Identification of cell signaling pathways based on biochemical reaction kinetics repositories

Student: Gustavo Estrela

Advisor: Marcelo da Silva Reis (Butantan Institute)

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Instituto de Matemática e Estatística
Centro de Toxinas, Resposta-imune e Sinalização Celular (CeTICS)
Laboratório Especial de Ciclo Celular, Instituto Butantan

Introduction

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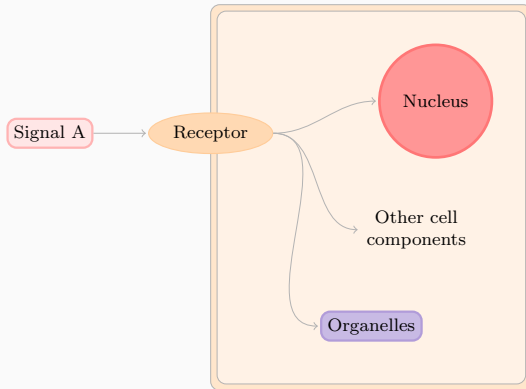
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Understanding the functioning of cell signaling is important in many biological areas.
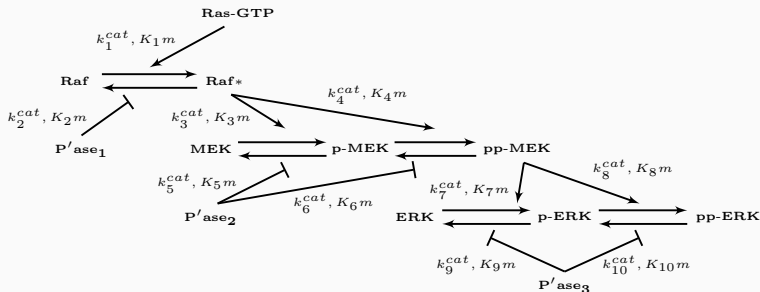
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We call the path of a signal a cell signaling pathway.

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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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.

Identification of Cell Signaling Pathways

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On her work, the problem of identification of cell signaling pathways is treated as a feature selection problem.

Feature Selection for Identification of Signaling Pathways

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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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Results of Wu's Methodology

Lulu Wu tested her methodology by trying to recreate models given a cut of the original model. However, the methodology worked satisfactorily only when the cut was similar to the original model.

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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.

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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- 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:

$$A \xrightarrow{k_1} B$$

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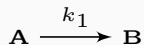
has rate of:

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Kinetic Modeling of Second Order Iteration

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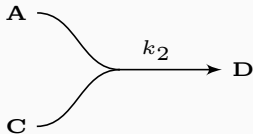
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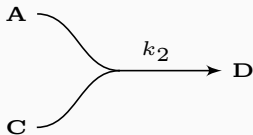
has rate of:

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

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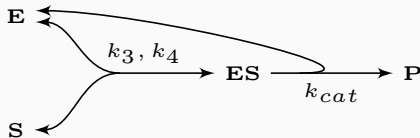
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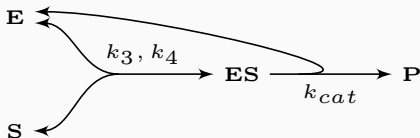
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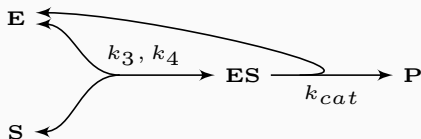
Can be divided in two first order reactions plus a second order reaction. However, with the appropriate assumptions, it is possible to use a Michaelis-Menten simplification of this reaction.

Michaelis-Menten Kinetics

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

$$\mathbf{S} \xrightarrow[\quad]{} \mathbf{P}$$

with

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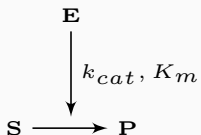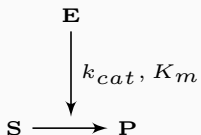
and it has rate of:

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

Kinetics of a System of Reactions

Suppose we want to model the kinetics of A on these reactions:
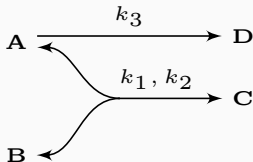
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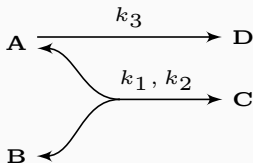
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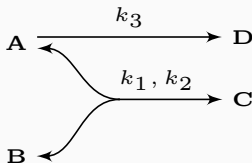
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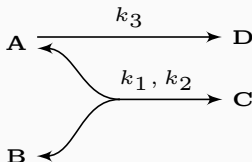
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- $A + B \longrightarrow C$, with rate $k_1[A][B]$,
- $C \longrightarrow A + B$, with rate $k_2[C]$,
- $A \longrightarrow D$, with rate $k_3[A]$.

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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:

$$p(D|M) = \int_{\Theta} p(D|M, \theta) p(\theta|M) d\theta$$

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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:

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

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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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The Thermodynamic Integral

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

The sampling of the power-posteriors are generated using Metropolis-Hastings algorithms in three steps.

Sampling from Power-posteriors

The sampling of the power-posteriors are generated using Metropolis-Hastings algorithms in three steps. In all of the steps, the proposal distribution used is multivariate lognormal.

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- if the acceptance rate is high, then increase the variance of the jump;
- if the acceptance rate is low, then decrease the variance of the jump.

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.

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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4. Repeat until some iteration limit.

Approximate Bayesian Computation

The result of the algorithm is a sample of the distribution

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

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ABC Sequential Monte Carlo

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

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

Development of SigNetMS

The SigNetMS Software

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.

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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;

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Posterior of temp. 3.06e-01 of parameter k_1 of model 1
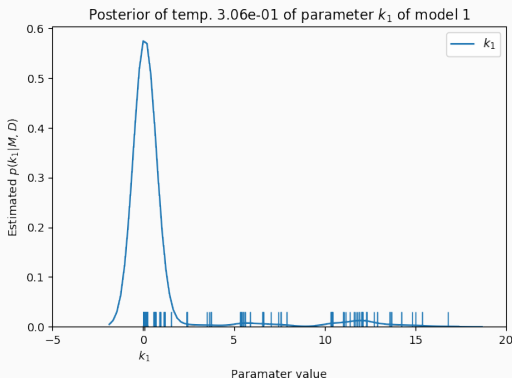
Fast integration and parameter sampling

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.

Our first implementation was not very efficient

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

Our first implementation was not very efficient

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

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Experiments and Results
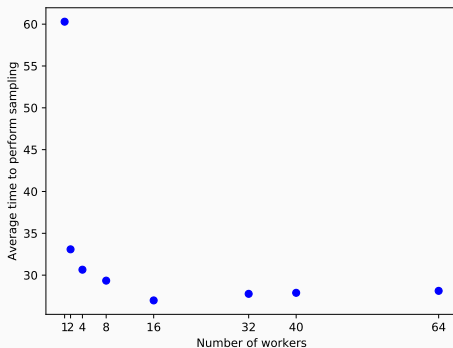
We prepared two experiments in this work:

Experiments and Results

We prepared two experiments in this work:

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

Comparison between ABC-SySBio and SigNetMS

ABC-SysBio and SigNetMS use different Bayesian approaches for model selection.

