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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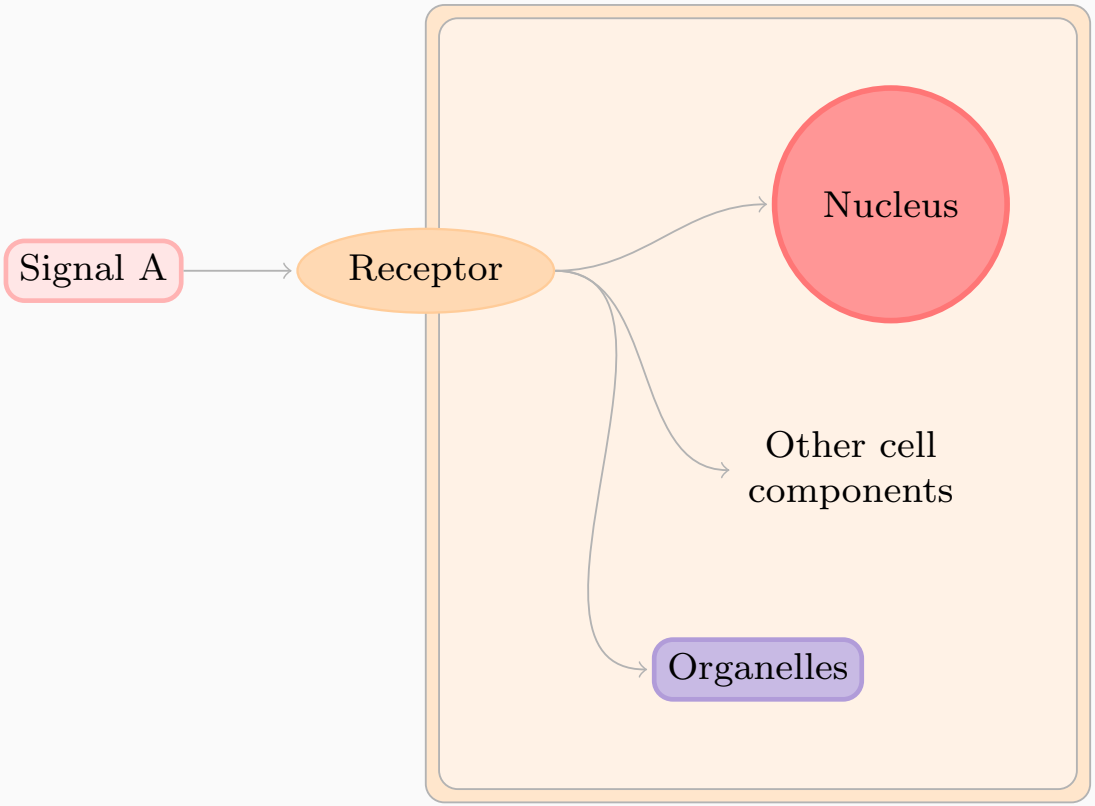

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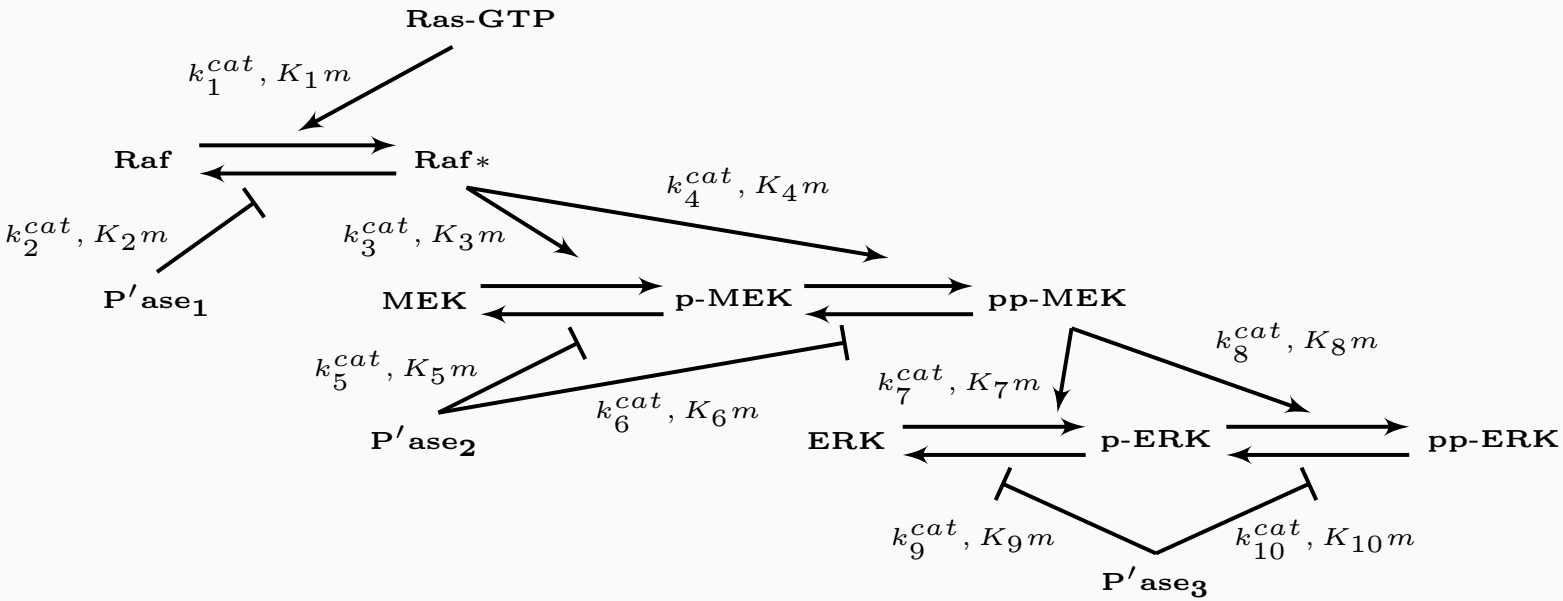
We call the path of a signal a cell signaling pathway.

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 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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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 difficulties encountered by Wu.

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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,

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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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- 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.

Fundamental Concepts

Kinetics Modeling of Chemical Reactions

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

Kinetic Modeling of First Order Iteration

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

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has rate of:

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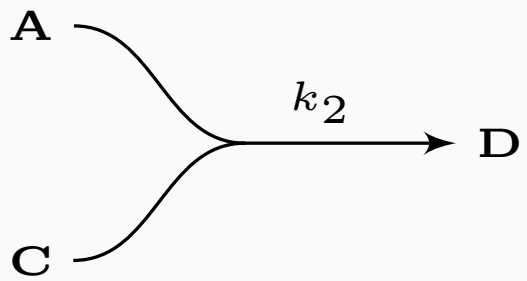
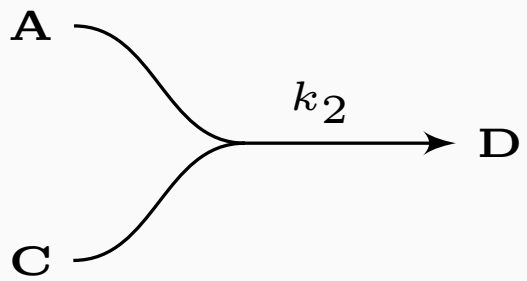
Kinetic Modeling of Second Order Iteration

A second order reaction:



Kinetic Modeling of Second Order Iteration

A second order reaction:

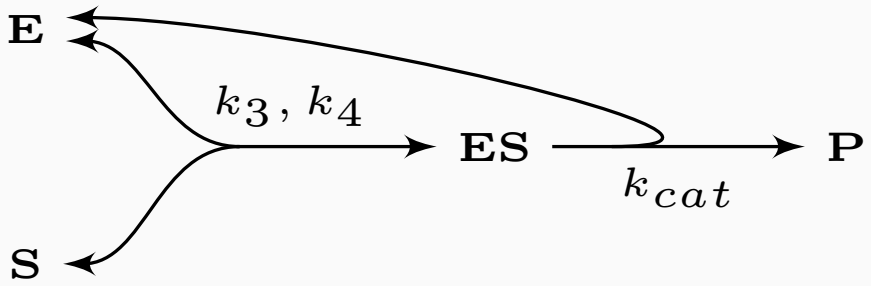


has rate of:

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

Kinetic Modeling of Enzymatic Reactions

An enzymatic reaction:



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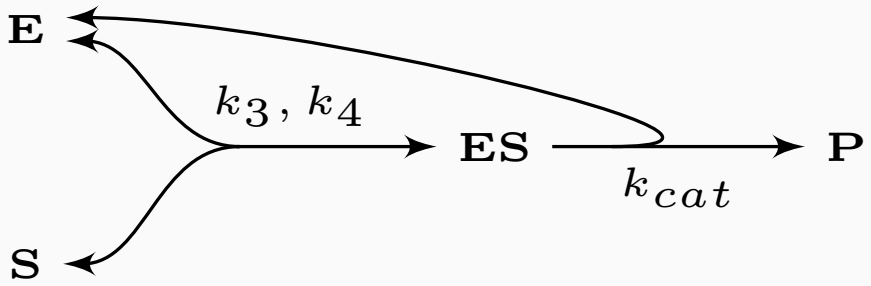

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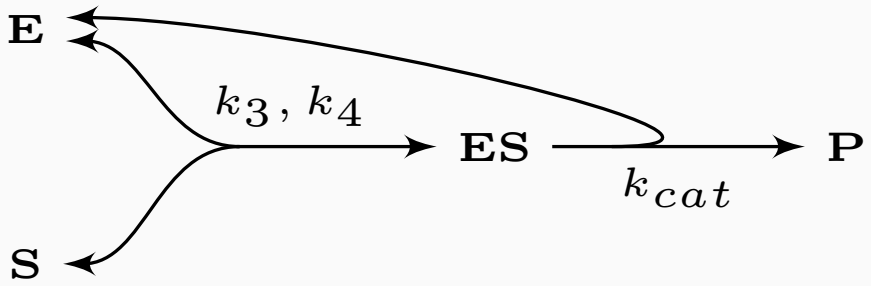
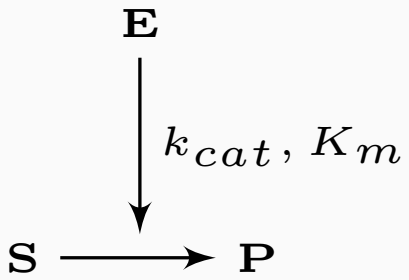


Can be divided in two first order reactions plus a second order reaction. However, with the appropriate assumptions, it is possible to use a Michaelis-Menten simplification of this reaction.

