# Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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May 2019

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This project receives funding from FAPESP

# Introduction

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

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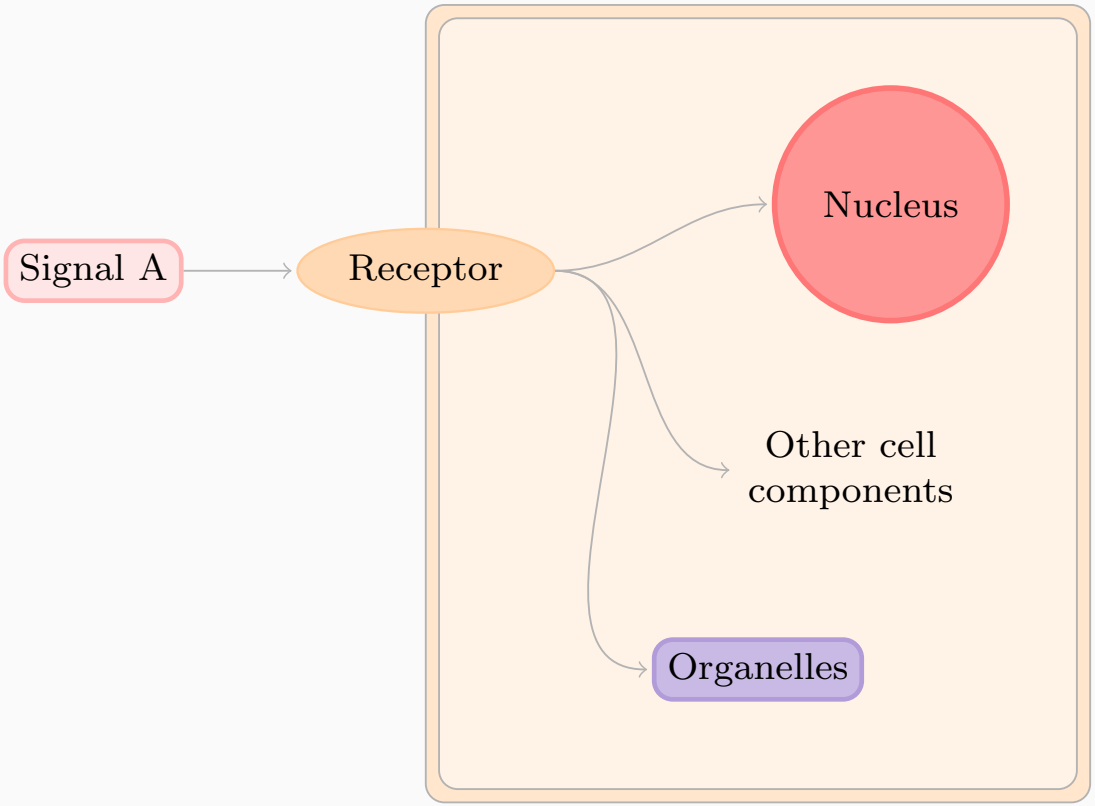

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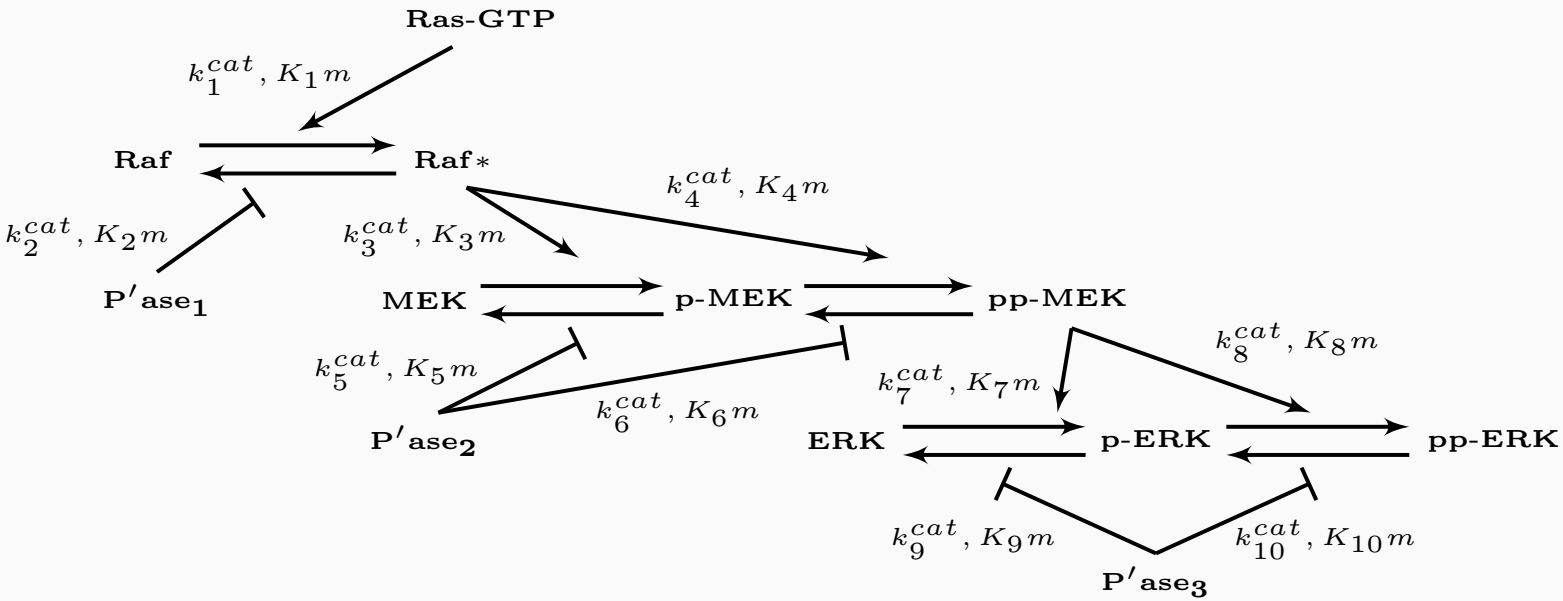
We call the path of a signal a cell signaling pathway.

# Cell Signaling Pathways

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



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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

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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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- 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 difficulty of penalizing complex models.

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We intend to use Bayesian approaches of model selection that allow us to create estimates of $p(M|D)$ or $p(D|M)$.

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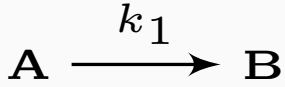
- second order interaction kinetics;
- Michaelis-Menten enzymatic kinetics.