Chossing a software for model selection

ABC-SysBio and SigNetMS use different Bayesian approaches for model selection. The first creates an estimate of $p(M|D)$,

Chossing a software for model selection

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

Experiment description

To compare both software we ran two experiments based on the same procedure:

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

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

The instance
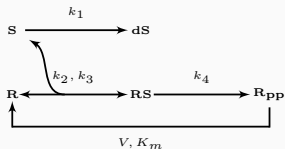
The "correct" model
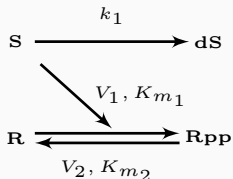
The simplification model
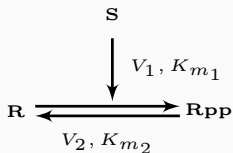
The incorrect model
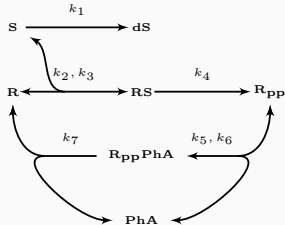
The generalization model
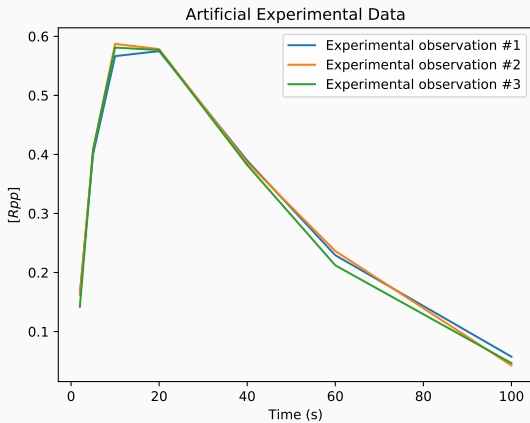
Artificial Experimental Data

Results on ABC-SysBio

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
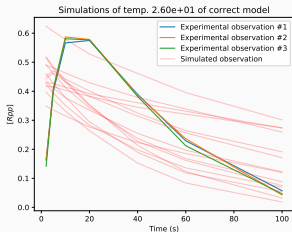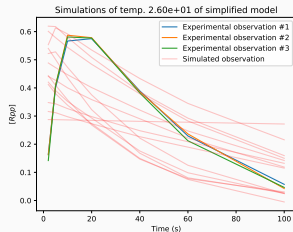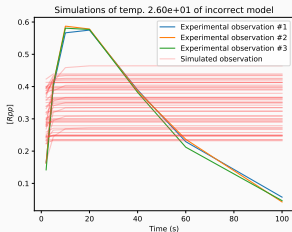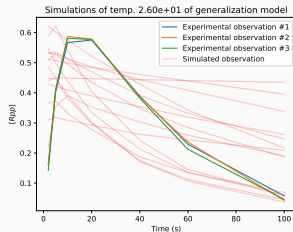
correct model

simplified model

incorrect model

generalization model

Results on SigNetMS

The ranking returned by SigNetMS on the first experiment is:

1. correct model

The ranking returned by SigNetMS on the first experiment is:

1. correct model
2. simplification model

The ranking returned by SigNetMS on the first experiment is:

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

The ranking returned by SigNetMS on the first experiment is:

