

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

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May 2019

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Centro de Toxinas, Resposta-imune e Sinalização Celular (CeTICS)  
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This project receives funding from FAPESP

# Introduction

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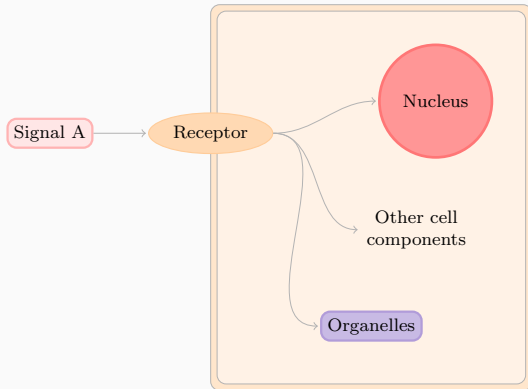
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Understanding the functioning of cell signaling is important in many biological areas.

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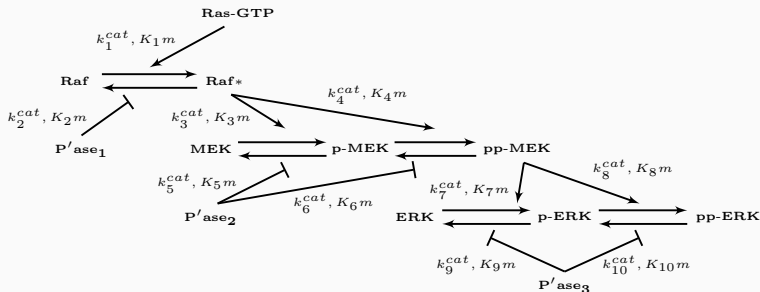
A signal propagates in an organism through chemical reactions that are caused by the change of concentration of chemical species.

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 and enzymatic 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.

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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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- Implementation and comparison of cost functions for model selection.
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- Observe the surface induced by the cost function over the search space.

# Fundamental Concepts

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## Kinetics Modeling of Chemical Reactions

# Mathematical Modeling of Reactions

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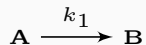
# Mathematical Modeling of Reactions

In this project we use three possible models of kinetics of an interaction:

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

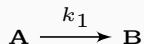
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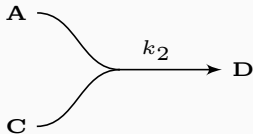


has rate of:

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

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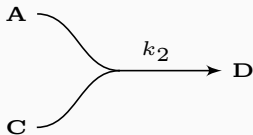
A second order reaction:





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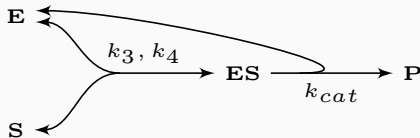


has rate of:

$$k_2[A][C].$$

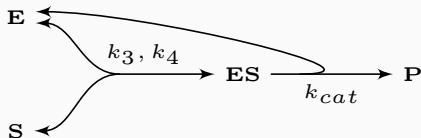
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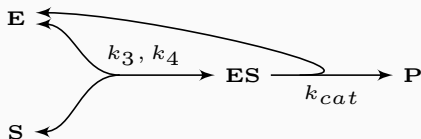
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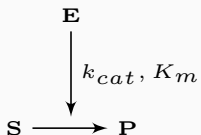
An enzymatic reaction:



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.

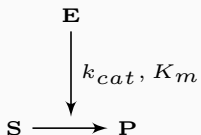
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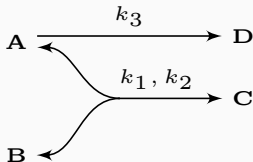


and it has rate of:

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

# Kinetics of a System of Reactions

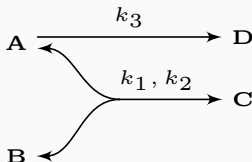
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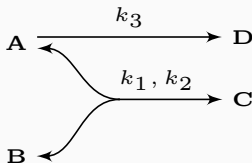
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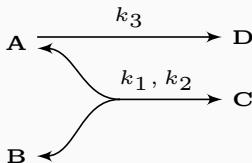


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- $A \longrightarrow D$ , with rate  $k_3[A]$ .

