problem

The feature selection problem consists in finding the best subset of a set of features, S, given a cost function c.

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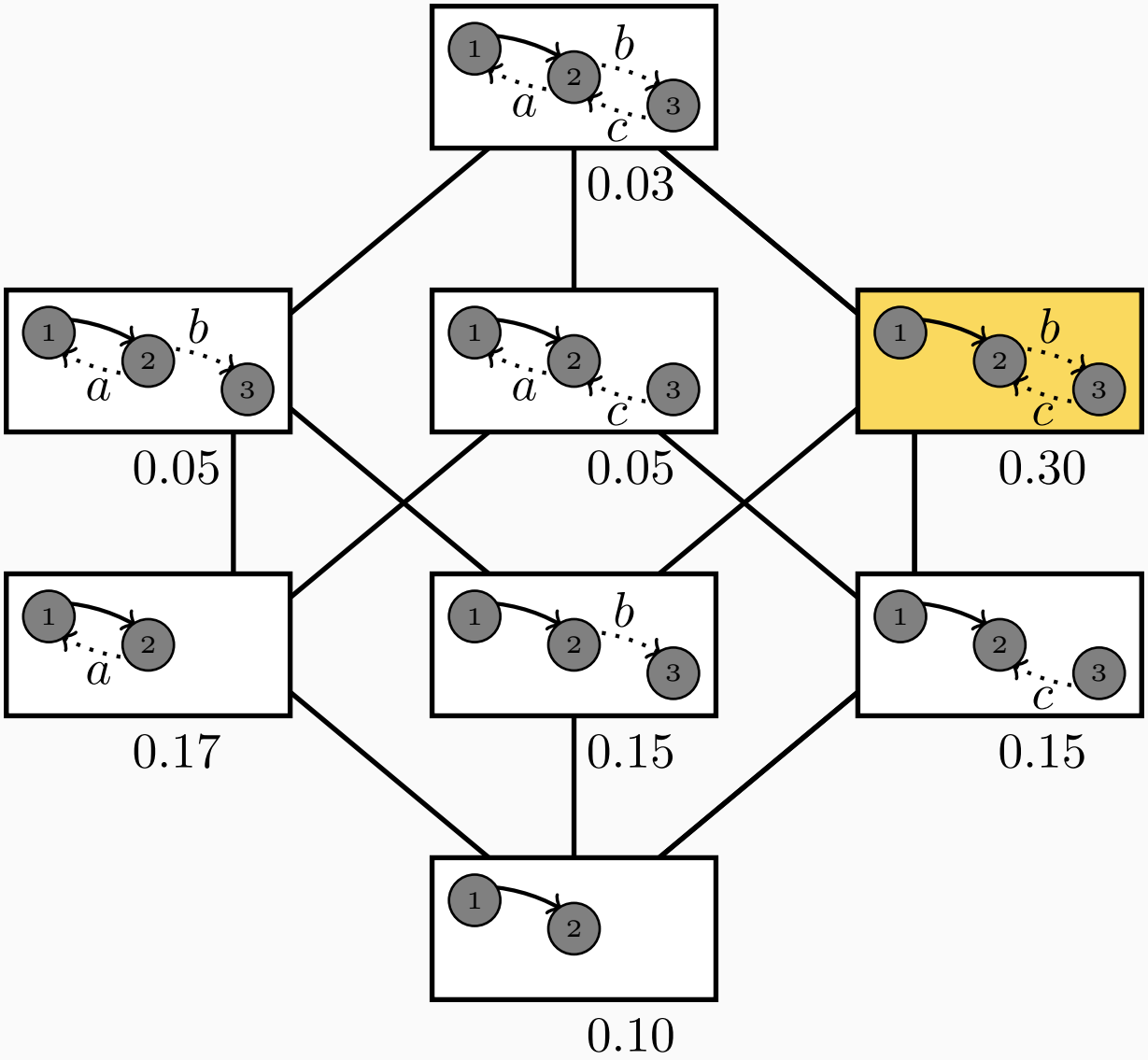
If we define the set of feature as a set of reactions, we can create a feature selection instance that represents a model selection instance.

Model selection as a feature selection problem



The set of features of our experiment

In the instance we prepared, the base model has zero reactions,

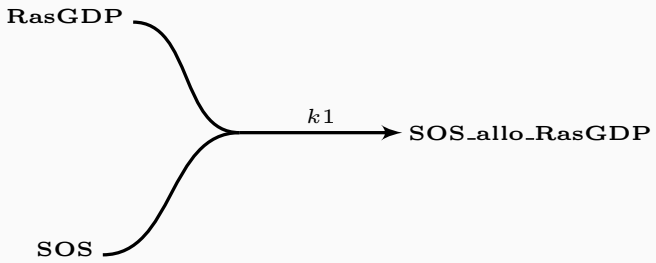
The set of features of our experiment

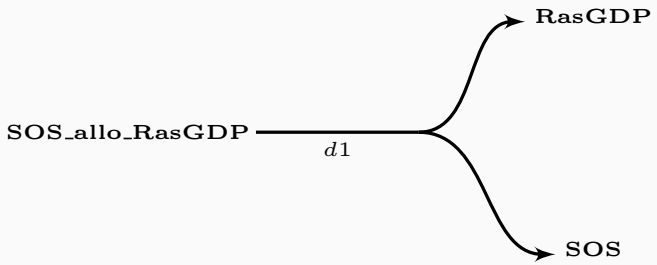
In the instance we prepared, the base model has zero reactions, and the set of features S is composed by 10 reactions,