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

correct model

simplified model

incorrect model

generalization model

Simulations of beta = 0.00e+00 of correct model

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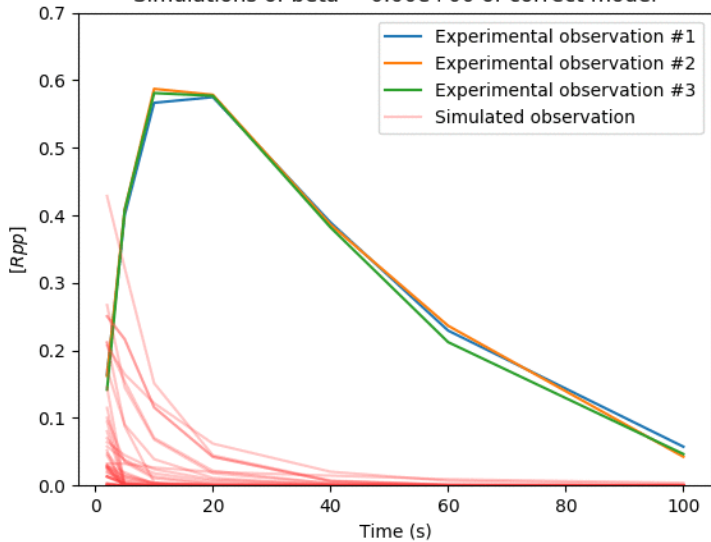
Simulations of beta = 4.32e-07 of correct model
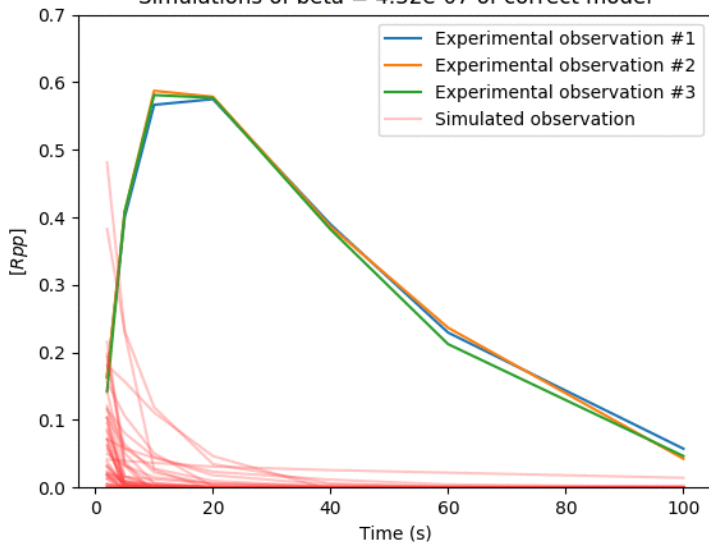
Simulations of beta = 6.92e-06 of correct model
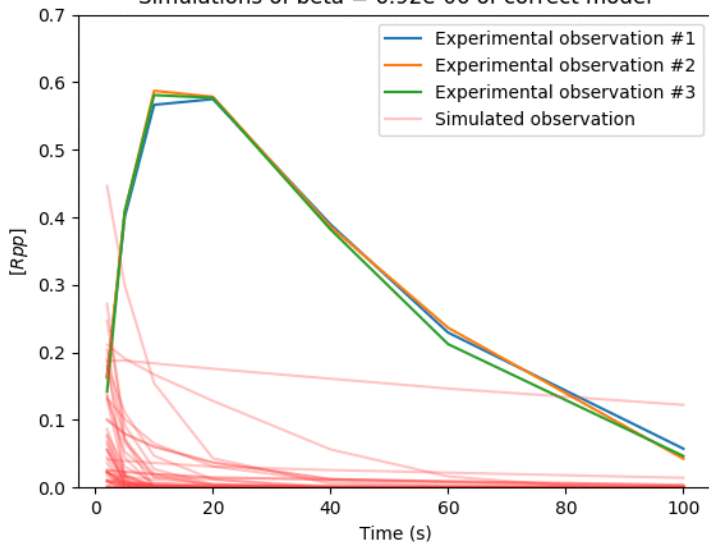
Simulations of beta = 3.50e-05 of correct model
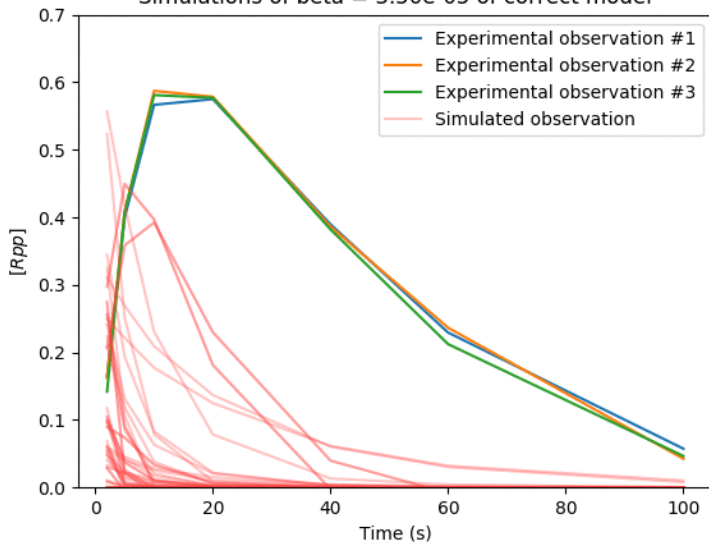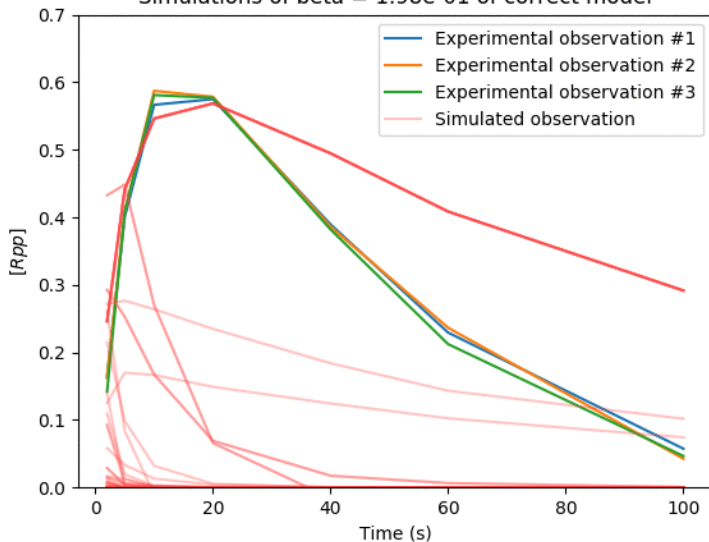
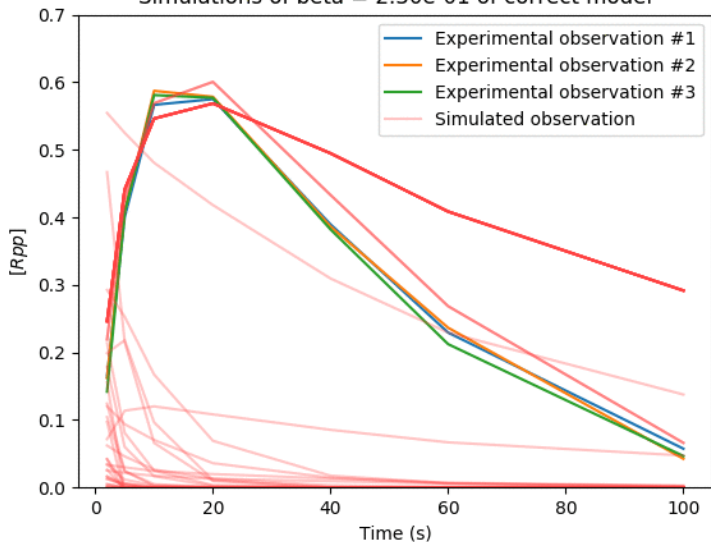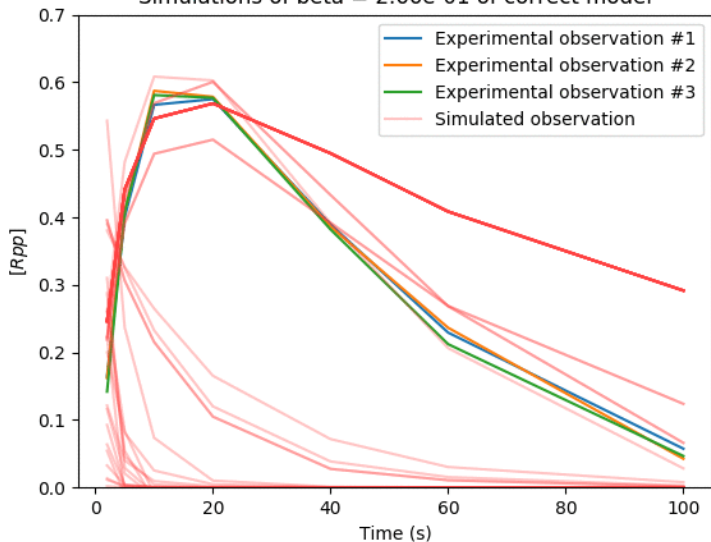Simulations of beta = 1.11e-04 of correct model
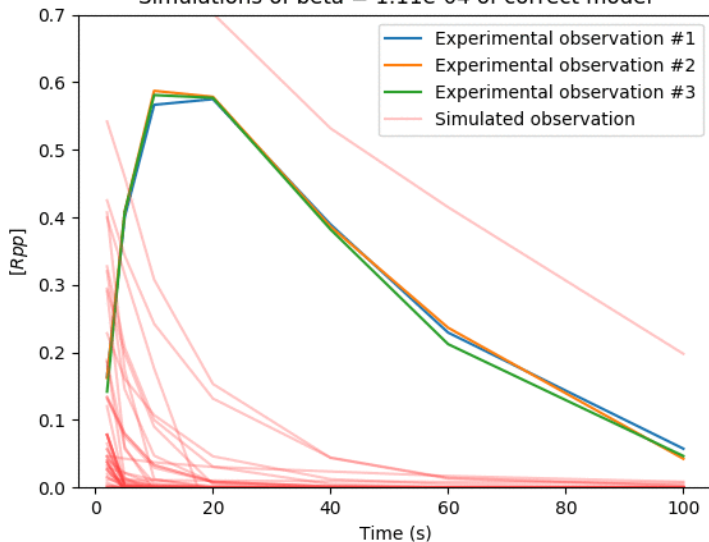
Simulations of beta = 2.70e-04 of correct model
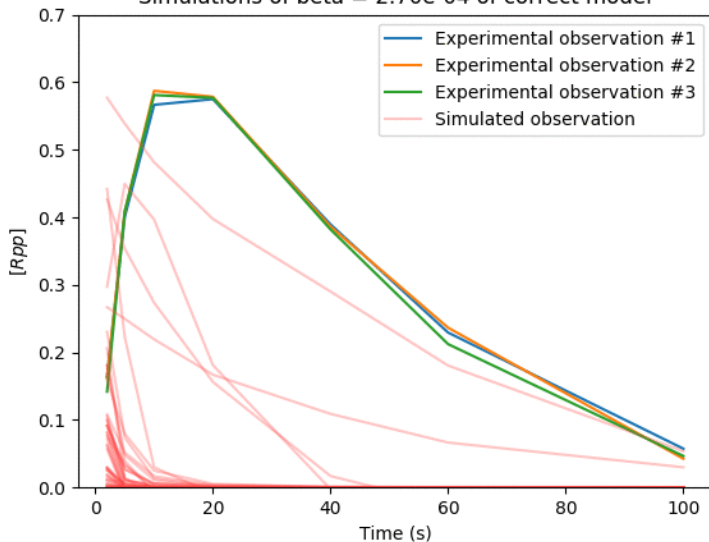
Simulations of beta = 5.60e-04 of correct model
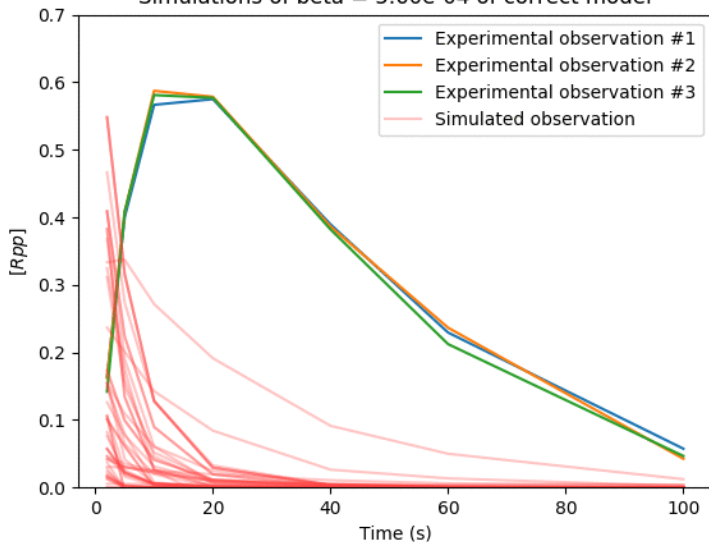
Simulations of beta = 1.04e-03 of correct model
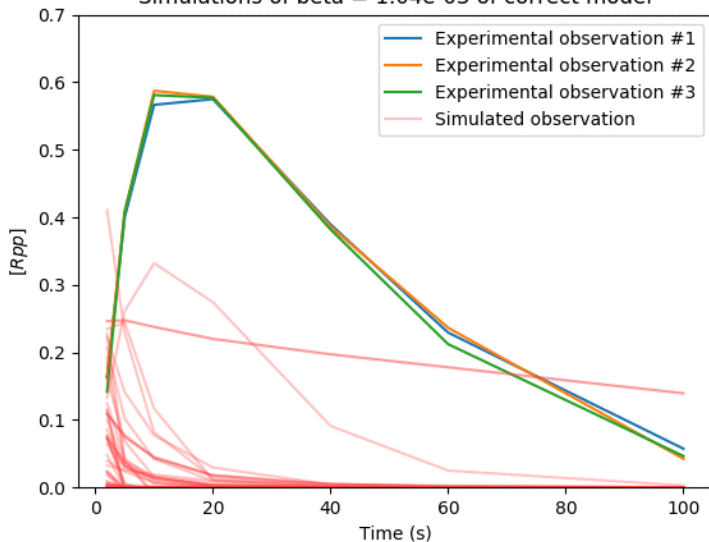
Simulations of beta = 1.77e-03 of correct model
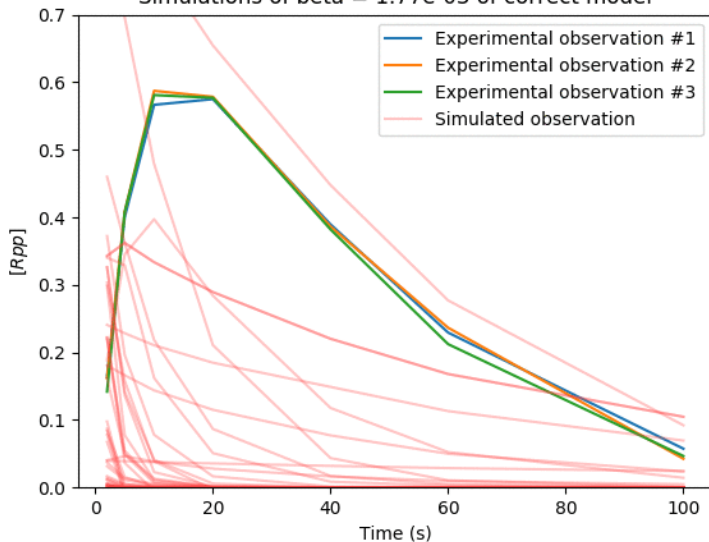
Simulations of beta = 2.84e-03 of correct model
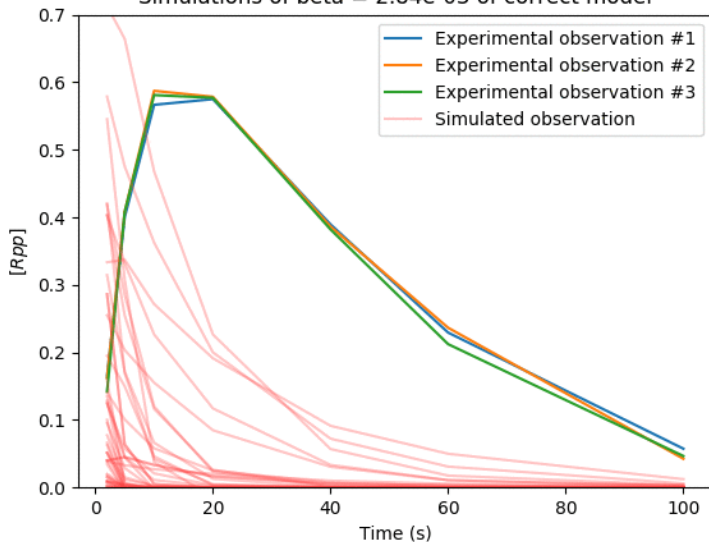
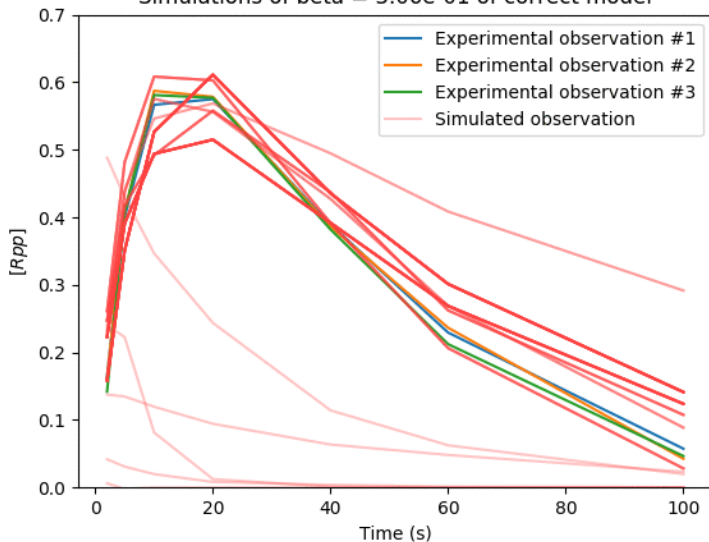Simulations of beta = 4.32e-03 of correct model