# Kinetic Modeling of First Order Iteration

A first order reaction:



# Kinetic Modeling of First Order Iteration

A first order reaction:

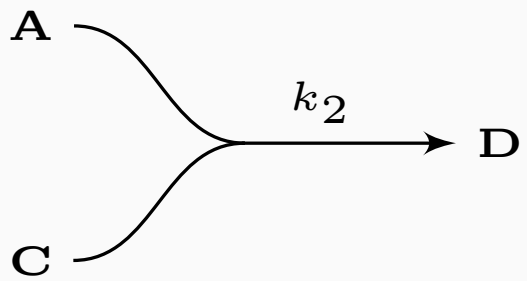
$$\mathbf{A} \xrightarrow{k_1} \mathbf{B}$$

has rate of:

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

# Kinetic Modeling of Second Order Iteration

A second order reaction:



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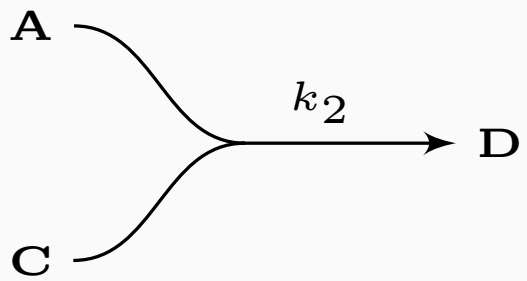


has rate of:

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

# Kinetic Modeling of Enzymatic Reactions

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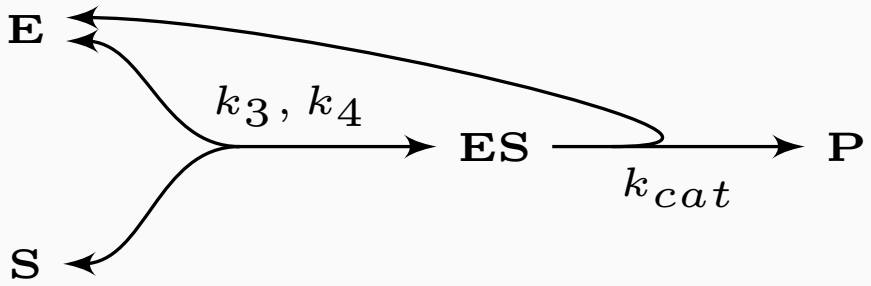

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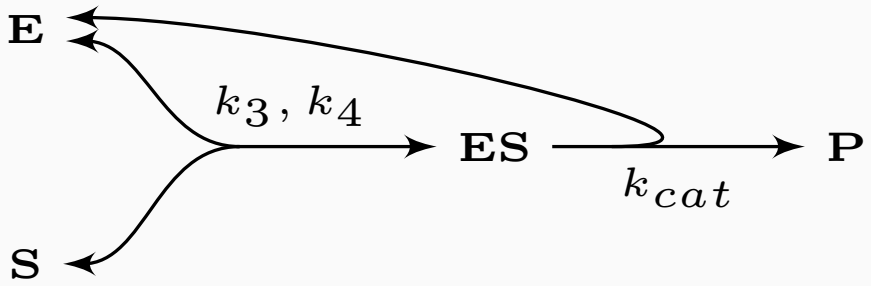


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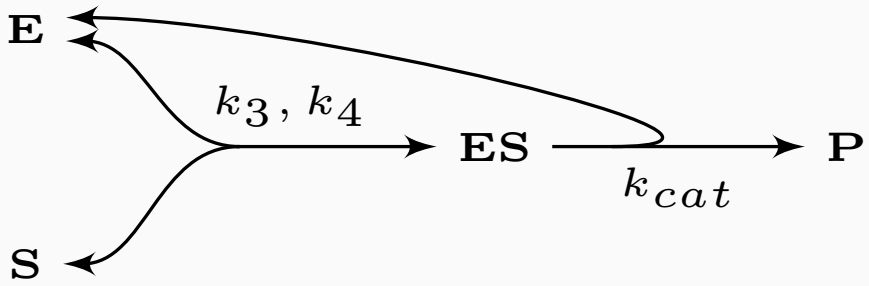
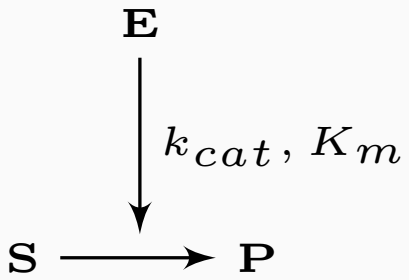



Can be divided in two first order reactions plus a second order reaction. However, with the appropriate assumptions, it is possible to use a Michaelis-Menten simplification of this reaction.

# Michaelis-Menten Kinetics

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



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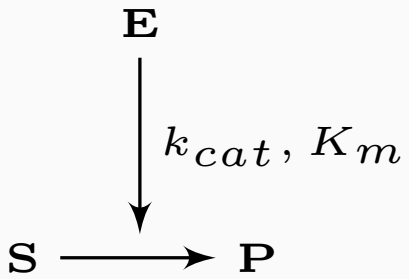
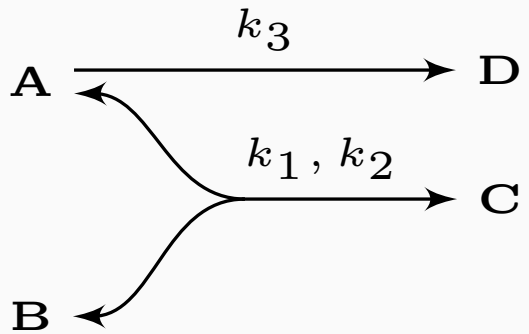



and it has rate of:

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

# Kinetics of a System of Reactions

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

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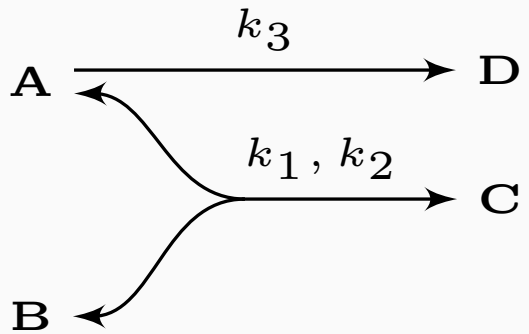


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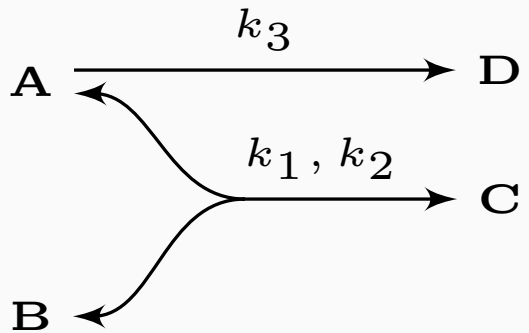


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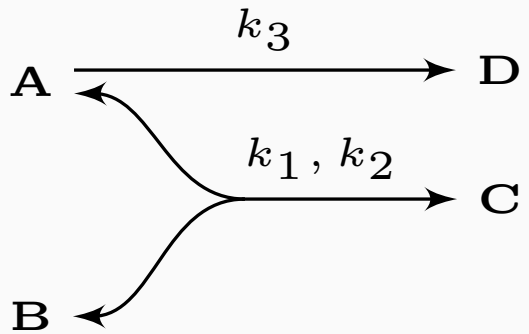


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- $A \longrightarrow D$, with rate $k_3[A]$.