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

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

## 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

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Ranking with Marginal Likelihood Estimation

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

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

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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

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

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 distribution 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.

## Ranking with Approximate Bayesian Computation

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4. Repeat until some iteration limit.

The result of the algorithm is a sample of the distribution

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

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ABC sequential Monte Carlo improves a simple ABC algorithm by using a sequence  $\epsilon_0 > \dots > \epsilon_T$  acceptance tolerances. The sample for a tolerance  $\epsilon_i$  is used to generate candidates for sample of tolerance  $\epsilon_{i+1}$ .

We can use the accepted parameters of tolerance  $\epsilon$  and model  $M$  to estimate

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

# Experiments on Model Selection

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- **SigNetMS**: an implementation of the Marginal Likelihood method created in this project.
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- Create 4 candidate models.
- For one of the models, choose a set of parameter values and time steps and simulate data.
- Add Gaussian noise to the simulations. Repeat two more times to generate three observations of the system.
- Neglect chosen parameter values and define prior distributions for every parameter.



## Experiment description

We ran two experiments based on the same procedure:

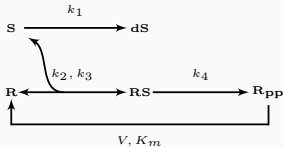
- Create 4 candidate models.
- For one of the models, choose a set of parameter values and time steps and simulate data.
- Add Gaussian noise to the simulations. Repeat two more times to generate three observations of the system.
- Neglect chosen parameter values and define prior distributions for every parameter.
- Rank the four models.

## Experiment #1

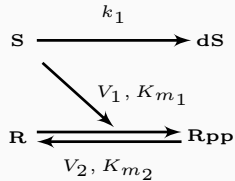
# Experiment #1

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

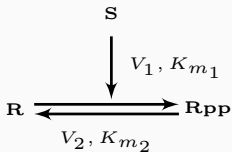
# Experiment #1



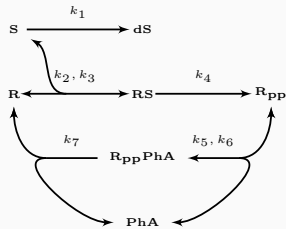
Model 1



Model 2



Model 3



Model 4

## Experiment #1

The model used to create the observations was Model 1.

## Experiment #1

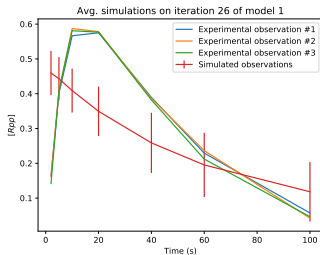
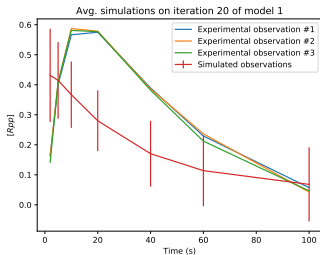
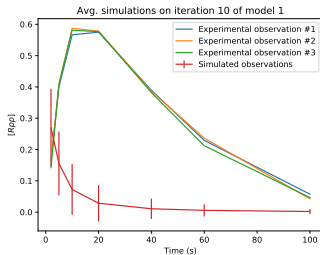
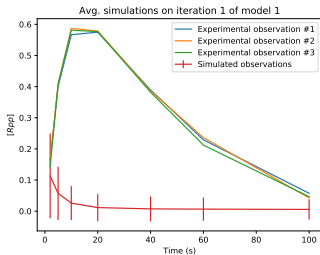
The model used to create the observations was Model 1.

The priors distribution used for all parameters is  $\text{Gamma}(1, 3)$ .