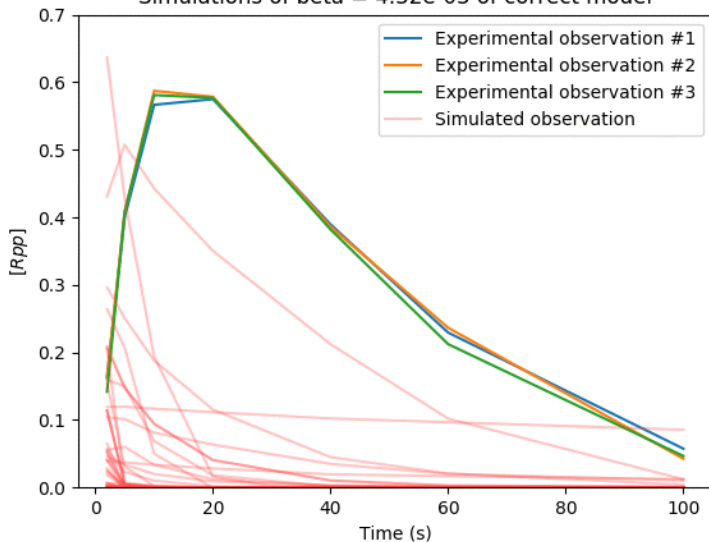
Simulations of beta = 6.33e-03 of correct model
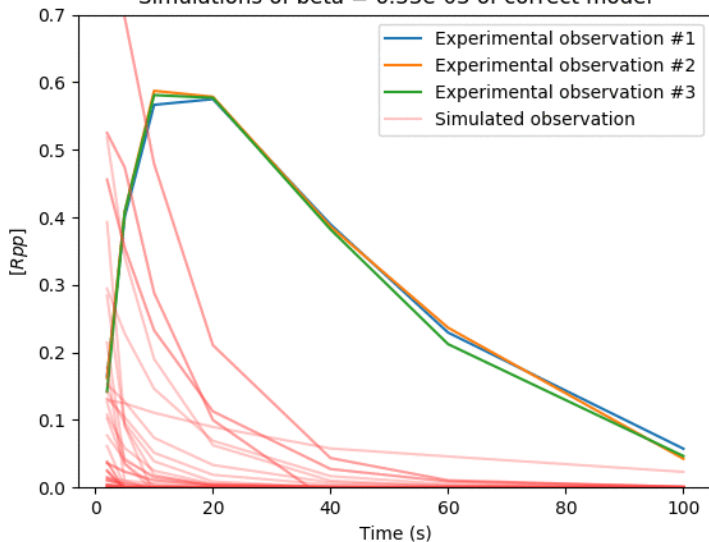
Simulations of beta = 8.96e-03 of correct model
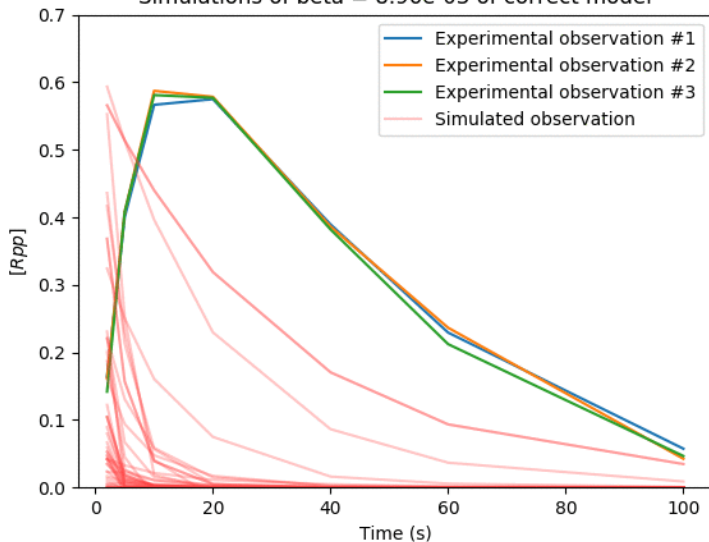
Simulations of beta = 1.23e-02 of correct model
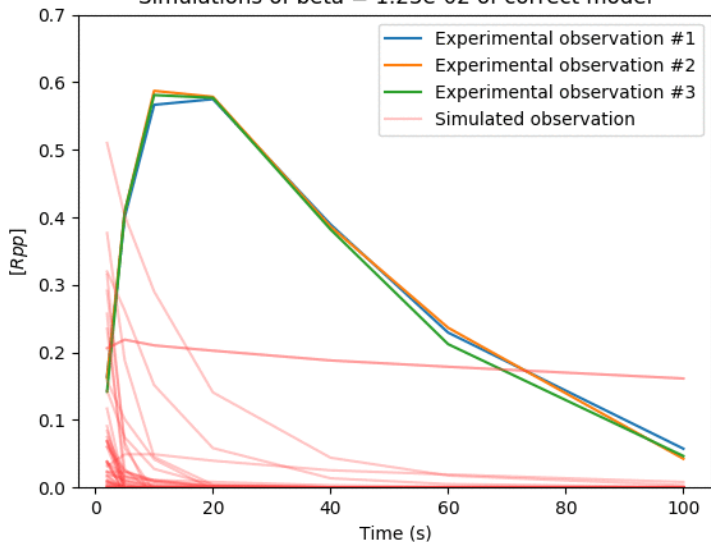
Simulations of beta = 1.66e-02 of correct model
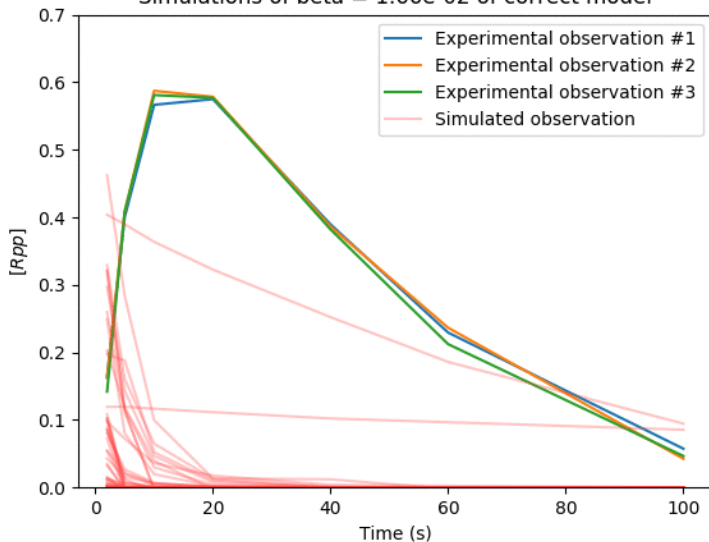
Simulations of beta = 2.19e-02 of correct model
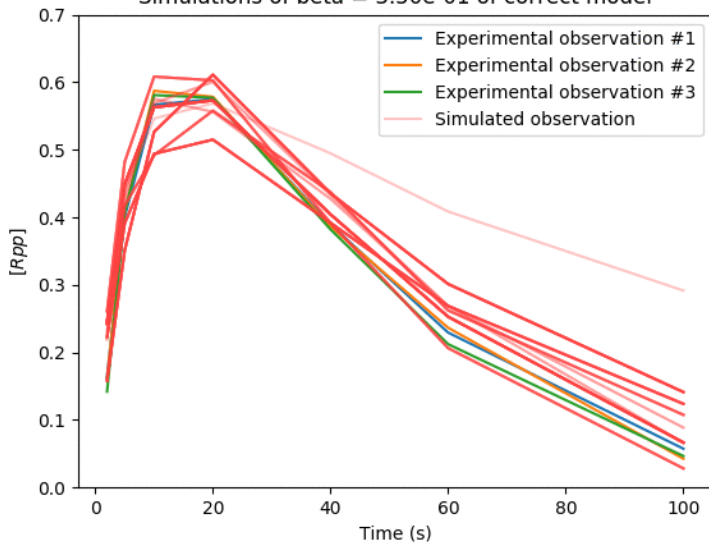
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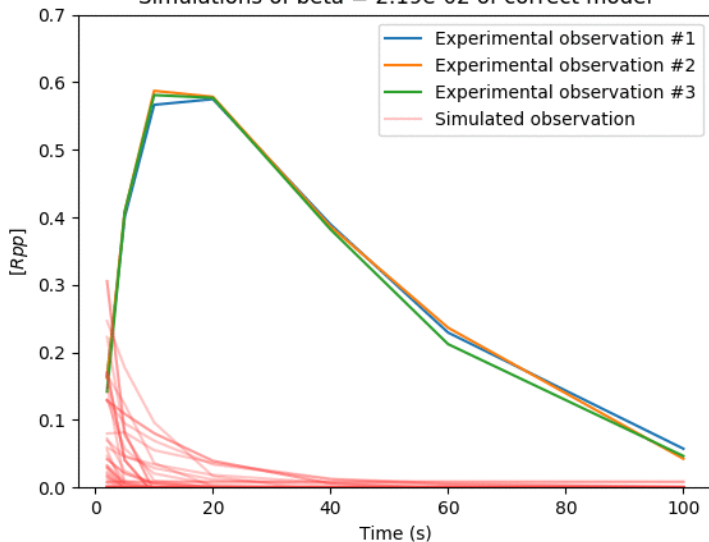
Simulations of beta = 2.83e-02 of correct model
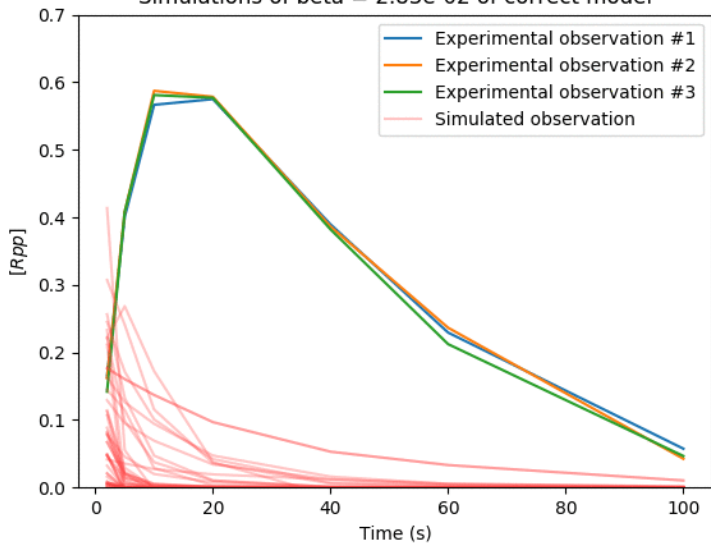
Simulations of beta = 3.61e-02 of correct model
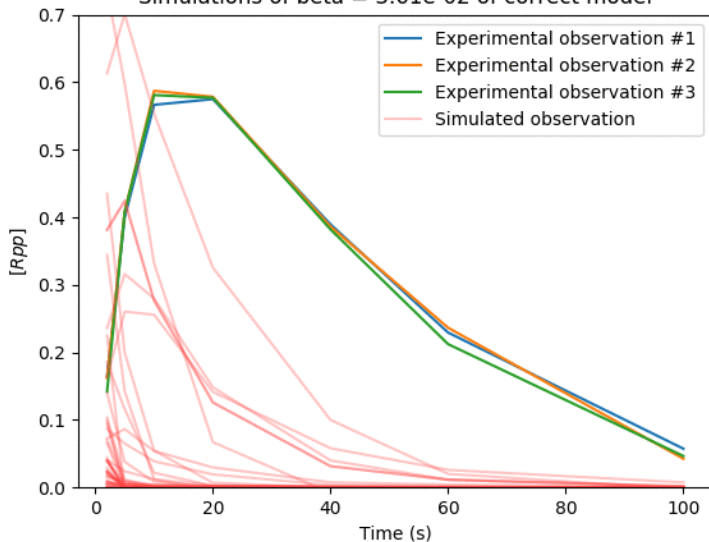
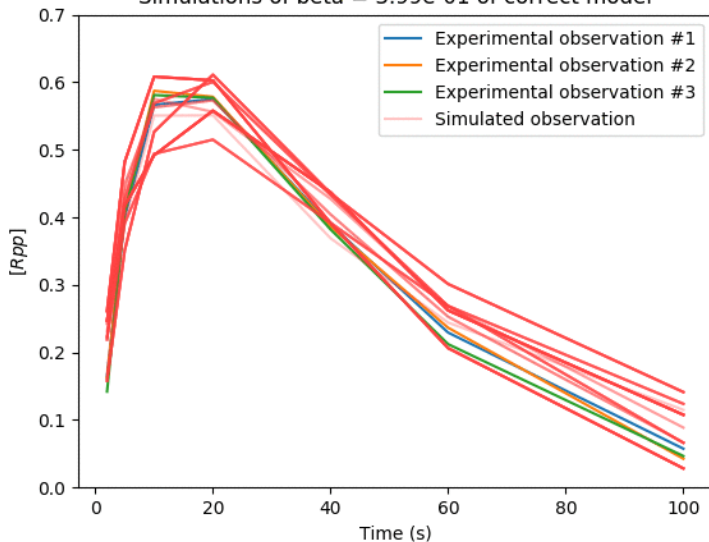Simulations of beta = 4.54e-02 of correct model
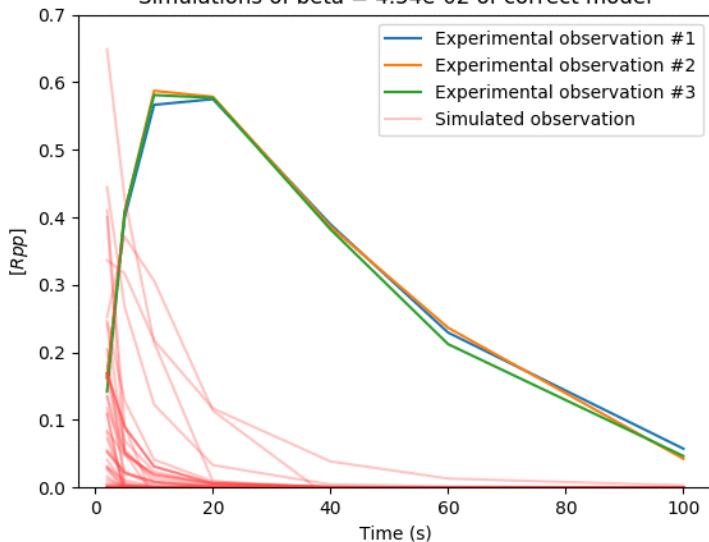
Simulations of beta = 5.63e-02 of correct model
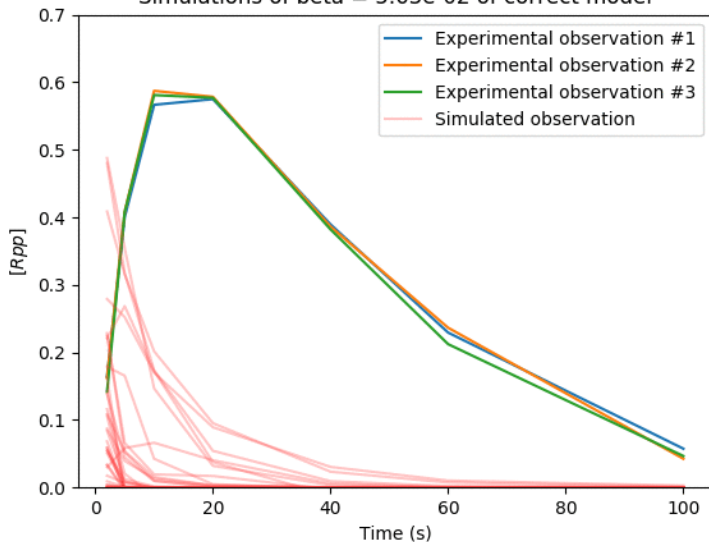
Simulations of beta = 6.92e-02 of correct model
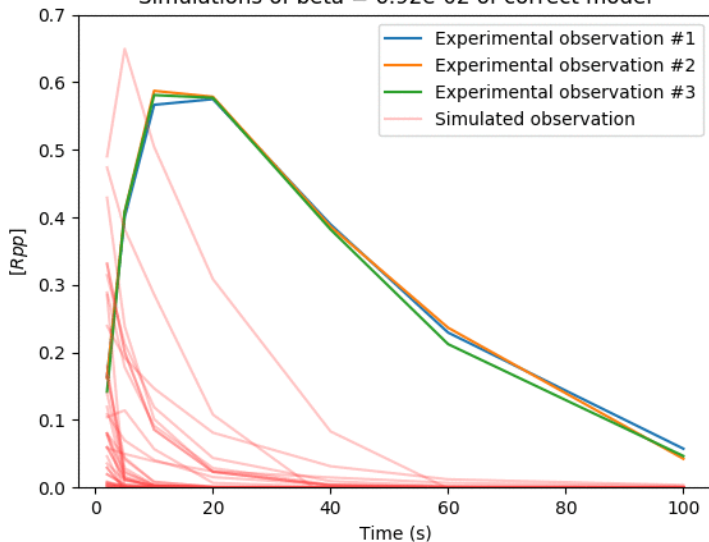
Simulations of beta = 8.41e-02 of correct model
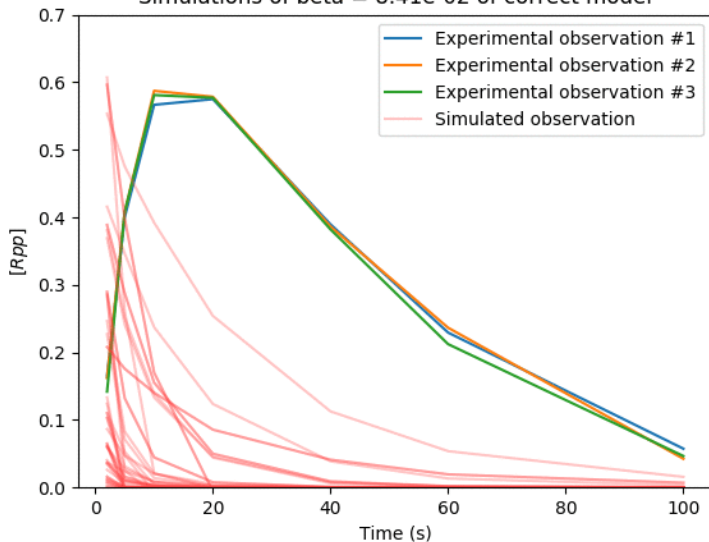
Simulations of beta = 1.01e-01 of correct model