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

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

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

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

# 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 $p_{\beta_t}(\boldsymbol{\theta})$.

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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

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# Approximate Bayesian Computation

Approximate Bayesian Computation (ABC) is a method that allows one to obtain samples of a distribution close to $p(\boldsymbol{\theta}, M|\boldsymbol{D})$. A general ABC implementation works as follow:

1. Sample a parameter candidate $(\theta^*, M^*)$ from some proposal distribution.
2. Generate simulations $\phi(M^*, \theta^*) = D^*$.
3. Calculate $d(D^*, D)$. If $d(D^*, D) < \epsilon$ for some previously specified $\epsilon$, then add $(\theta^*, M^*)$ to the sample.
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 $\epsilon$ and model $M$ to estimate

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

# 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

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

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

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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 a model given experimental data.

# 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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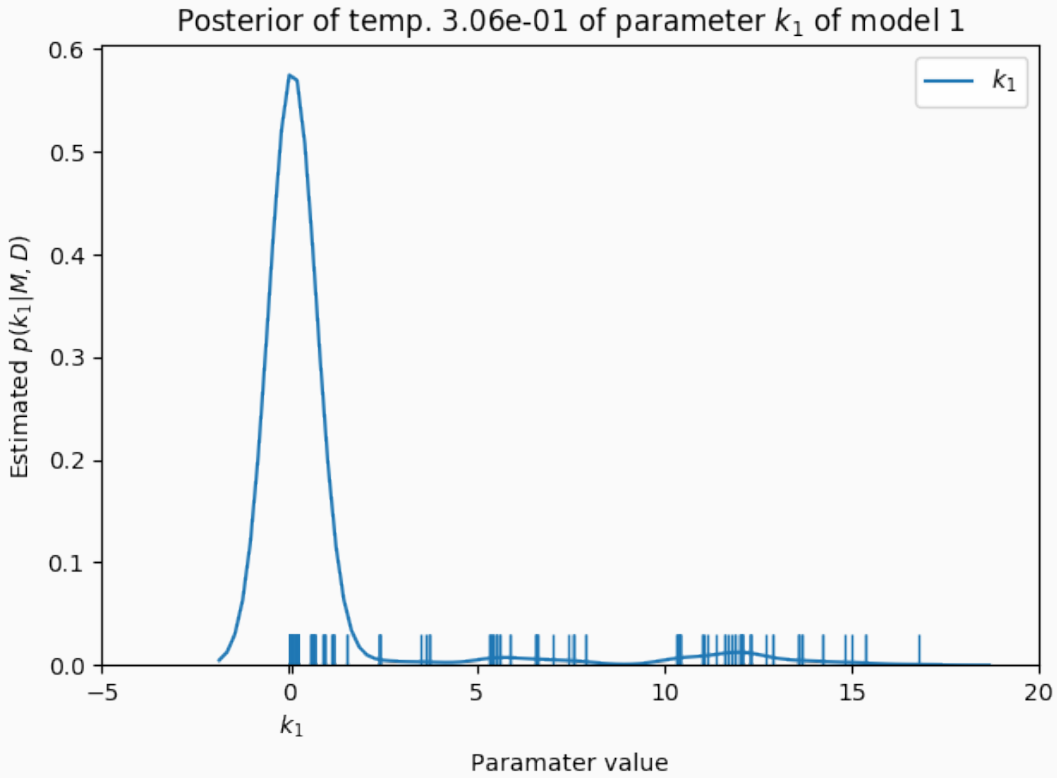

# Fast integration and parameter sampling

# Problems with efficiency

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For each step we need to evaluate the likelihood function, and numerically integrate the system. That makes sampling the most time consuming procedure of SigNetMS.

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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

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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

| Number of Integrations | Average time (seconds) to perform a sequence of integrations | |
|---|---|---|
| | String Evaluation | `sympy.autowrap` |
| 10 | 2.98 | 0.9 |
| 100 | 35.3 | 6.6 |
| 200 | 72.1 | 13.1 |
| 400 | 139.1 | 26.9 |

# 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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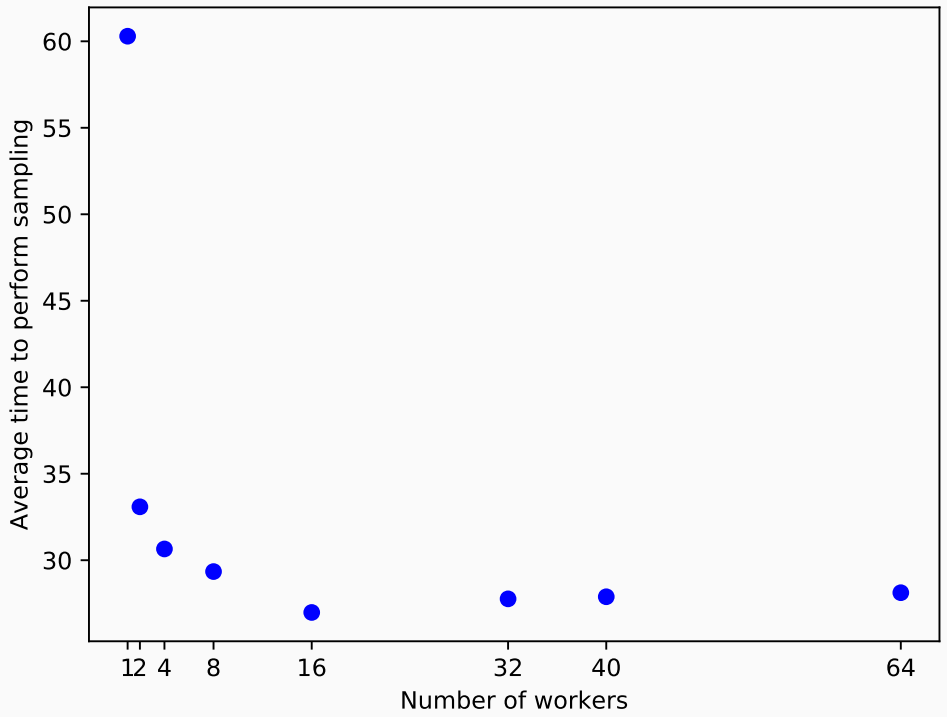

# Experiments and Results

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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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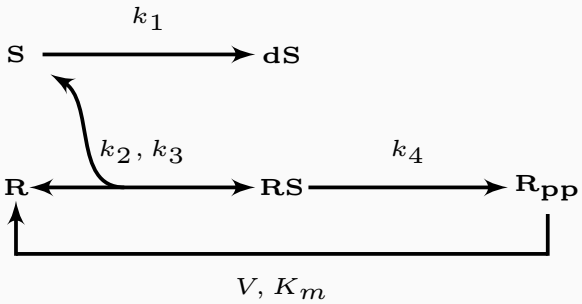
- Rank the four models.