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

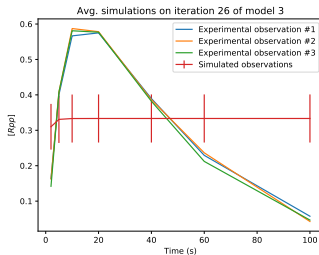
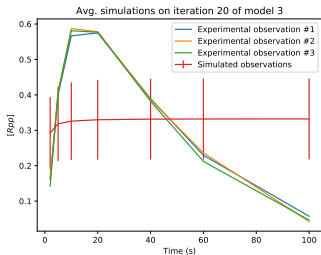
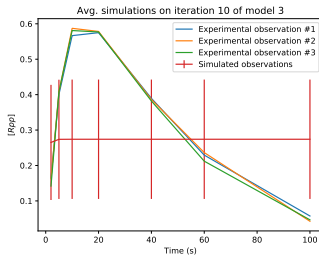
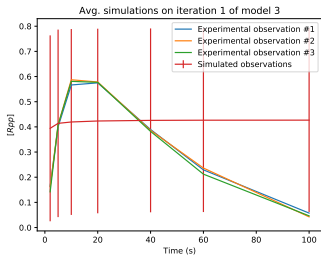
$$3 > 2 > 4 > 1$$

# Results on ABC-SysBio





# Results on ABC-SysBio



The ranking returned by SigNetMS on the first experiment is:

$$1 > 2 > 4 > 3;$$

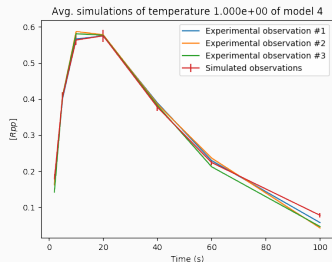
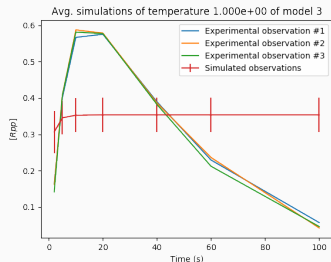
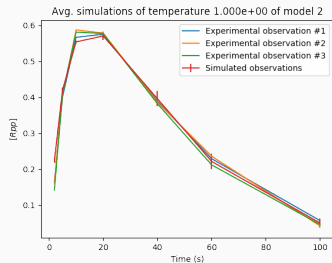
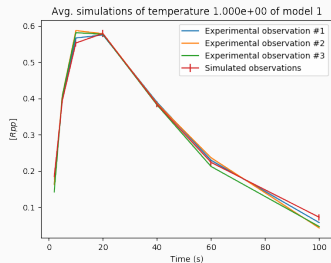
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$$1 > 2 > 4 > 3;$$

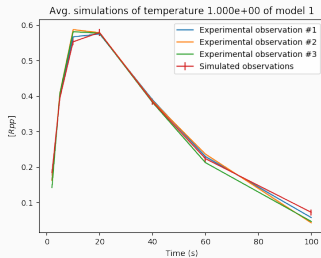
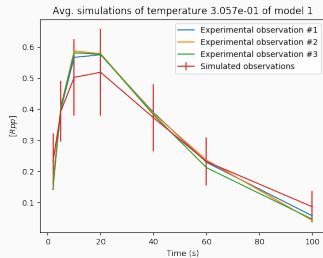
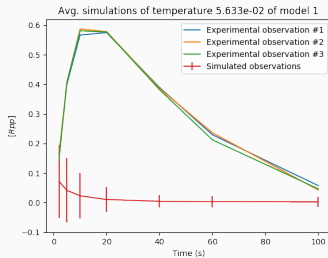
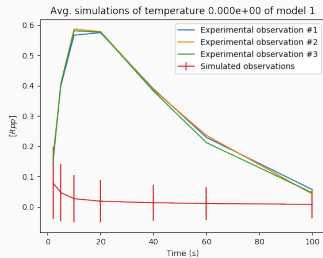
which is very similar to the ranking presented originally by Vyshemirsky and Girolami (2007):