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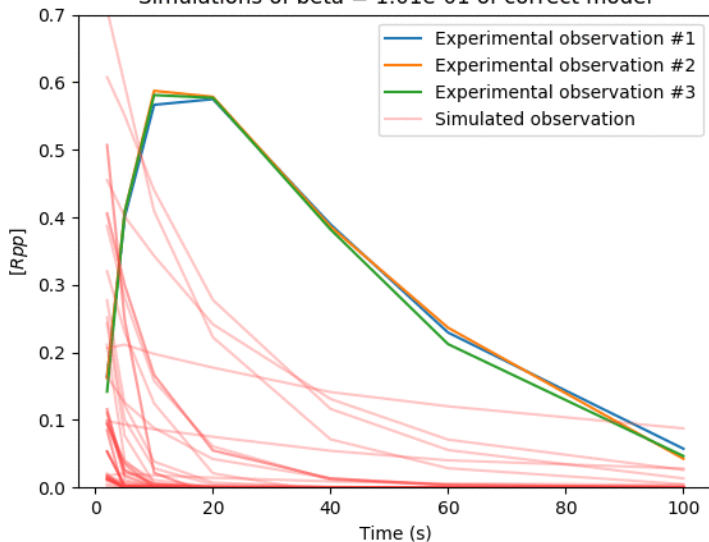
Simulations of beta = 1.21e-01 of correct model
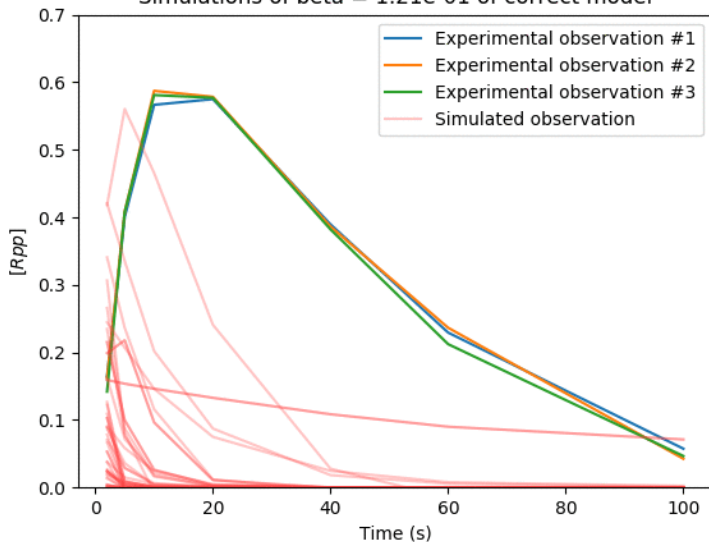
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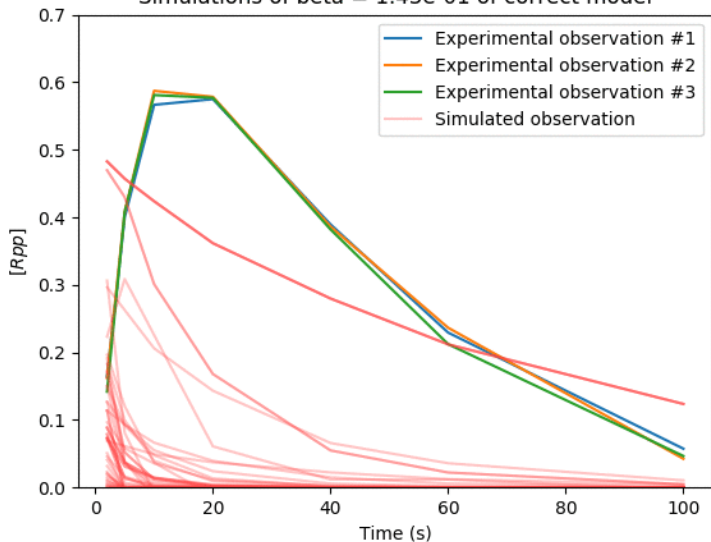
Simulations of beta = 1.69e-01 of correct model