In this presentation we show results of the first experiment only.

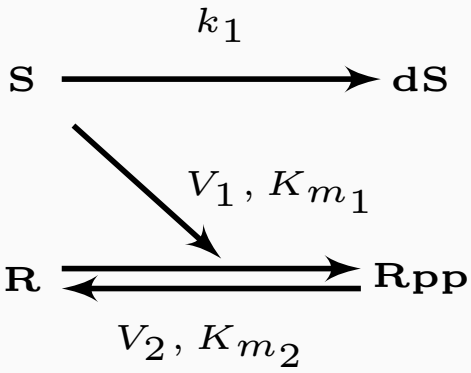
# The instance

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

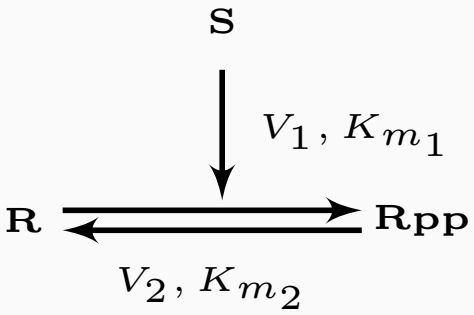
# The instance



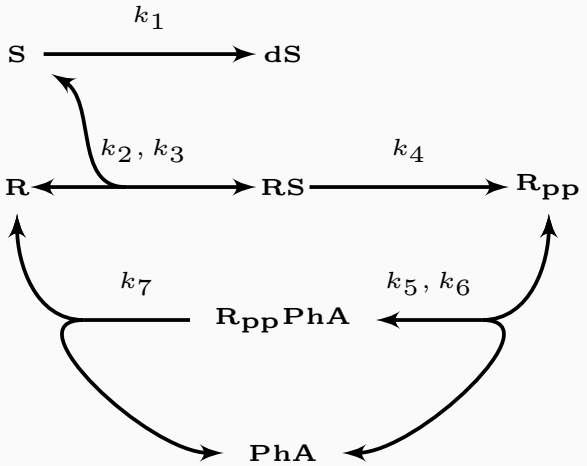

The "correct" model




The simplification model

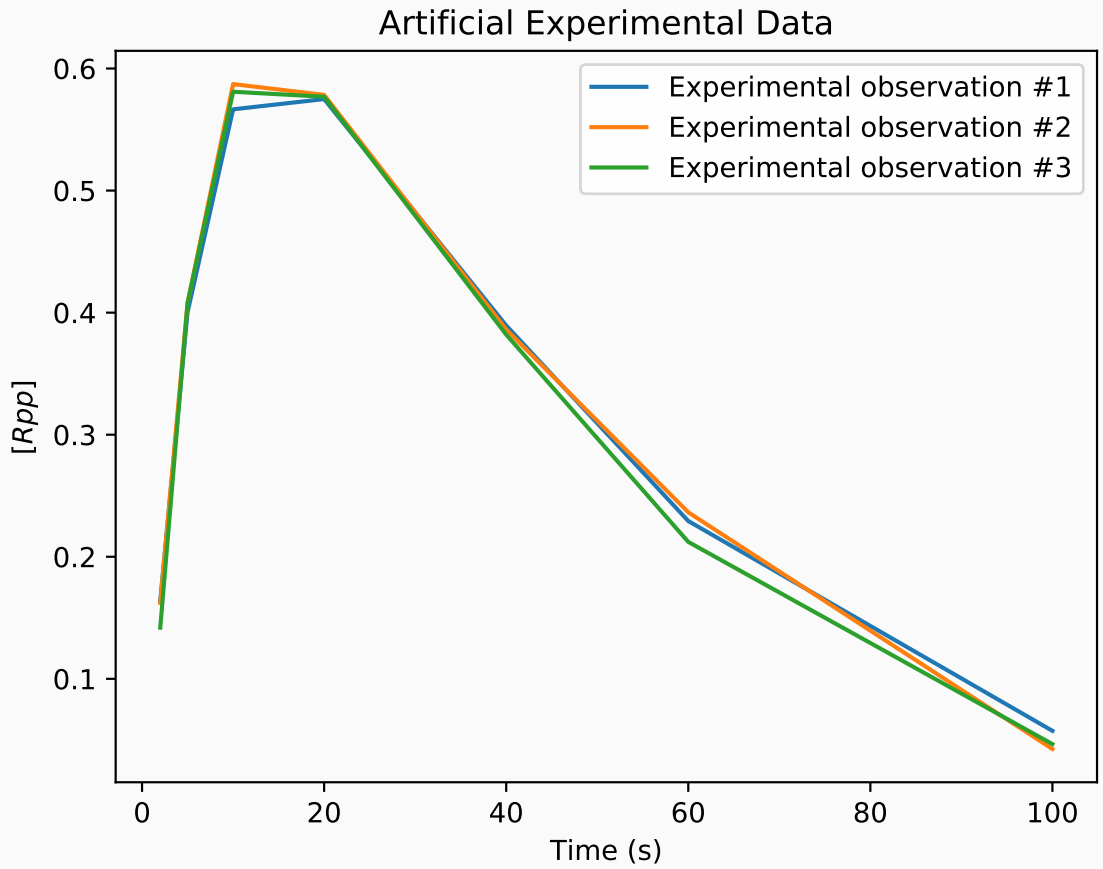



The incorrect model




The generalization model

# The instance



# Results on ABC-SysBio

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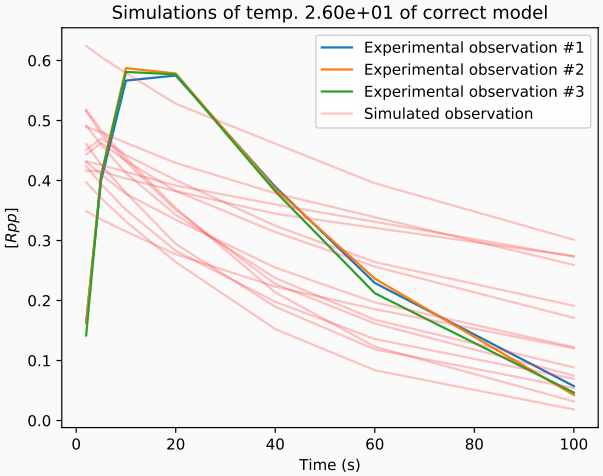
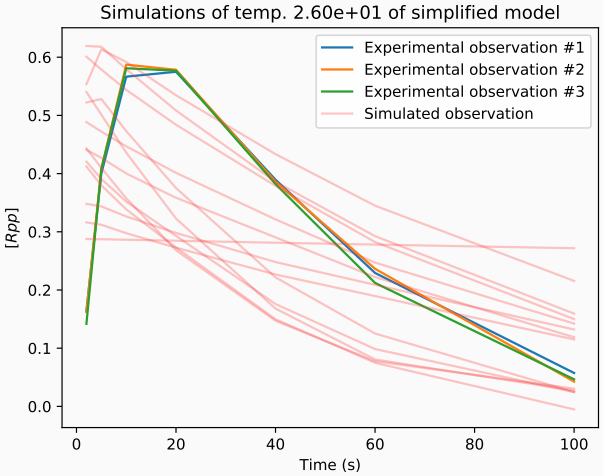
The ABC-SysBio software returned the following ranking of models:

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

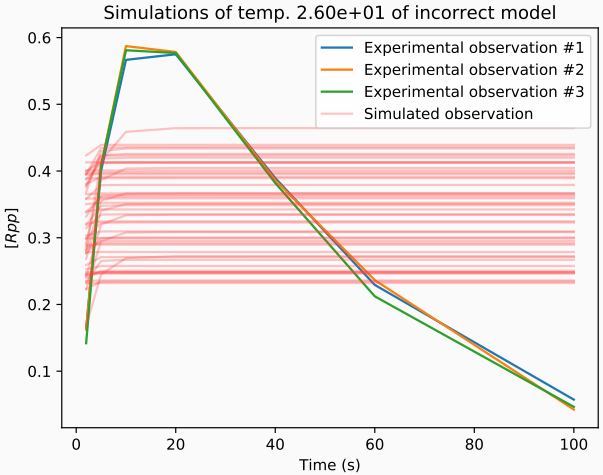
# Results on ABC-SysBio



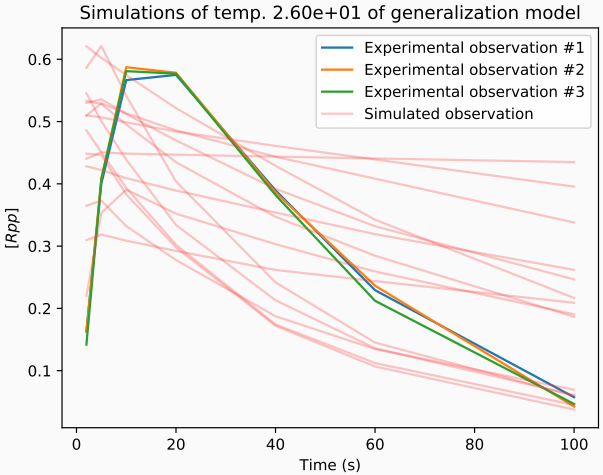

correct model




simplified model




incorrect model




generalization model

# Results on SigNetMS

The ranking returned by SigNetMS on the first experiment is:

1. correct model

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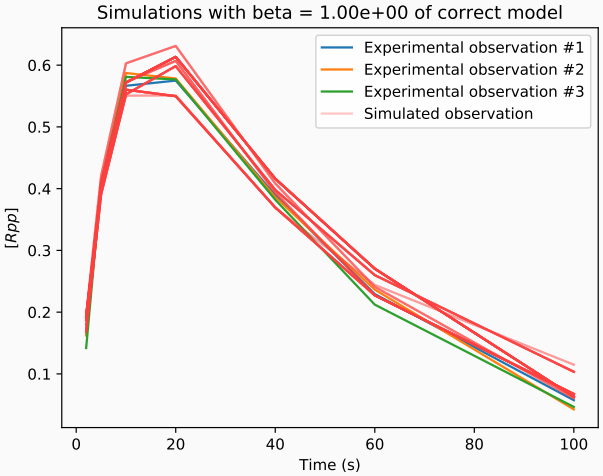
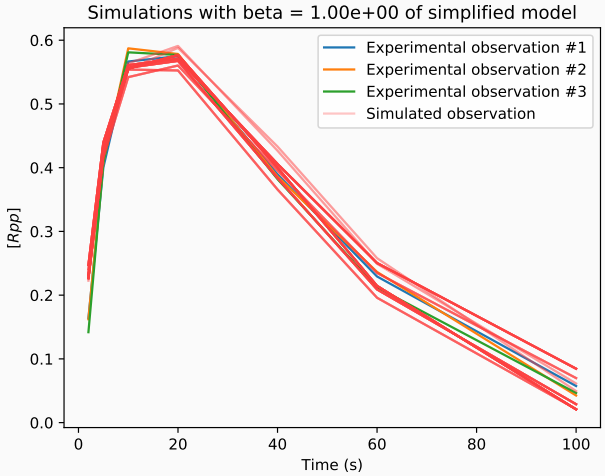
3. generalization model
4. incorrect model