$$1 > 4 > 2 > 3.$$

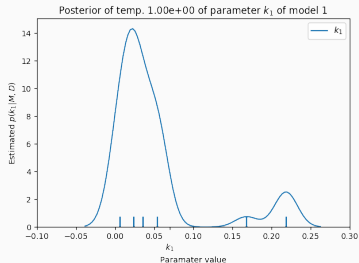
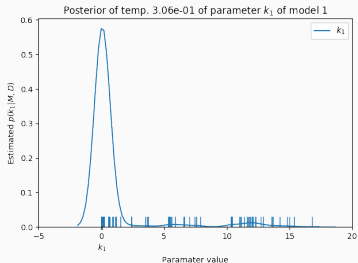
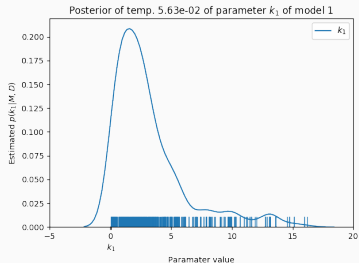
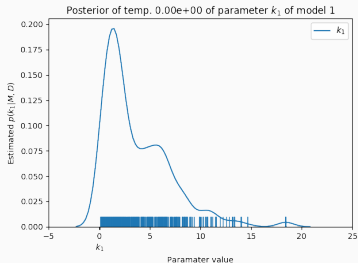
# Results on SigNetMS



# Results on SigNetMS



# Results on SigNetMS



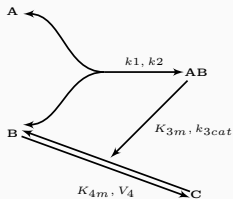
## Experiment #2

## Experiment #2

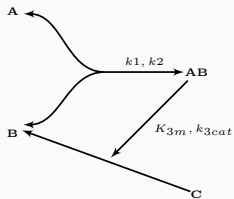
This experiment is very similar to the later and it was designed by us.



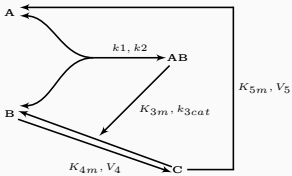
## Experiment #2



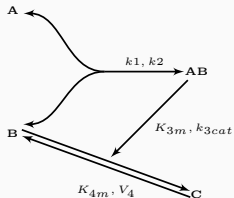
Model 1



Model 2



Model 3



Model 4

## Experiment #2

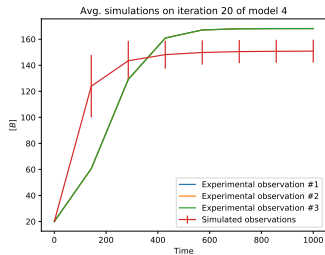
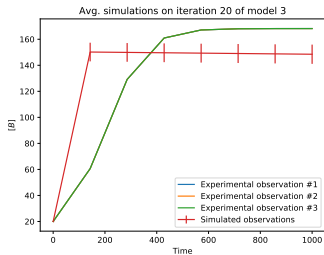
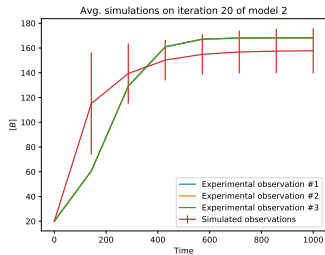
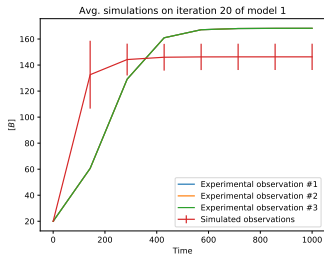
We used the following prior distributions for model parameters:

Parameter	Models	Prior
$k_1$	1, 2, 3, 4	$\text{Gamma}(1, 0.01)$
$k_2$	1, 2, 3, 4	$\text{Gamma}(2, 0.5)$
$k_{3cat}$	1, 2, 3, 4	$\text{Gamma}(4, 1)$
$K_{3m}$	1, 2, 3, 4	$\text{Gamma}(2, 1500)$
$V_4$	1, 3, 4	$\text{Gamma}(2, 1)$
$K_{4m}$	1, 3, 4	$\text{Gamma}(2, 100)$
$V_5$	3	$\text{Gamma}(2, 0.4)$
$K_{5m}$	3	$\text{Gamma}(2, 100)$