Michaelis-Menten Kinetics

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



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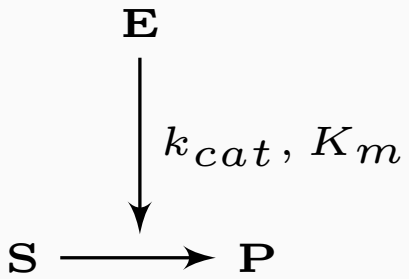
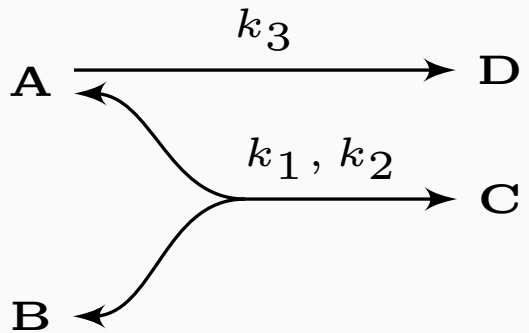


and it has rate of:

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

Kinetics of a System of Reactions

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



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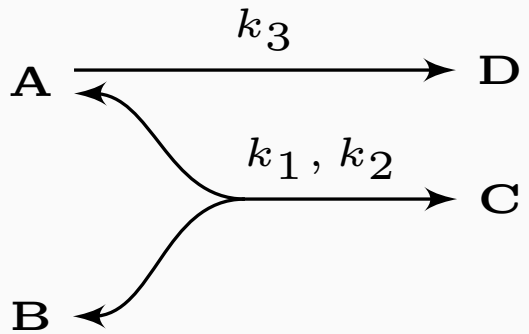

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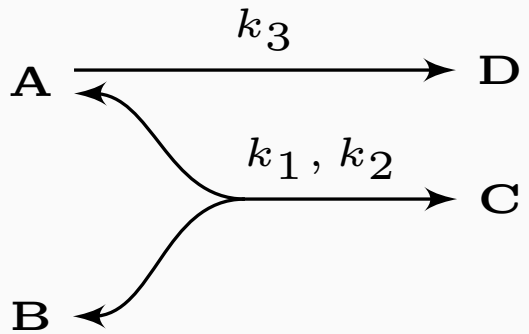

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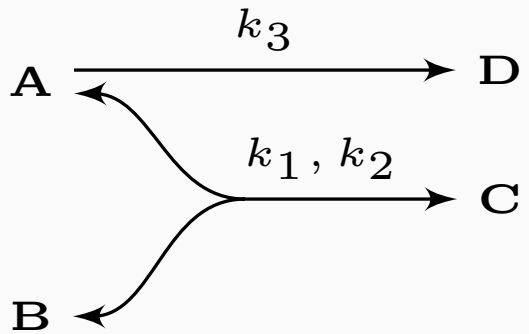

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- $C \longrightarrow A + B$, with rate $k_2[C]$,
- $A \longrightarrow D$, with rate $k_3[A]$.

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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

Ranking with Marginal Likelihood Estimation

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If we consider that a model M with parameters θ correctly represent the signaling pathway and that there is a Gaussian observation error on D. Then, the likelihood of observing experimental data D is:

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

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

We define a power-posterior distribution as:

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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

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

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.

Approximate Bayesian Computation

The result of the algorithm is a sample of the distribution

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

ABC Sequential Monte Carlo

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

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

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

Experiments on Model Selection

Software used for Model Ranking Experiments

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- **SigNetMS:** an implementation of the Marginal Likelihood method created in this project.
- **ABC-SysBio:** an implementation of ABC-SMC.

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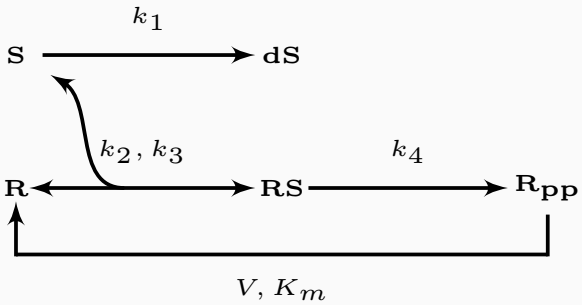
- Neglect chosen parameter values and define prior distributions for every parameter.
- Rank the four models.

Experiment #1

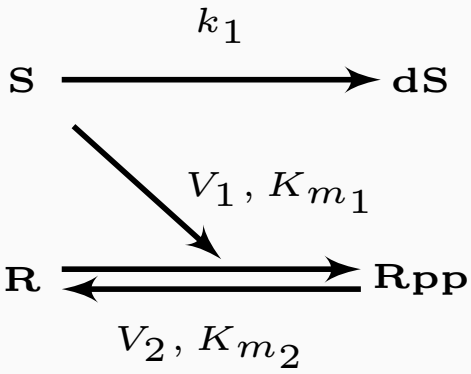
Experiment #1

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

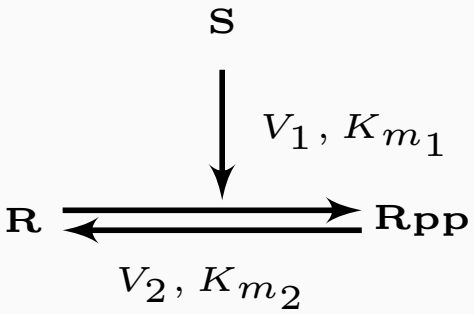
Experiment #1



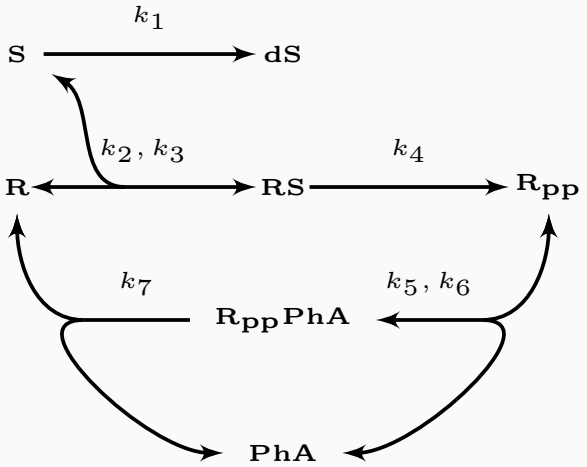
Model 1



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.

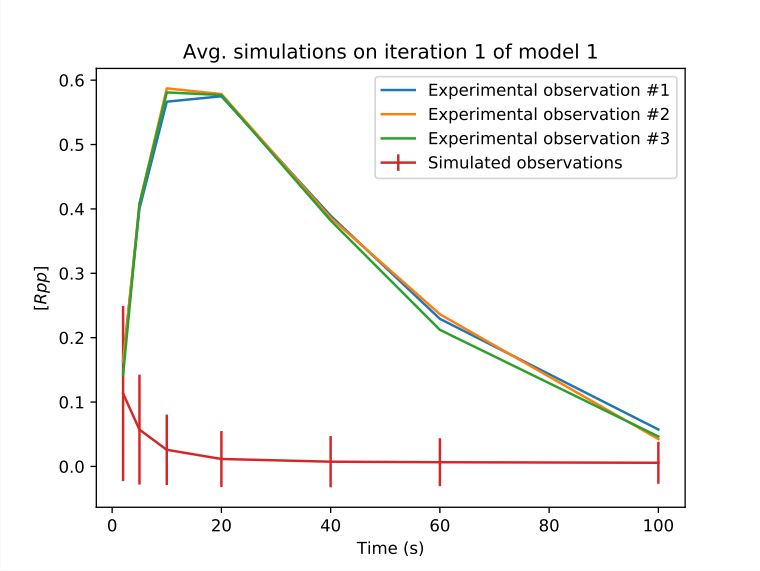
The priors distribution used for all parameters is $Gamma(1, 3)$.

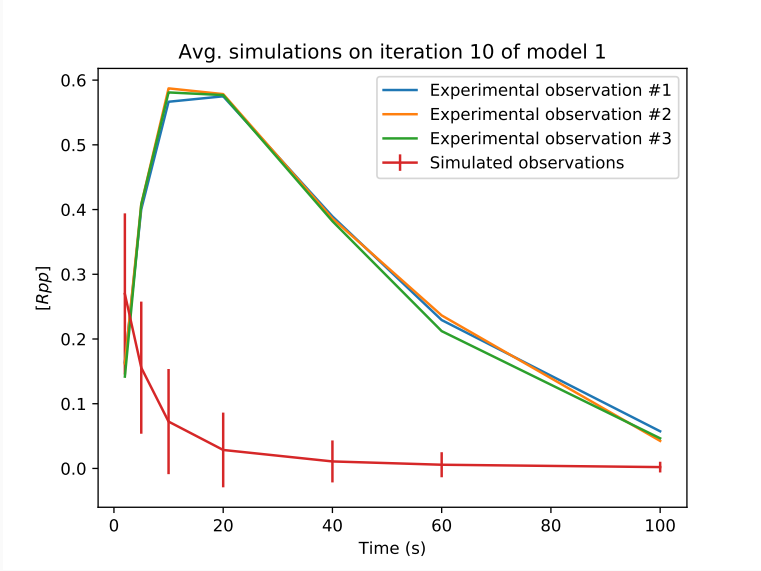
Results on ABC-SysBio

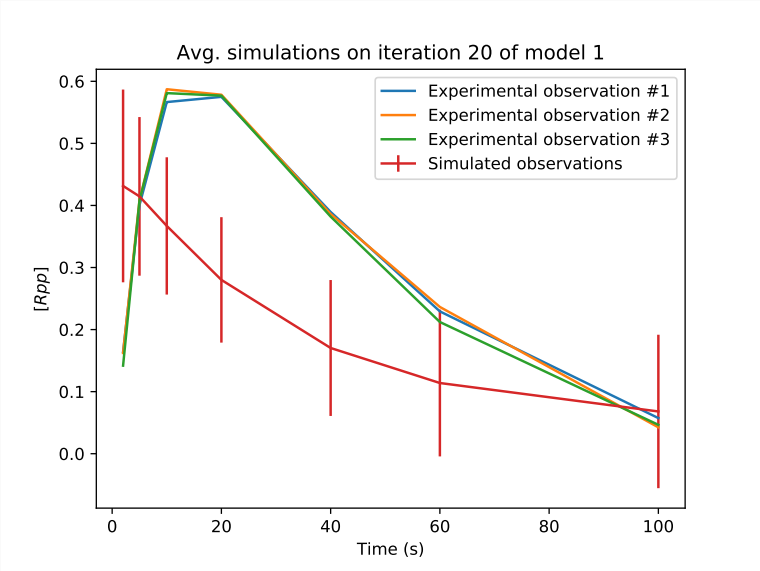
The ABC-SysBio software returned the following ranking of models:

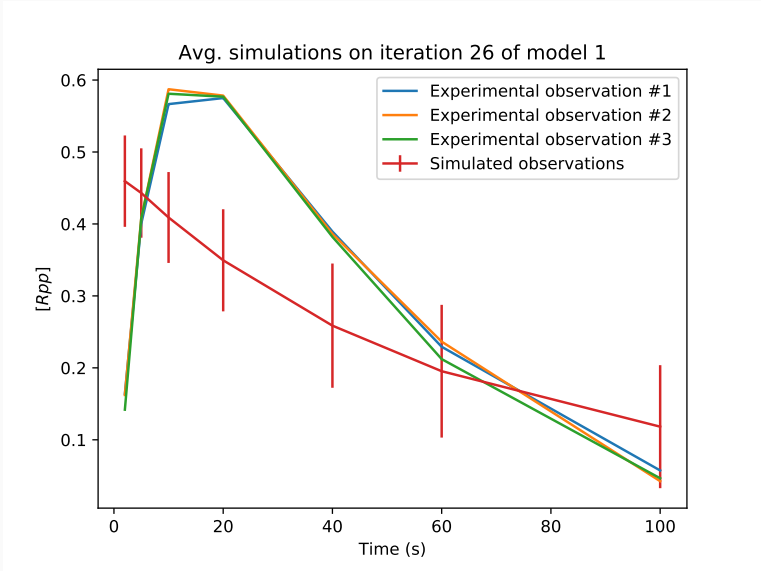
$$3 > 2 > 4 > 1$$

Results on ABC-SysBio

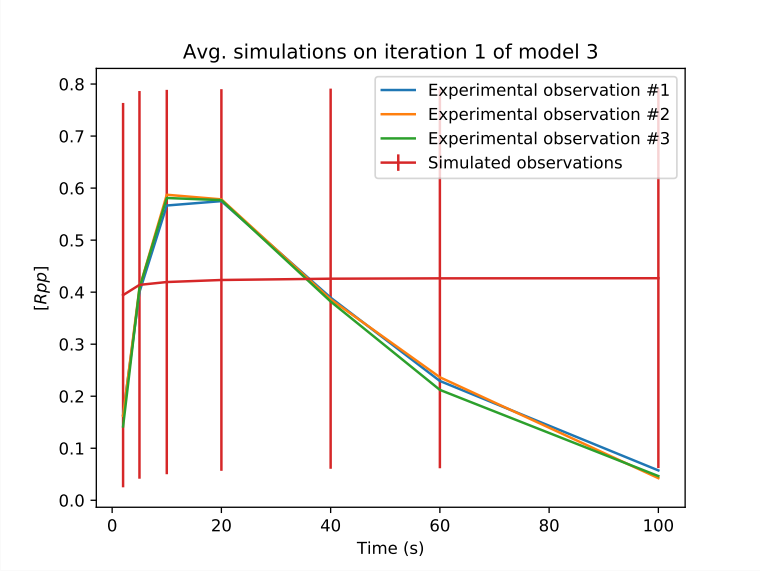


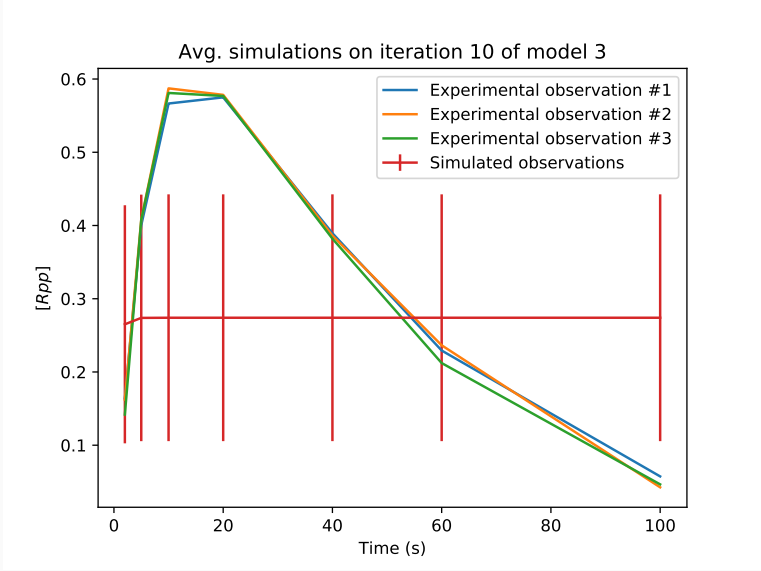


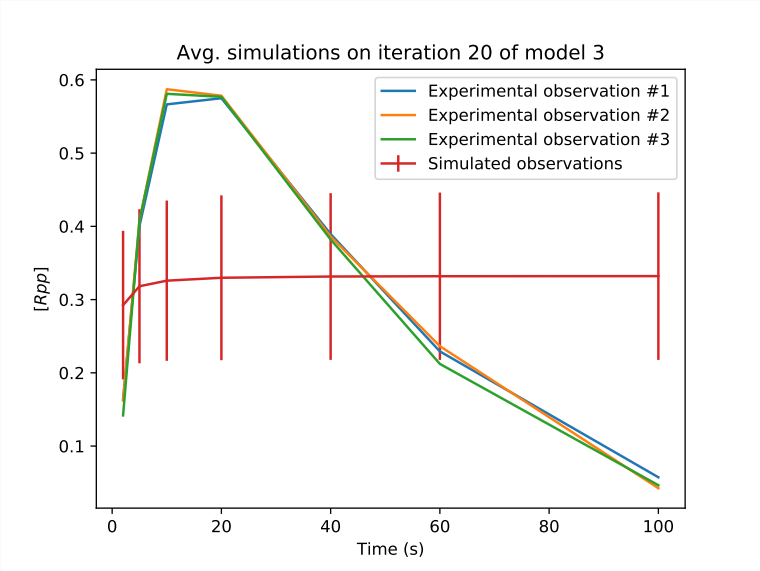


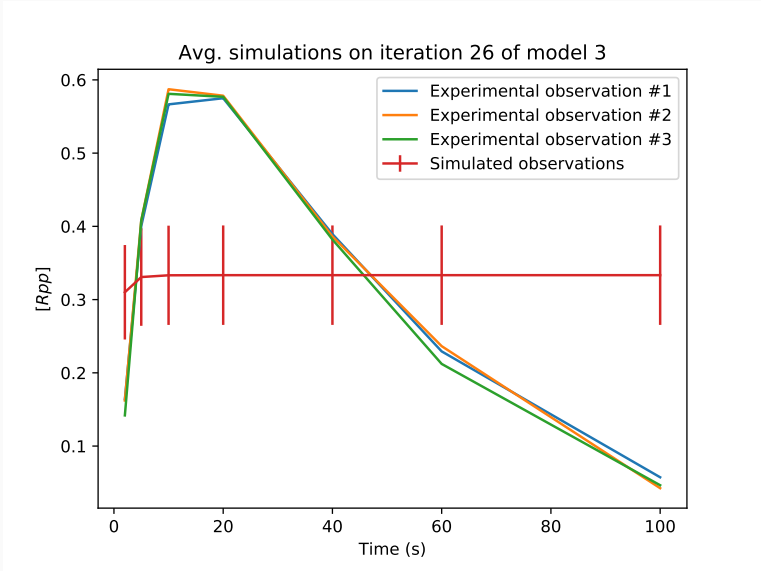


Results on ABC-SysBio









Results on SigNetMS

The ranking returned by SigNetMS on the first experiment is:

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

Results on SigNetMS

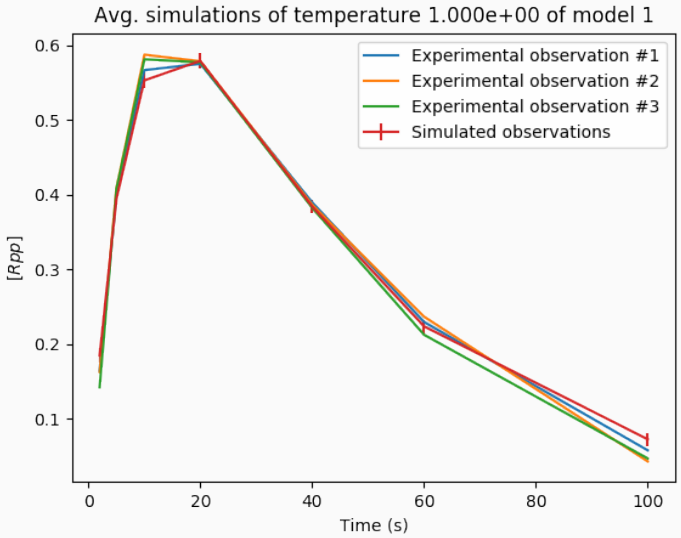
The ranking returned by SigNetMS on the first experiment is:

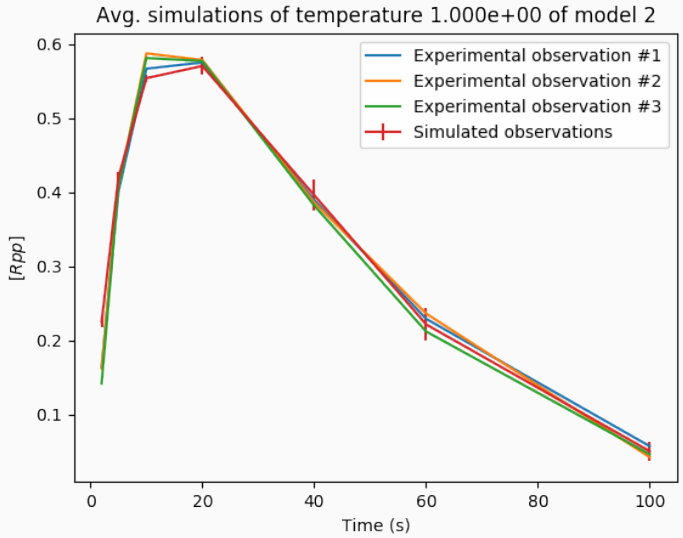
$$1 > 2 > 4 > 3;$$

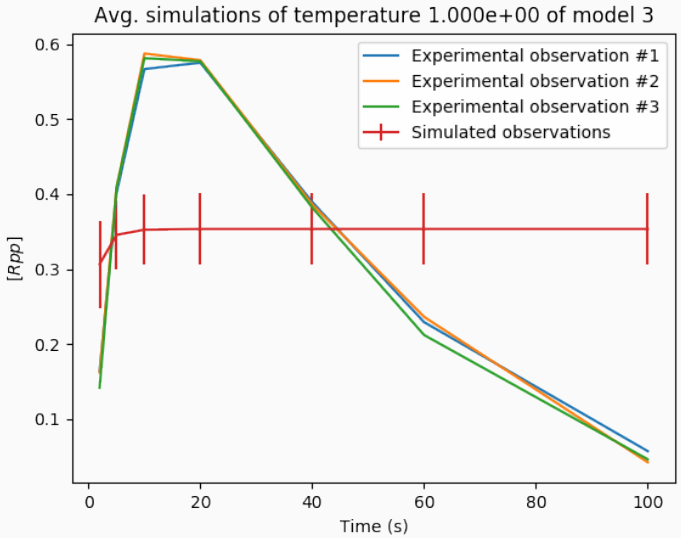
which is very similar to the ranking presented originally by Vyshemirsky and Girolami (2007):

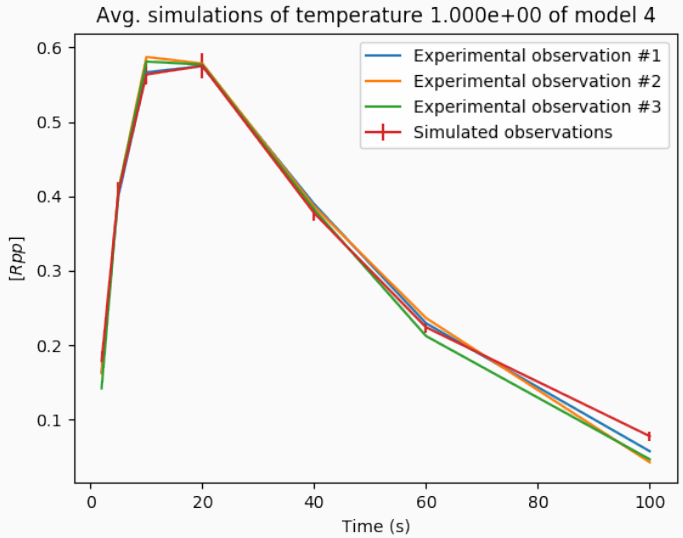
$$1 > 4 > 2 > 3.$$

Results on SigNetMS









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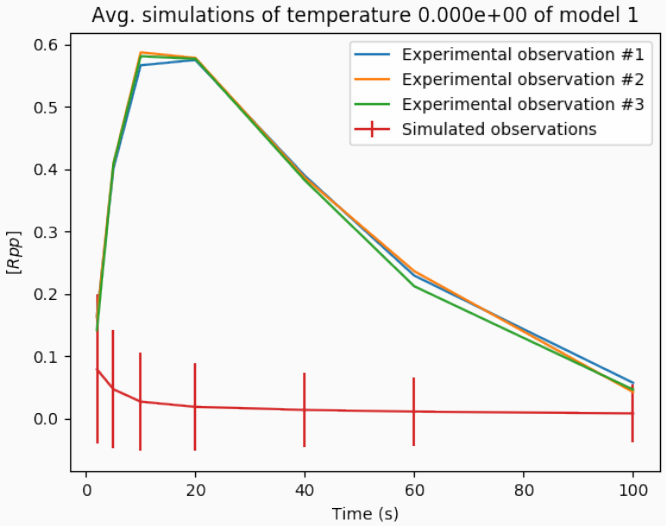