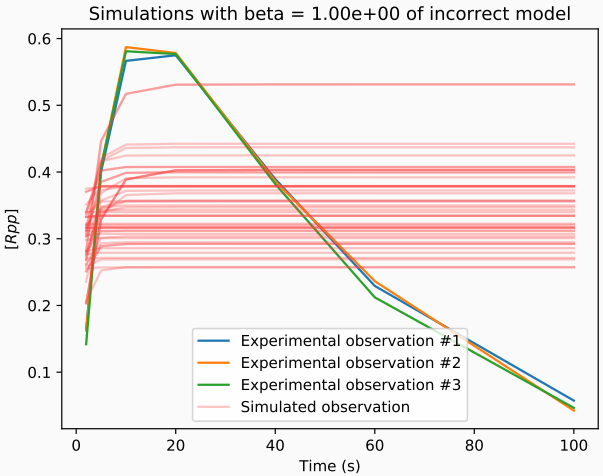
# Results on SigNetMS



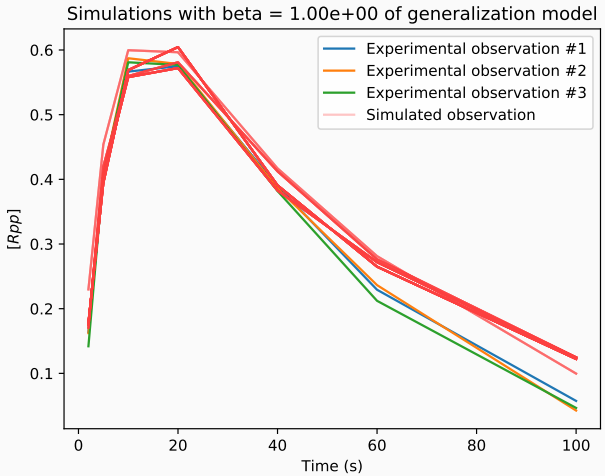

correct model




simplified model




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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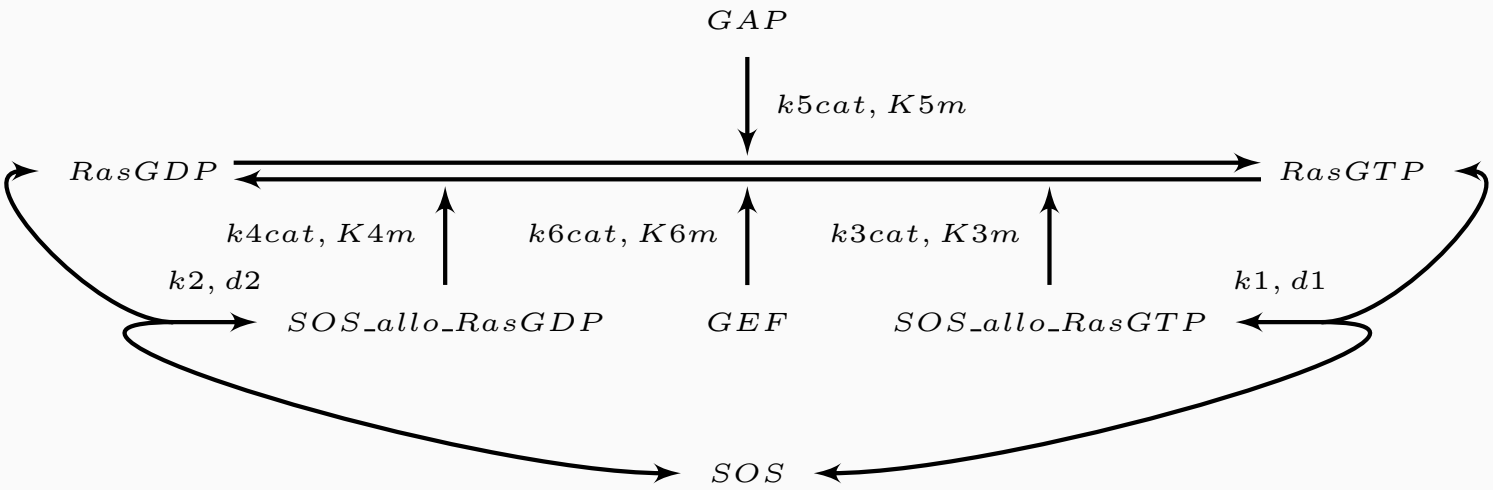

# The model selection instance

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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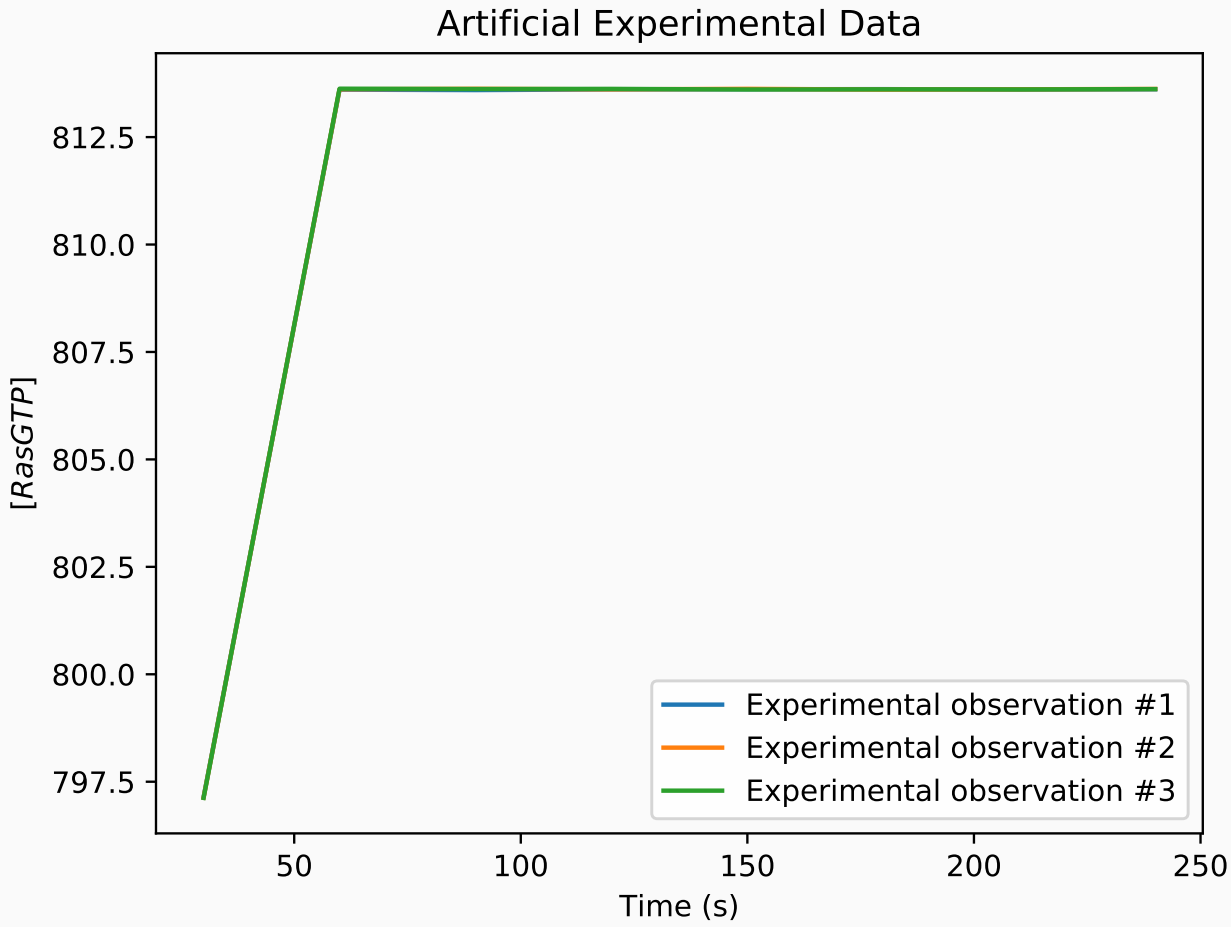