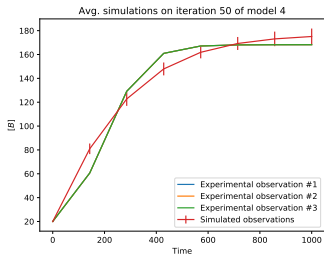
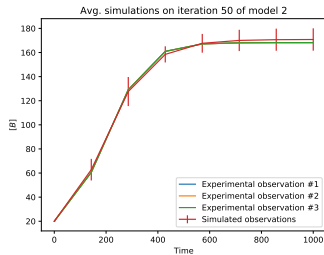
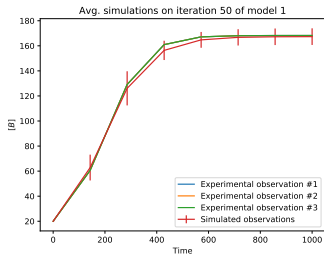
The ABC-SysBio software returned the following ranking of models:

$$2 > 1 > 4 > 3$$

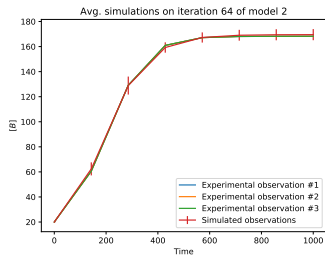
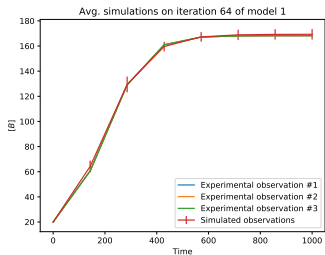
# Results on ABC-SysBio



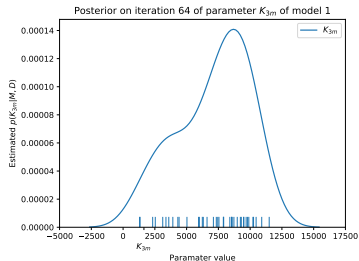
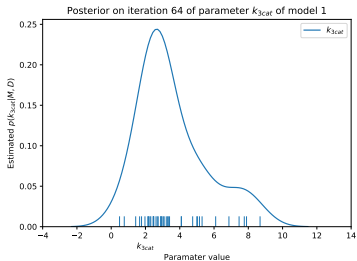
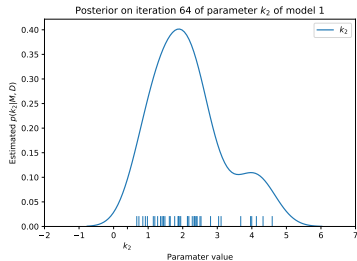
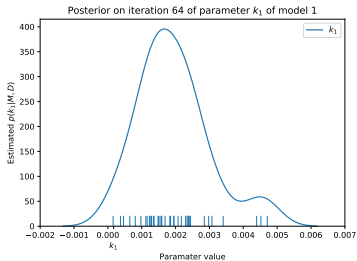
# Results on ABC-SysBio