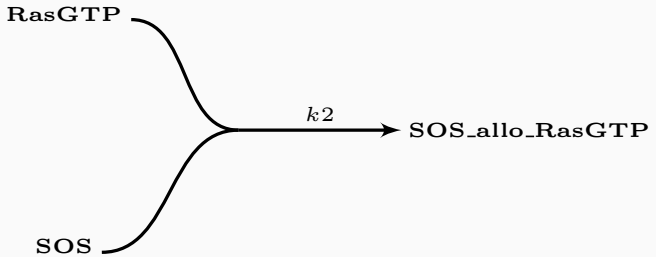
The set of features of our experiment

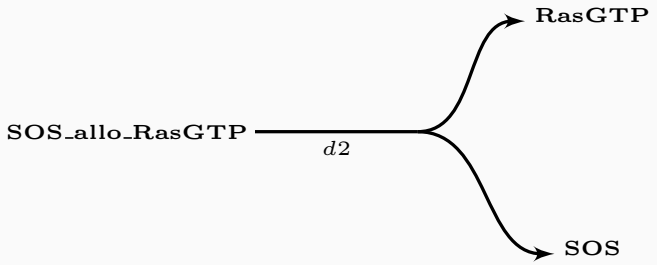
In the instance we prepared, the base model has zero reactions, and the set of features S is composed by 10 reactions, 8 of them present on the correct model.

The set of features of our experiment









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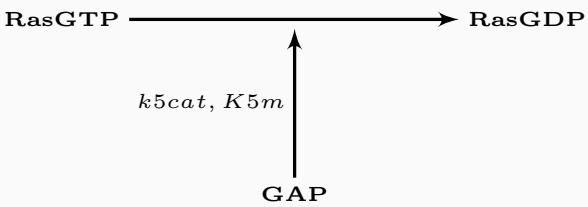

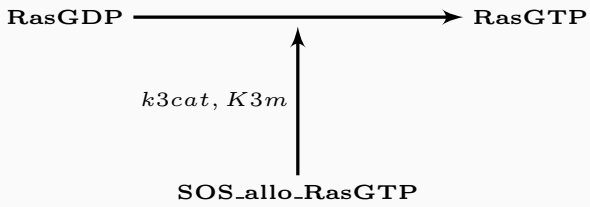

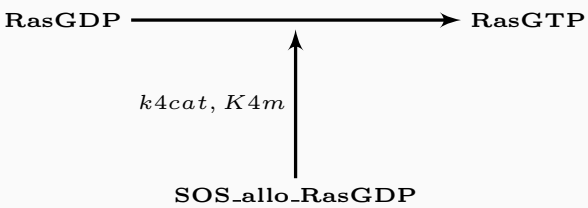

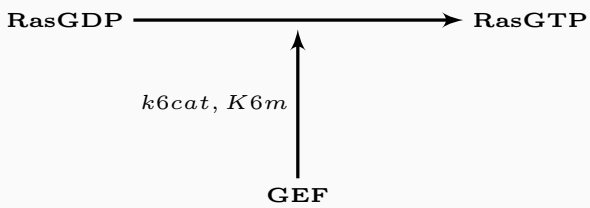

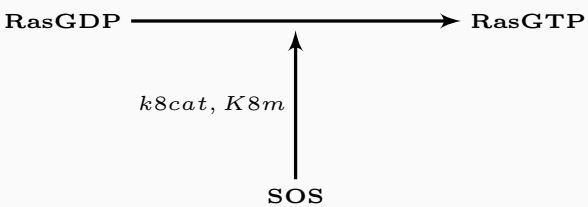

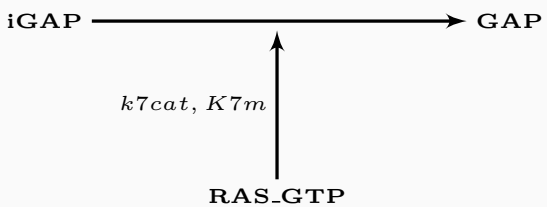

Finding a solution

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Finding a solution

In the SFS procedure, we start from the bottom of the search space. And for every iteration, we select the best adjacent model that has one more reaction.