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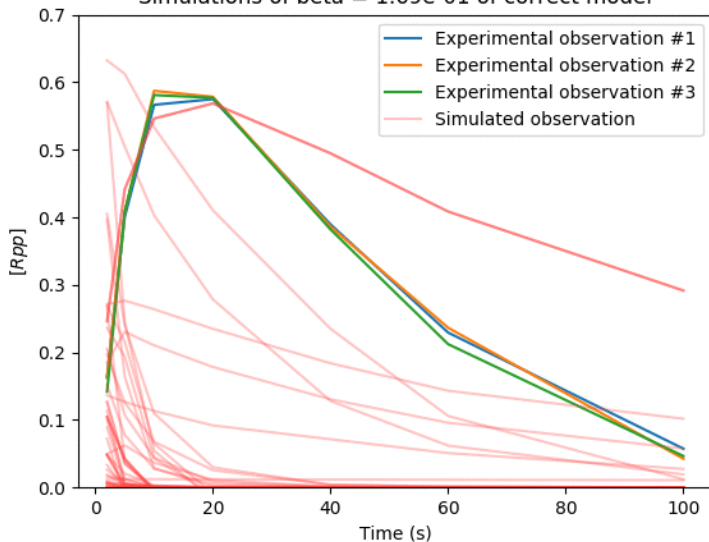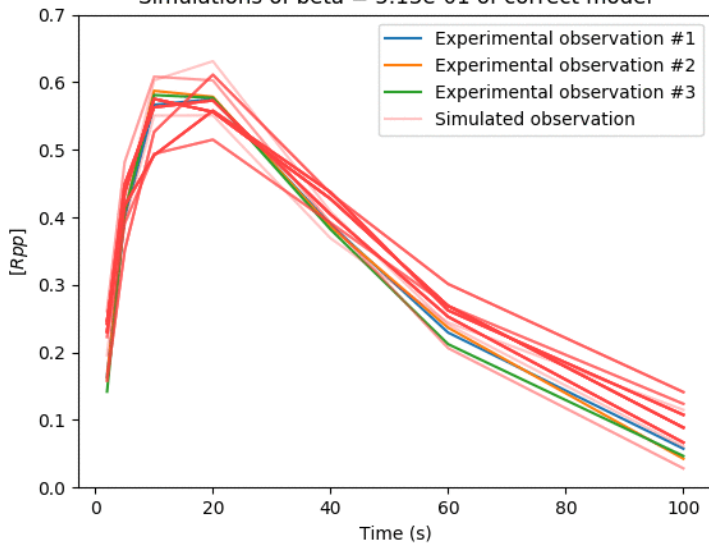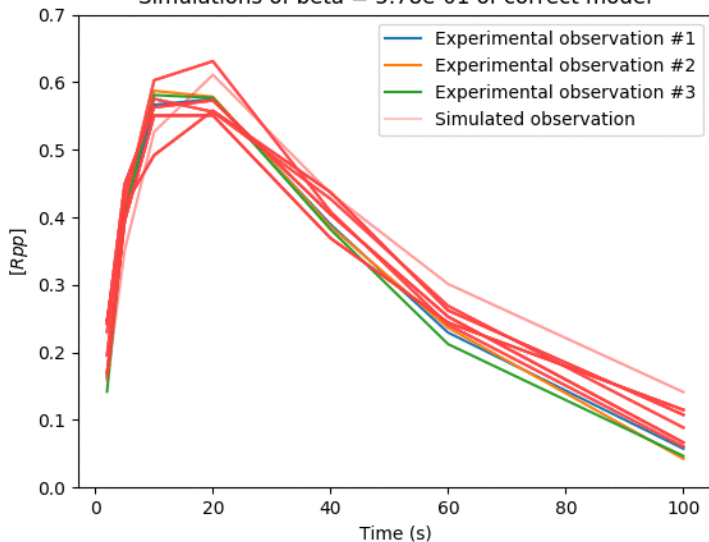
Simulations of beta = 1.98e-01 of correct model