# Results on ABC-SysBio



# Results on ABC-SysBio

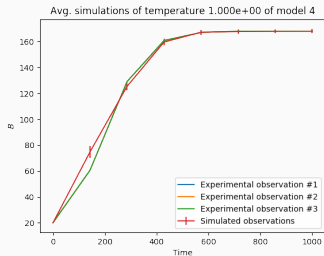
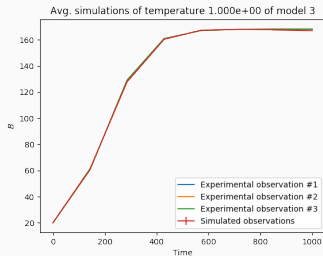
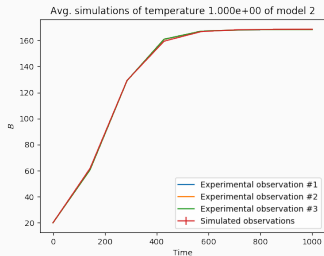
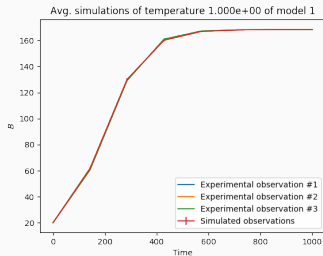


SigNetMS returned the following ranking of models:

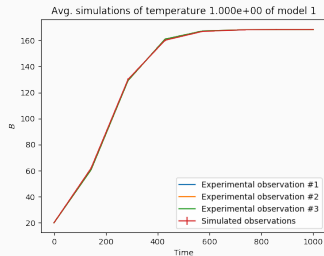
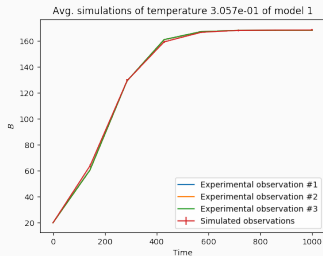
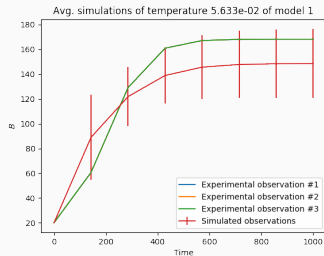
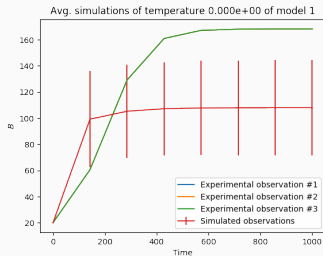
$$2 > 1 > 3 > 4$$



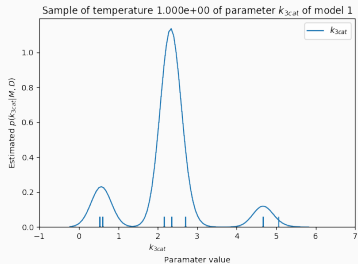
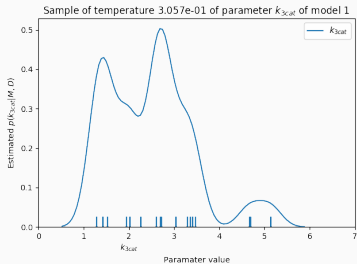
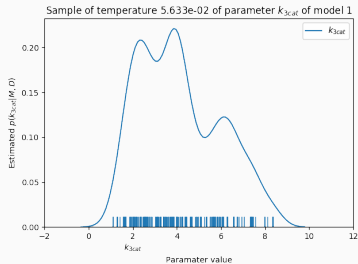
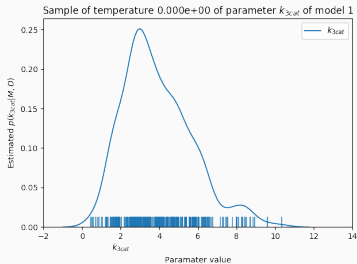
# Results on SigNetMS



# Results on SigNetMS



# Results on SigNetMS



## **Future Work**

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

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- Studies of databases of chemical kinetics such as SABIO-RK and BRENDA.



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

- Complete program credits requirement.
- Improve computationally SigNetMS, since we chose it as our cost function for models.
- Studies of databases of chemical kinetics such as SABIO-RK and BRENDA.
- Creation of a relational database of chemical interactions focused on our further applications.

- Define a wrapper on featsel that allows the use of SigNetMS as a cost function.

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- Choice of a feature selection search algorithm.
- Apply the method in ERK signaling pathways of tumor cell lines Y1 and HEK293.

Thank you!