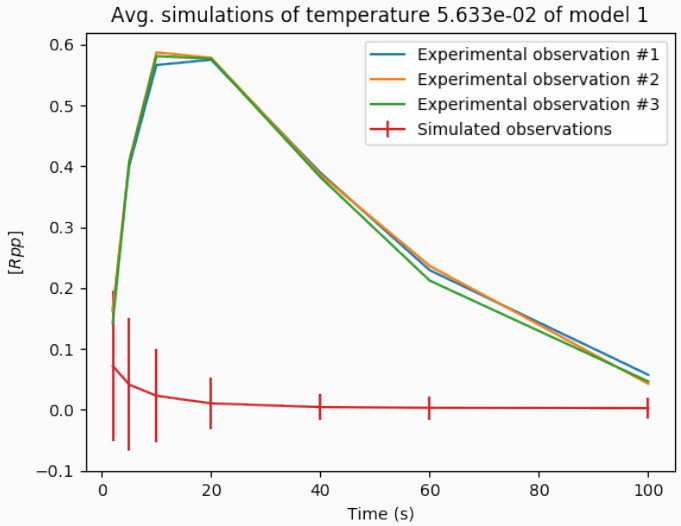

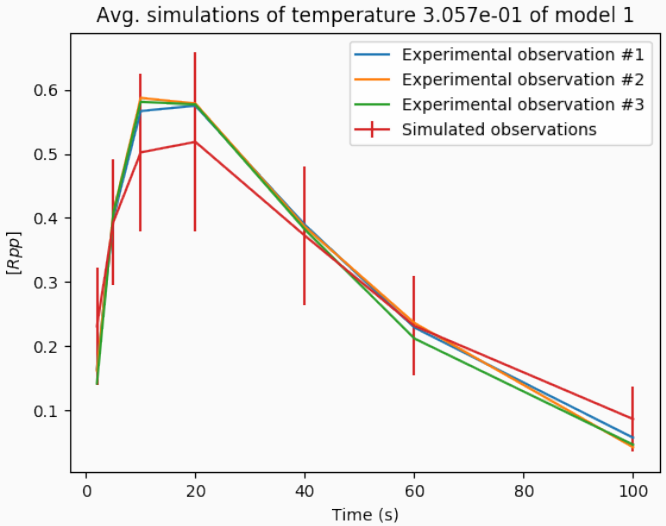

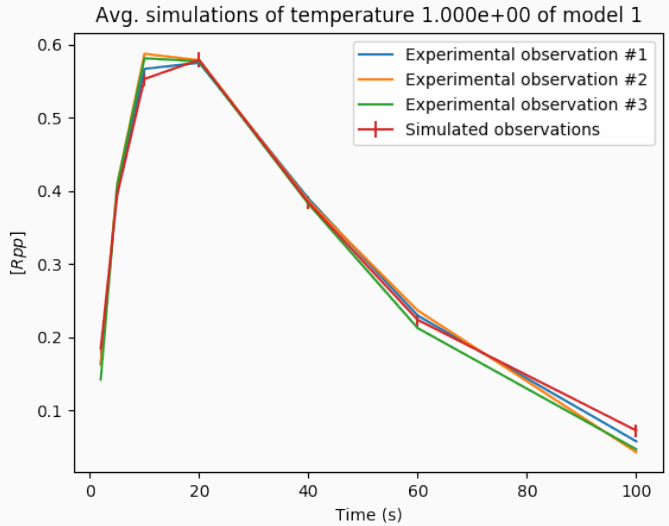

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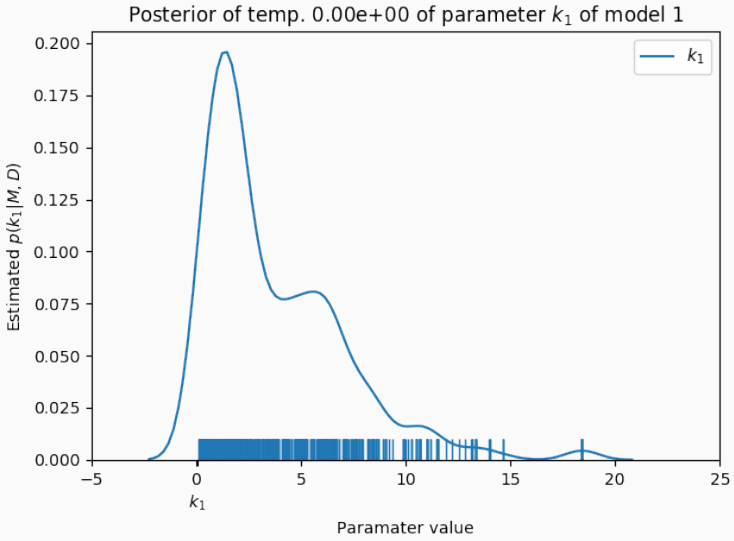
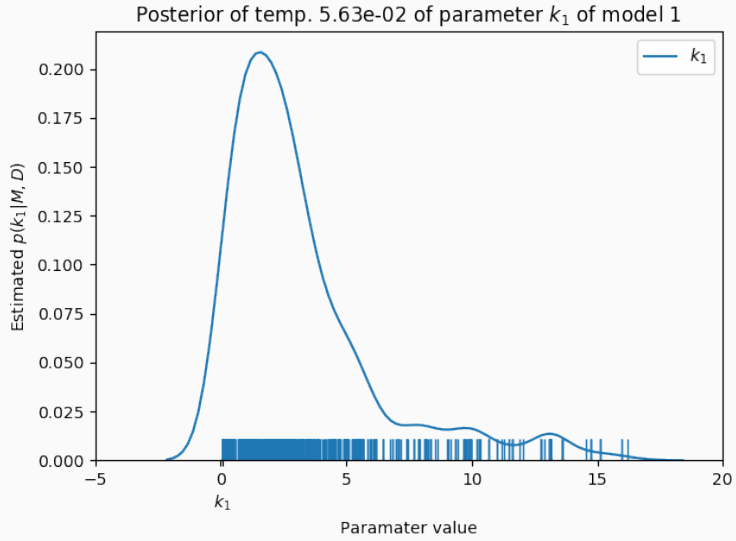
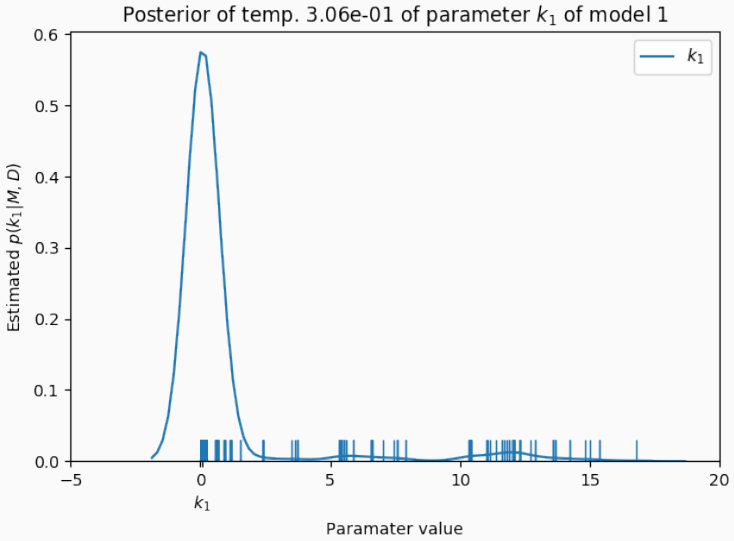
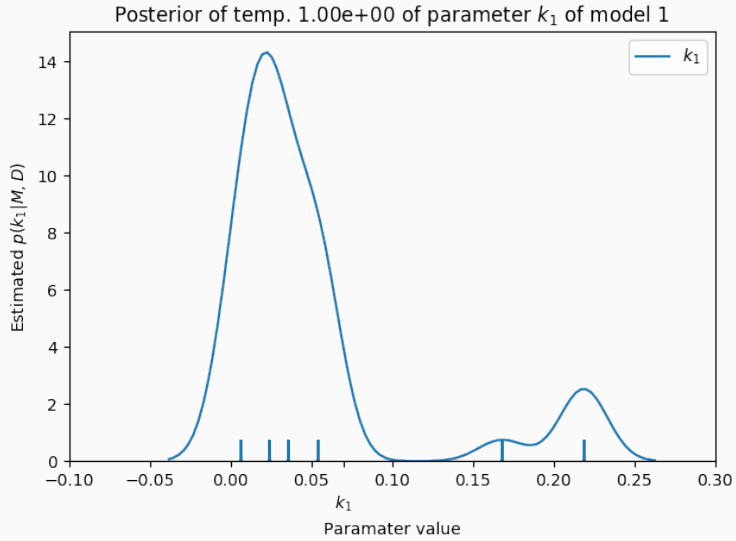






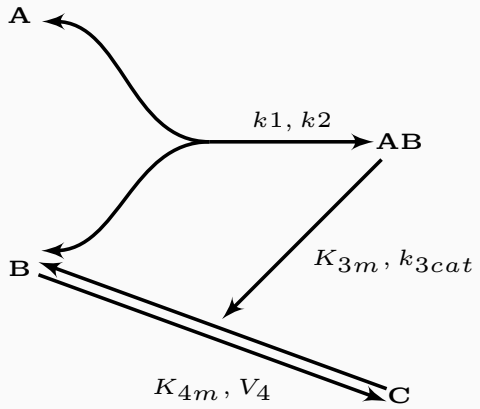


Experiment #2

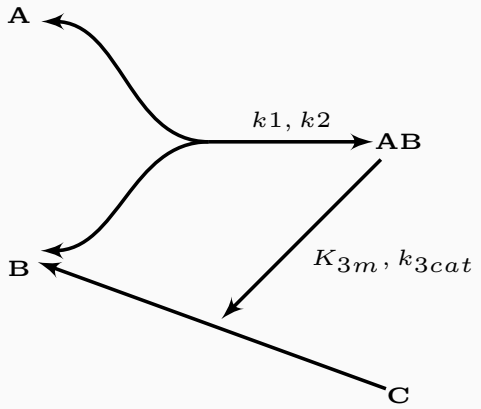
Experiment #2

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

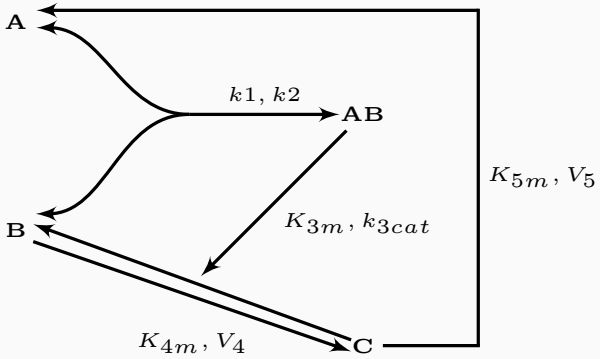
Experiment #2



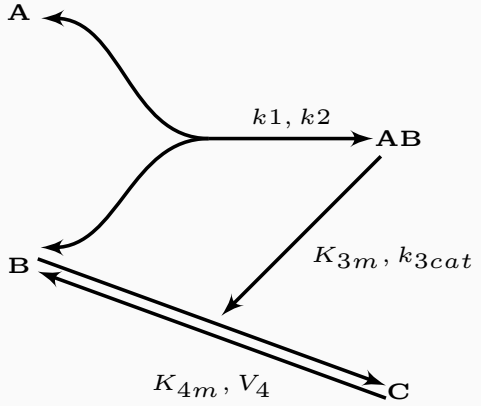
Model 1



Model 2



Model 3



Model 4

Experiment #2

We used the following prior distributions for model parameters:

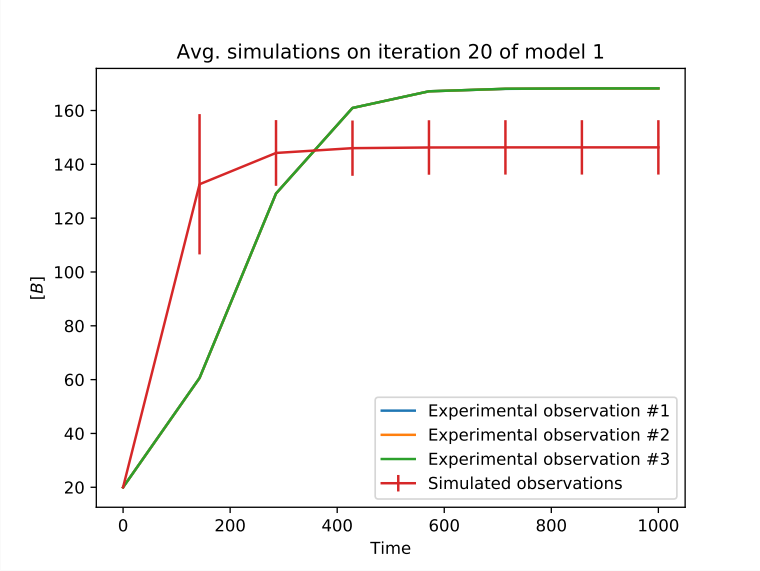
Parameter	Models	Prior
$k1$	1, 2, 3, 4	$Gamma(1, 0.01)$
$k2$	1, 2, 3, 4	$Gamma(2, 0.5)$
k_{3cat}	1, 2, 3, 4	$Gamma(4, 1)$
K_{3m}	1, 2, 3, 4	$Gamma(2, 1500)$
V_4	1, 3, 4	$Gamma(2, 1)$
K_{4m}	1, 3, 4	$Gamma(2, 100)$
V_5	3	$Gamma(2, 0.4)$
K_{5m}	3	$Gamma(2, 100)$

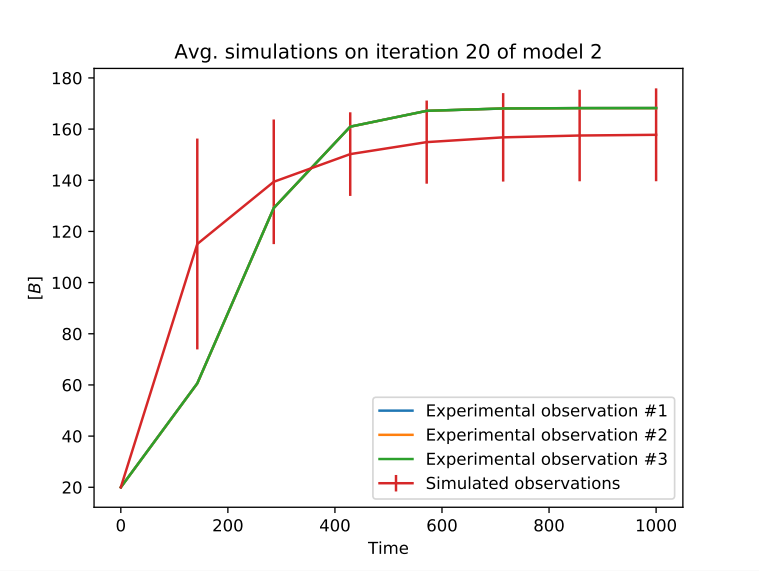
Results on ABC-SysBio

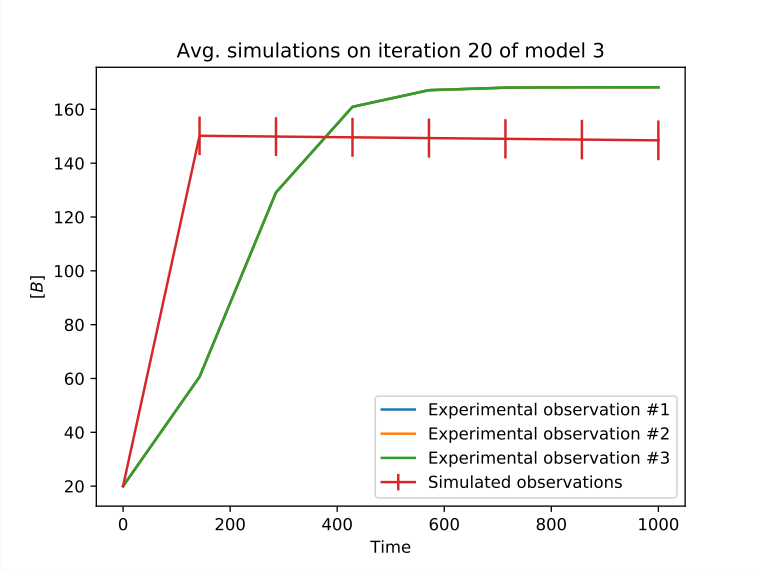
The ABC-SysBio software returned the following ranking of models:

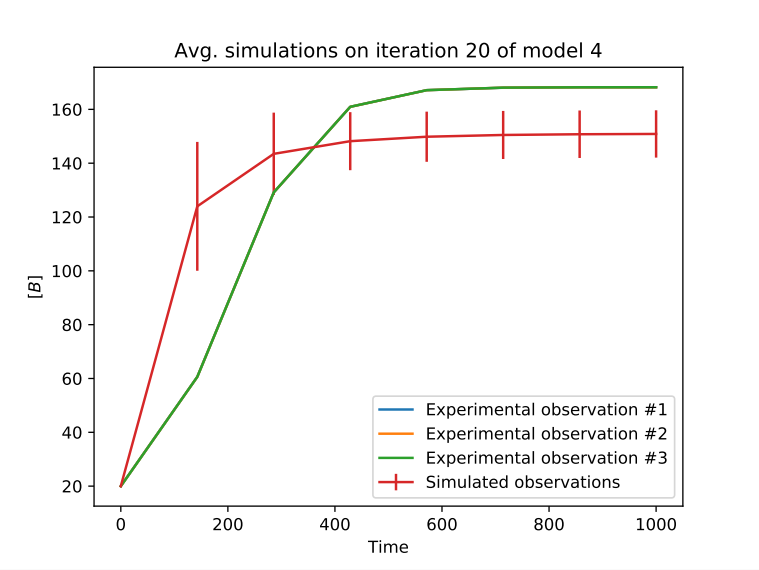
$$2 > 1 > 4 > 3$$

Results on ABC-SysBio

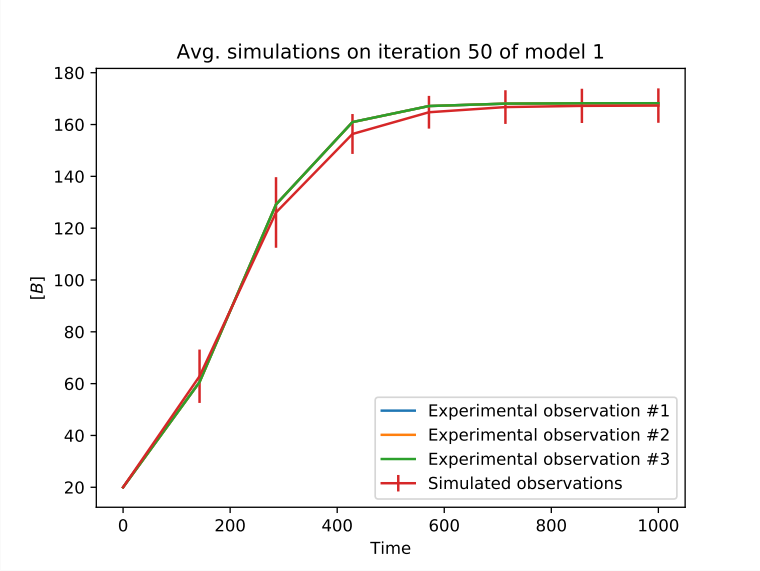


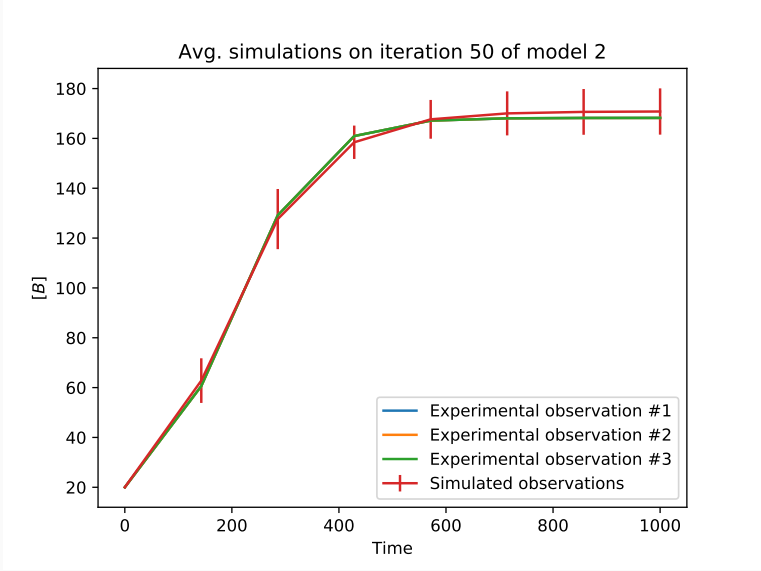


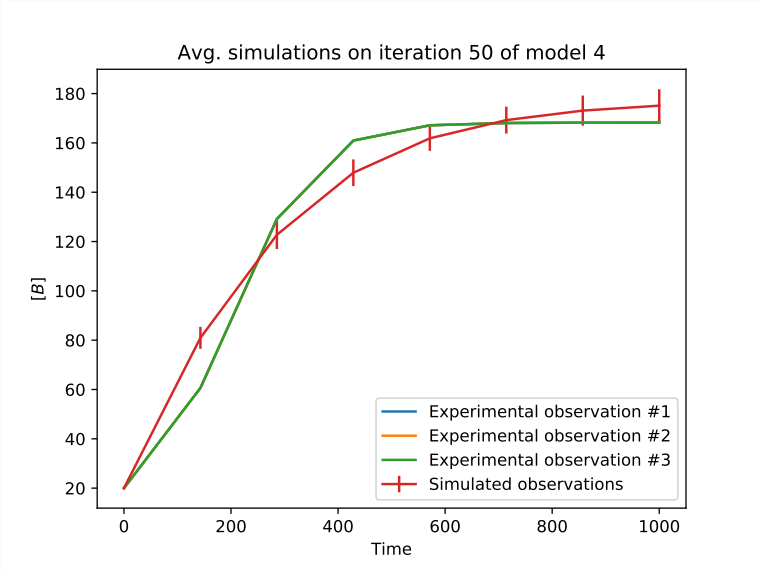




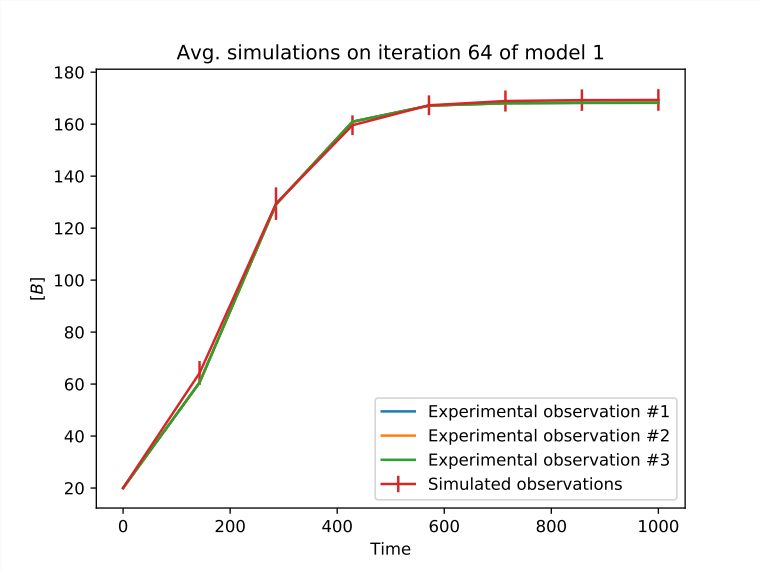
Results on ABC-SysBio

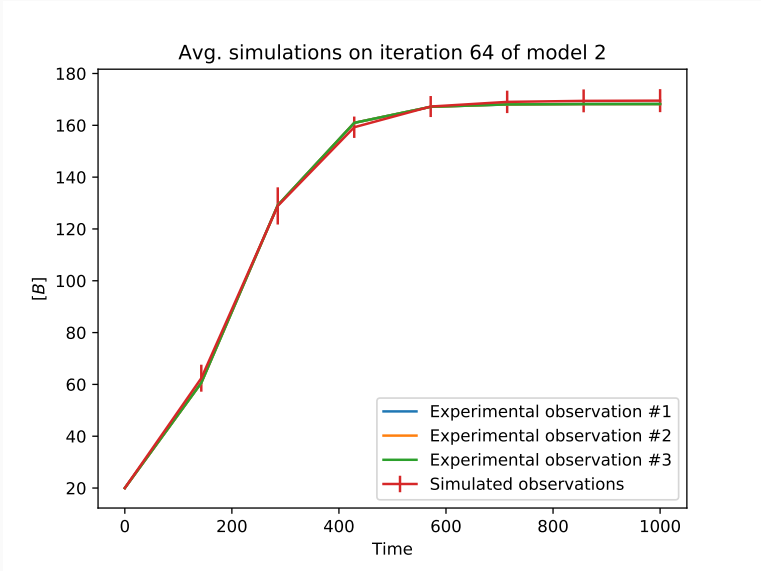






Results on ABC-SysBio