# Model selection as a feature selection problem

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

# Model selection as a feature selection problem

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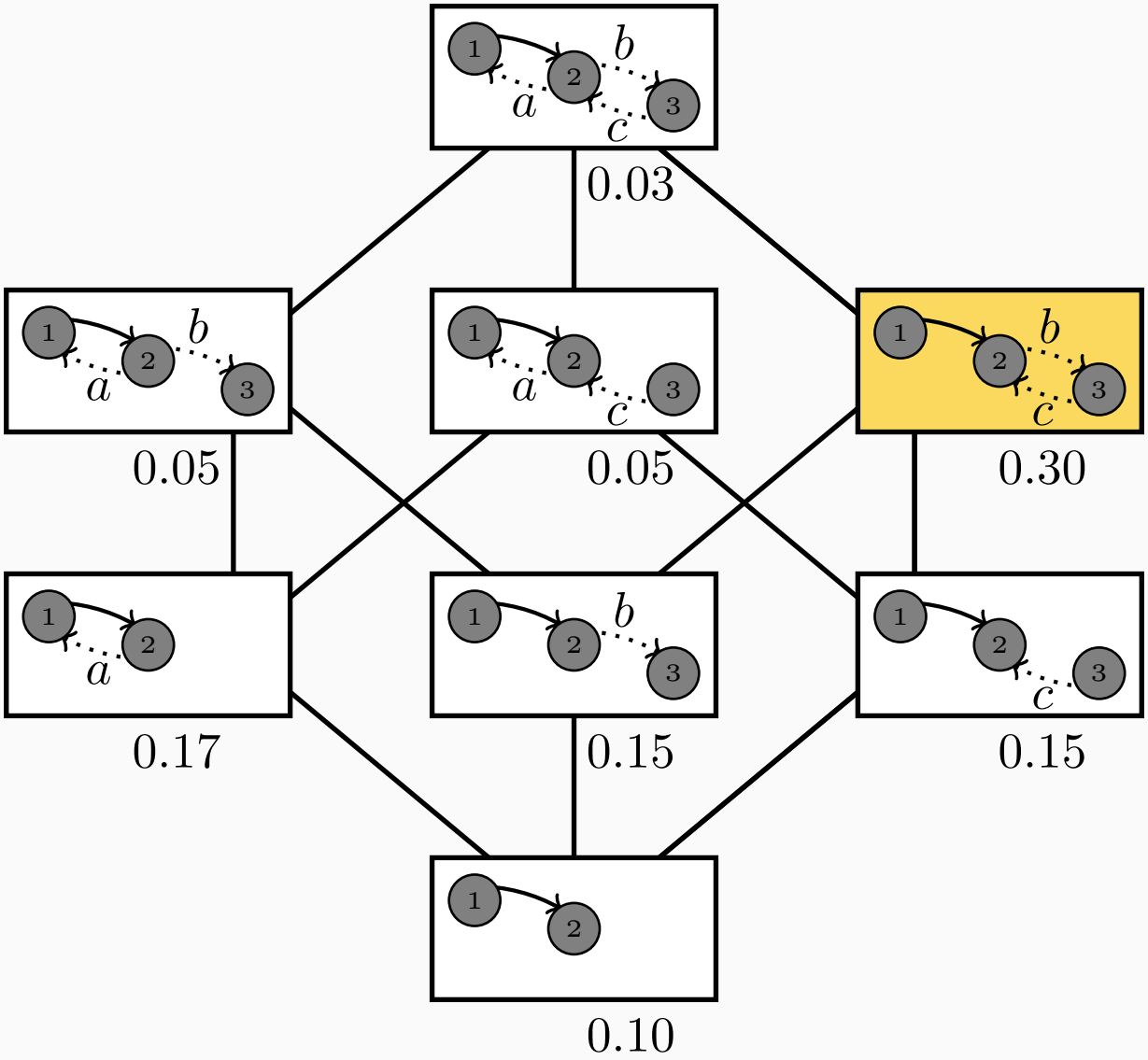
If we define the set of feature as a set of reactions, we can create a feature selection instance that represents a model selection instance.

# 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,

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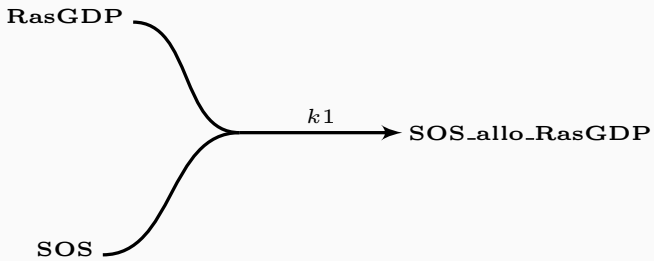
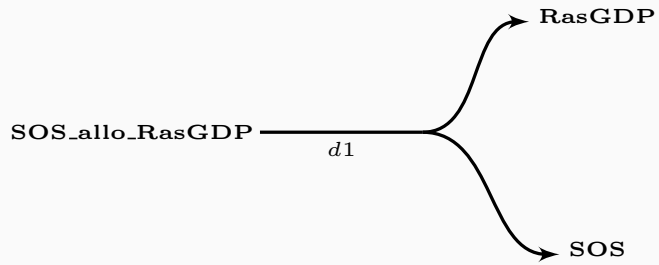
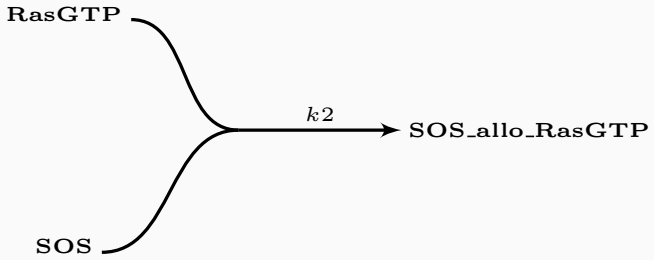
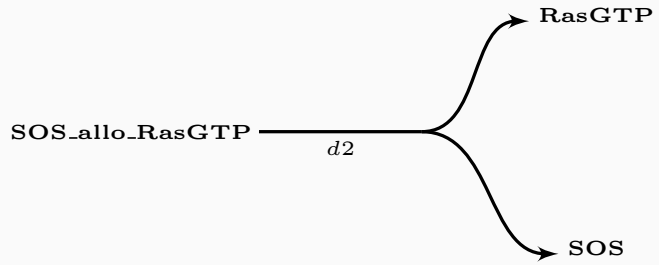
In the instance we prepared, the base model has zero reactions, and the set of features $S$ is composed by 10 reactions, 8 of them present on the correct model.

# The set of features of our experiment



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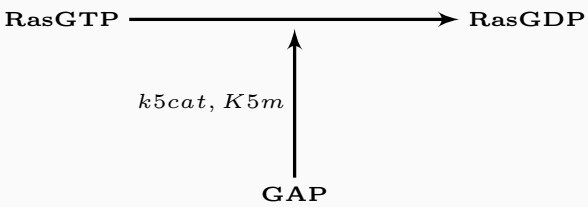