Simulations of beta = 2.30e-01 of correct model

Simulations of beta = 2.66e-01 of correct model

Simulations of beta = 3.06e-01 of correct model

Simulations of beta = 3.50e-01 of correct model

Simulations of beta = 3.99e-01 of correct model
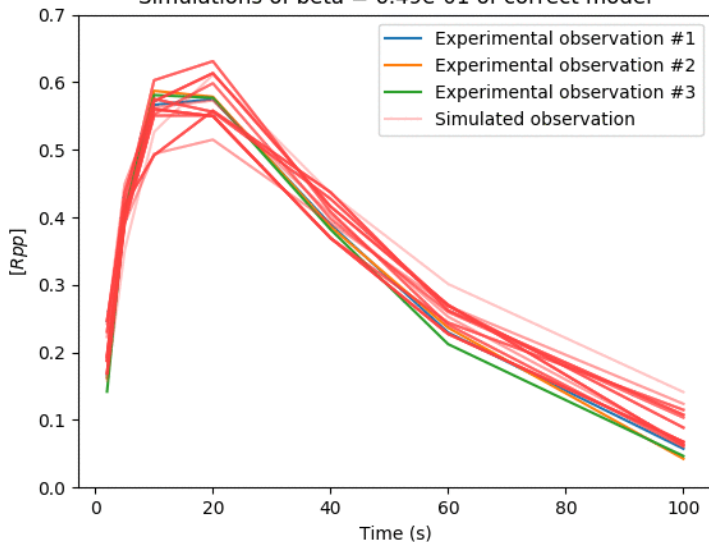
Simulations of beta = 4.53e-01 of correct model