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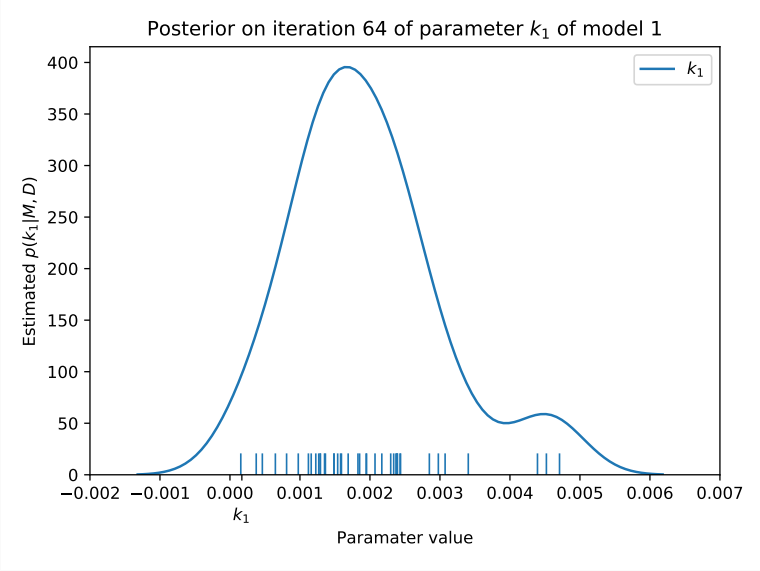
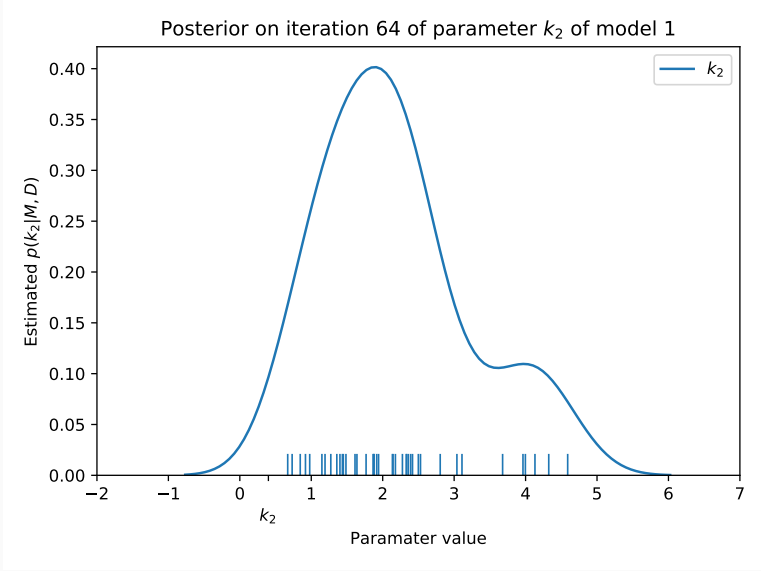
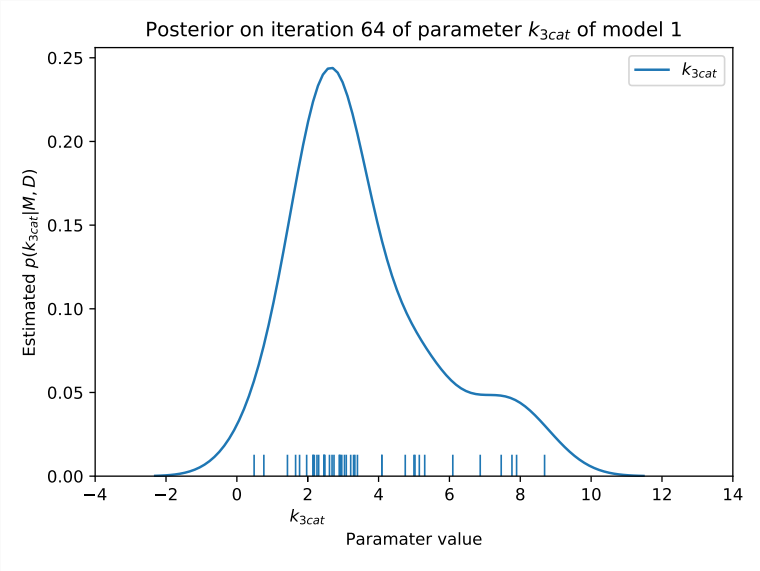
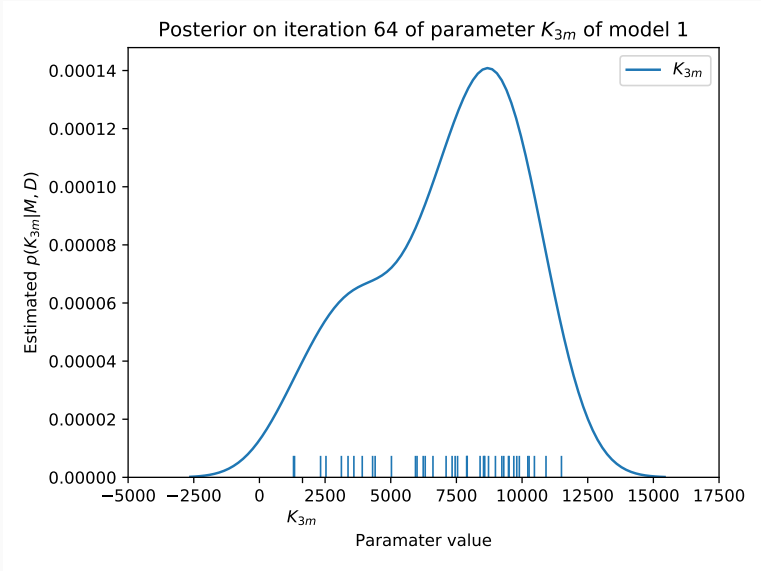






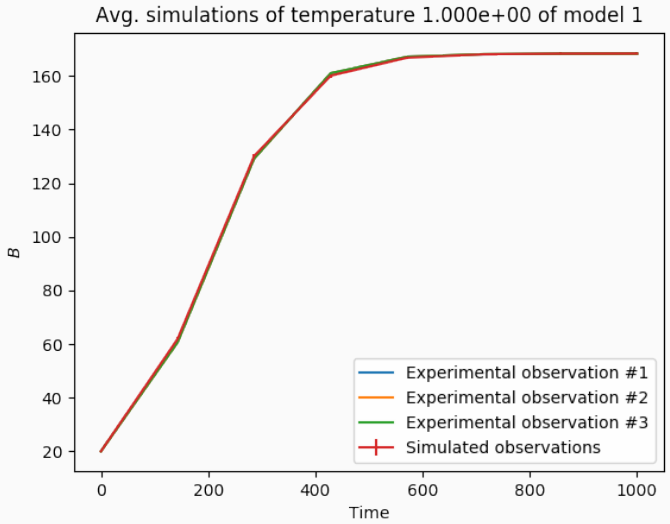


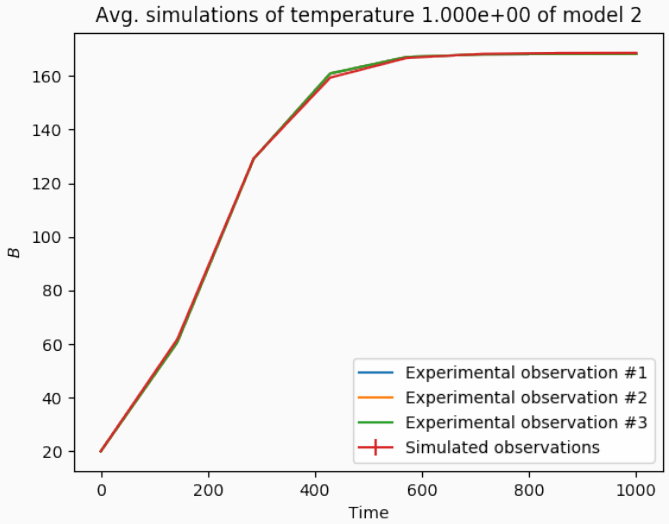
Results on SigNetMS

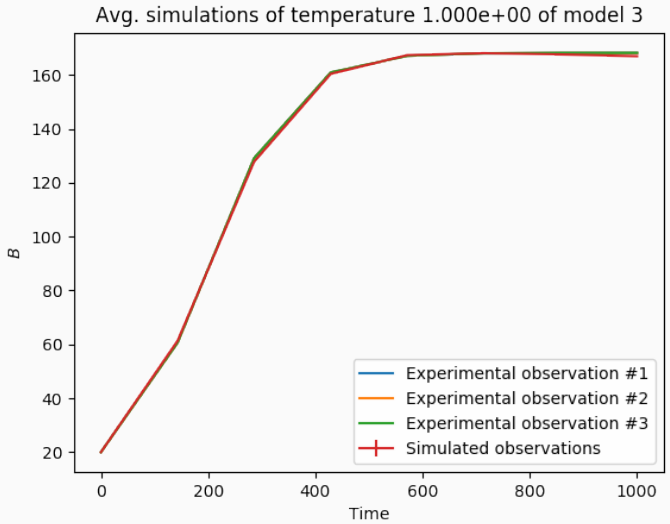
SigNetMS returned the following ranking of models:

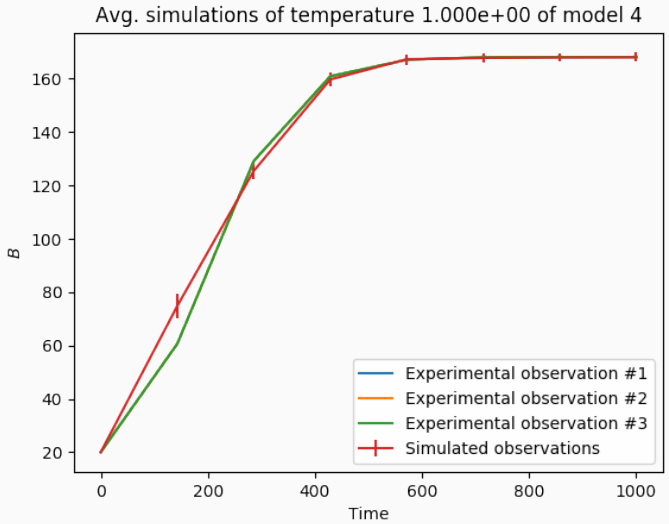
$$2 > 1 > 3 > 4$$

Results on SigNetMS

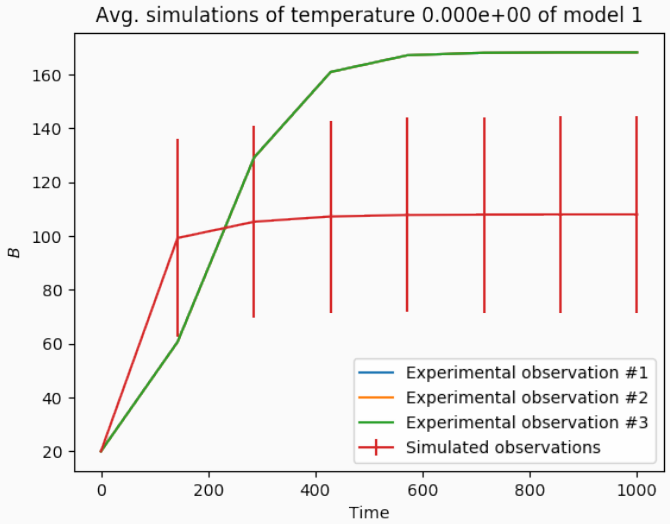


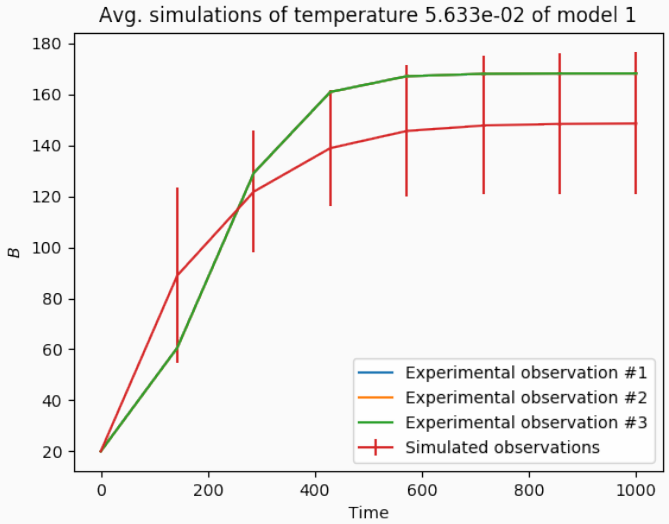


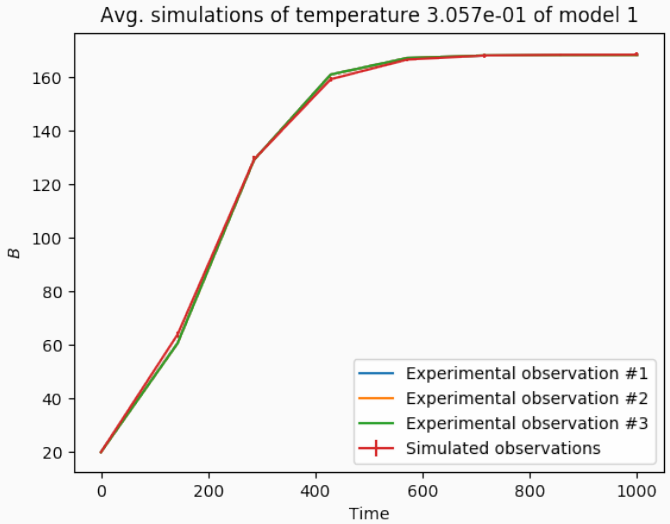


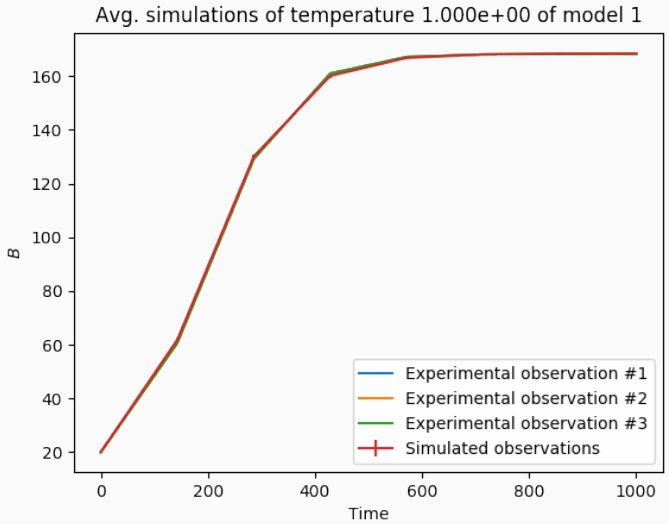


Results on SigNetMS

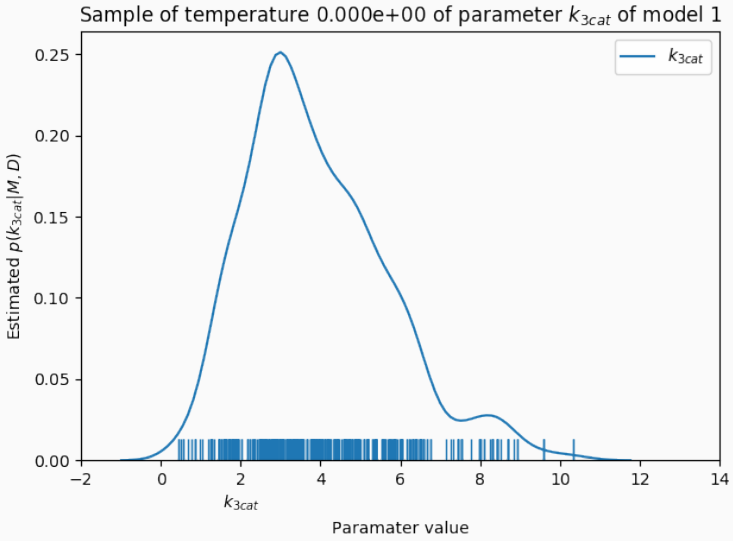


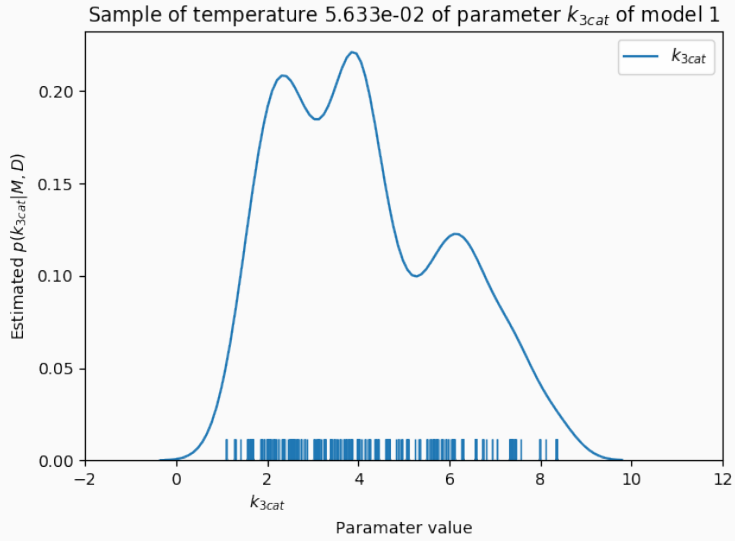


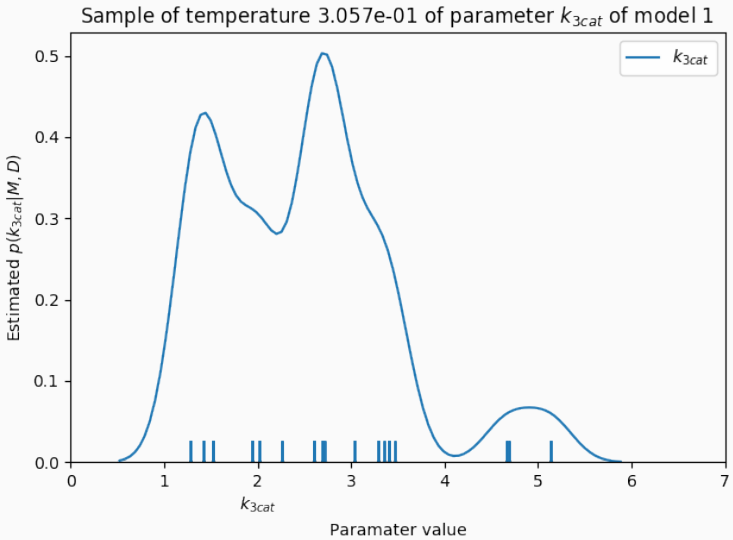


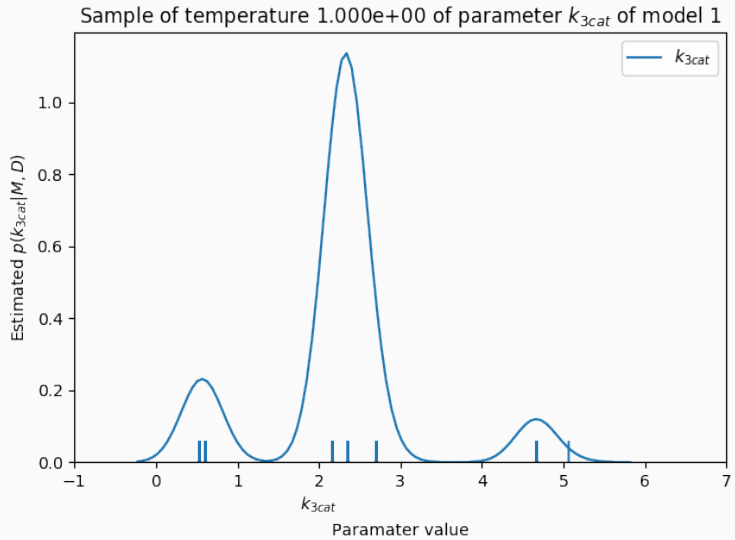


Results on SigNetMS









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

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

Thank you!