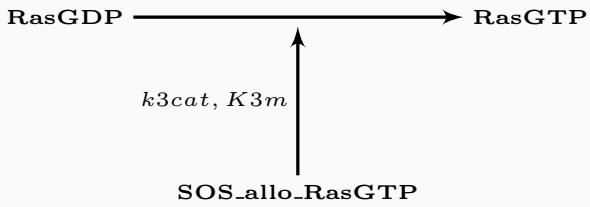


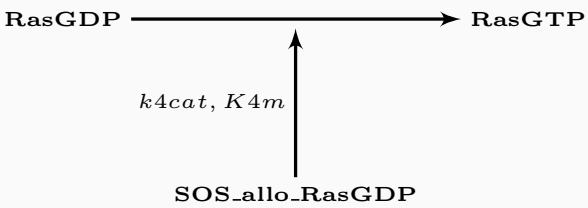


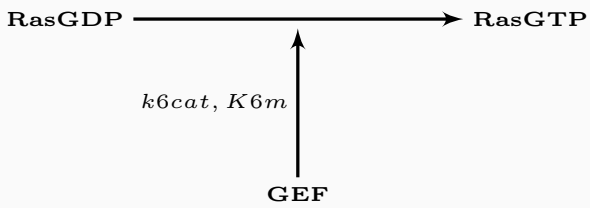


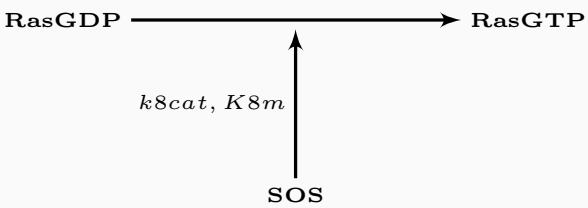


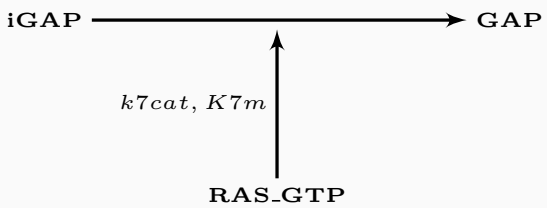

# Finding a solution

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The search space $\mathcal{P}(S)$, has $2^{10}$. Therefore, a heuristic is necessary to traverse the space. We used the Sequential Forward Selection (SFS) algorithm.

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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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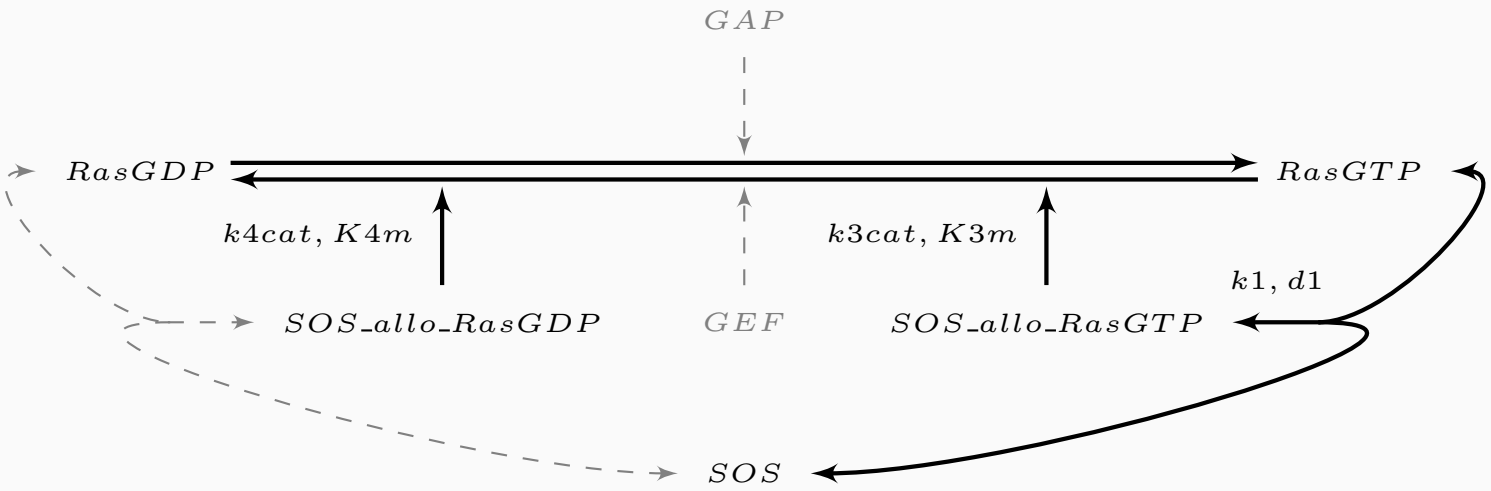

# Results of the search

Simulations generated by the found model

# Results of the search

Simulations generated by the correct model

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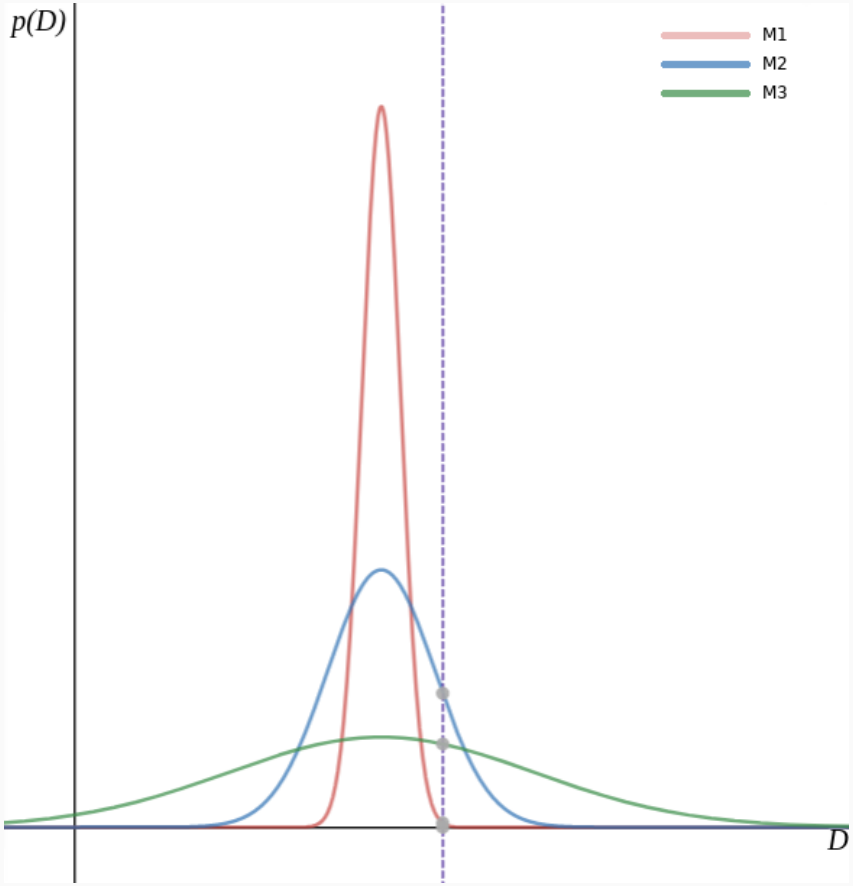
# Results of the search

In this experiment, we experienced a known feature of marginal likelihood approaches: intermediate complexity models are preferred.



# Conclusions

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- the implementation of the SigNetMS software;
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- the experimentation of feature selection on model selection using a marginal likelihood approach to define the cost function.

# Suggestions for future work

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- efficiency improvements on SigNetMS;
- treatment of numerical instabilities on numerical integrations of SigNetMS;
- 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!