Results of the search

Characteristic Vector	Score	Cost function time (seconds)
0000000000	330721.05	851.3
0010000000	245681.93	1083.4
0010010000	211.62	4257.4
0011010000	-1.32	5007.71
0011011000	-4.27	4458.7
0111011000	-7.90	5035.7

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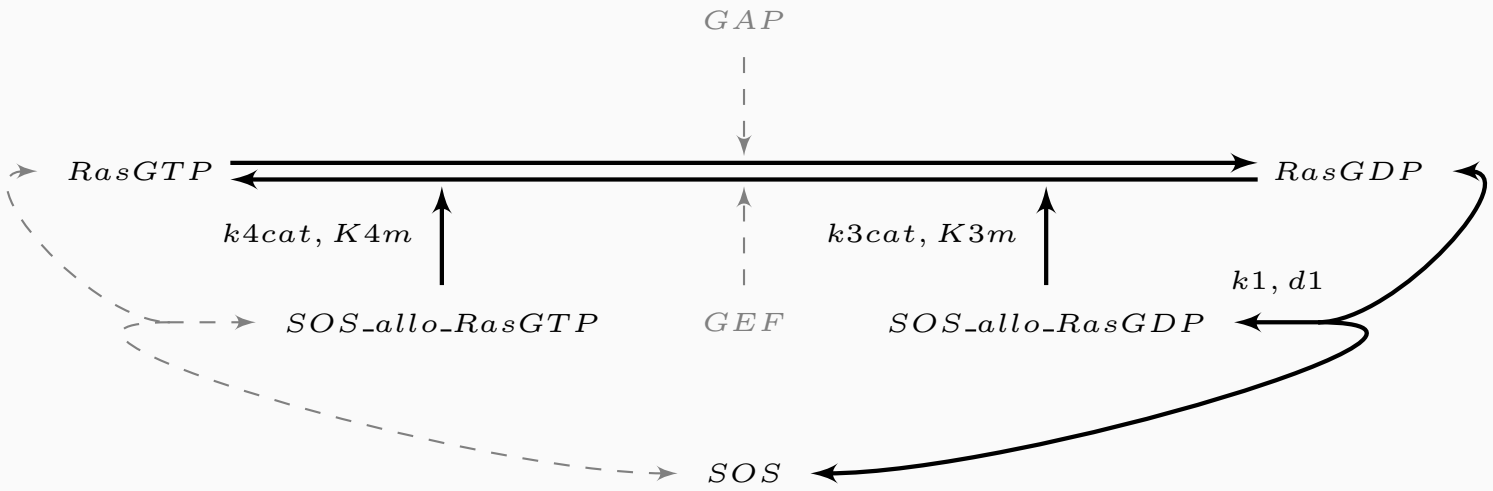

Results of the search

Simulations generated by the found model

Results of the search

Simulations generated by the correct model

Results of the search

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Results of the search

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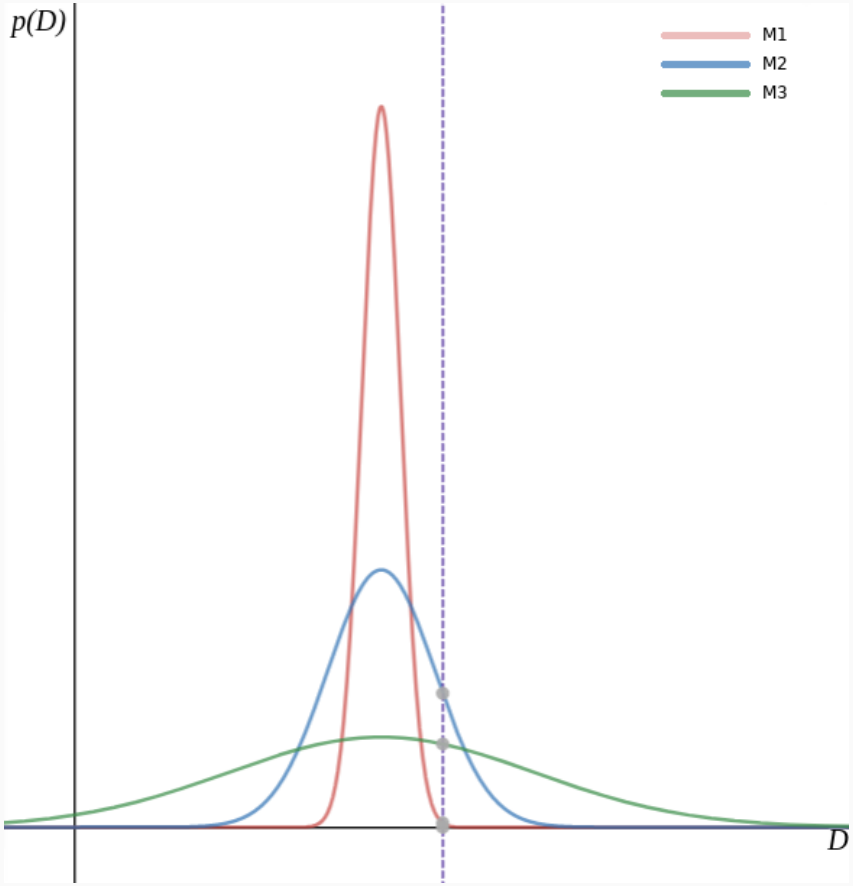

Conclusions

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- the implementation of the SigNetMS software;
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Suggestions for future work

We also suggest a few topics for future related work:

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- efficiency improvements on SigNetMS;
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- solving the model selection problem as a U-Curve problem;
- experimentation on heterogeneous conditions of experimental measurements;
- application of the methodology on real instances.

Thank you!