Legend:
- Experimental observation #1
- Experimental observation #2
- Experimental observation #3
- Simulated observation

X-axis: Time (s)
Y-axis: $[R_{pp}]$
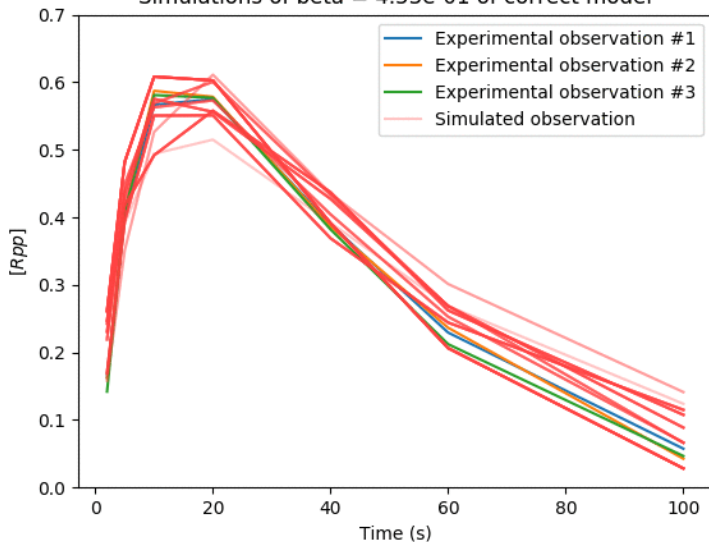
Simulations of beta = 5.13e-01 of correct model

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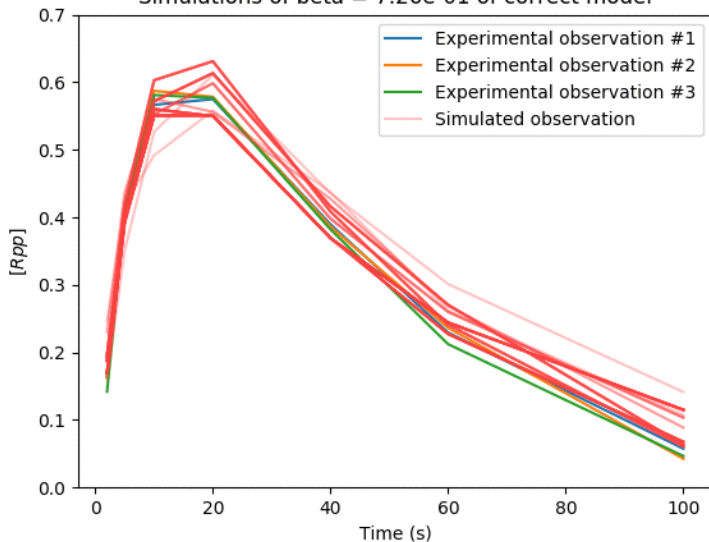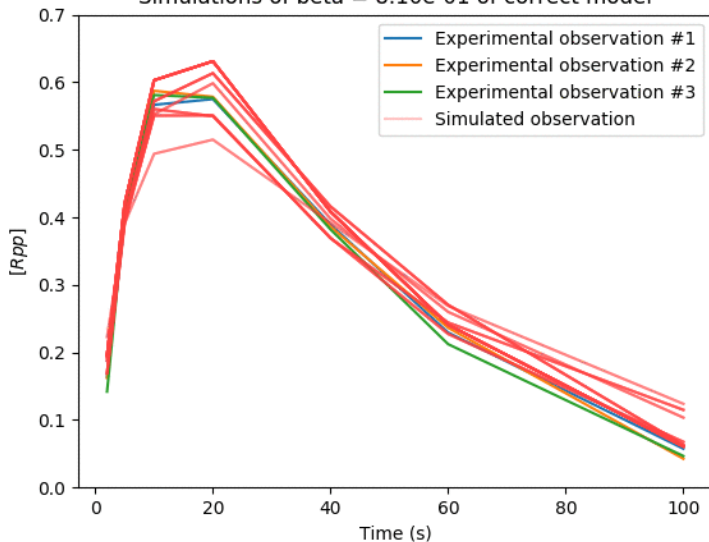
Simulations of beta = 5.78e-01 of correct model
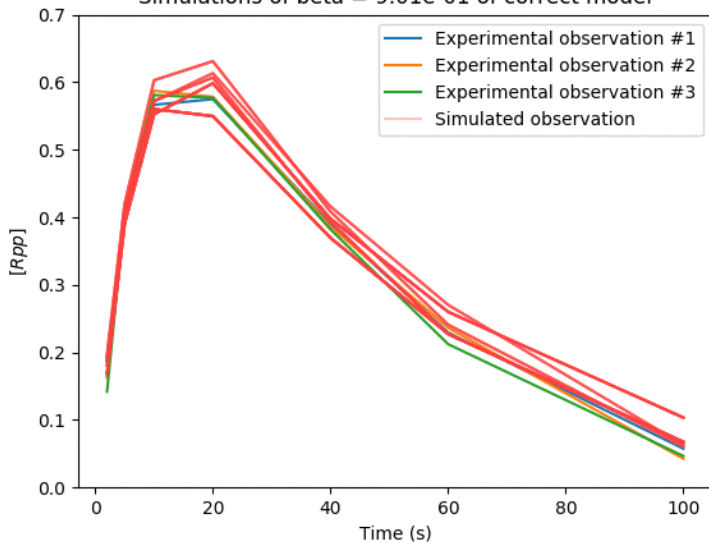
Simulations of beta = 6.49e-01 of correct model
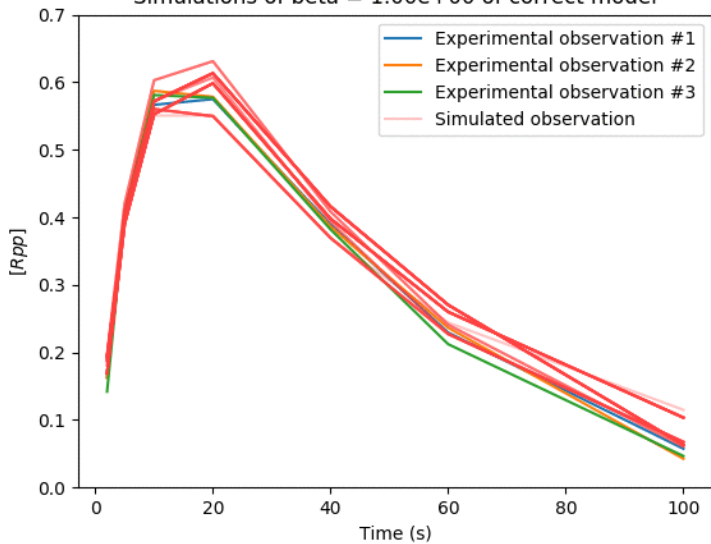
Simulations of beta = 7.26e-01 of correct model

Simulations of beta = 8.10e-01 of correct model

Simulations of beta = 9.01e-01 of correct model

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Simulations of beta = 1.00e+00 of 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.

We proposed a Ras switch pathway to experiment on.

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The model selection instance

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

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

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

The set of features of our experiment

The set of features of our experiment

Finding a solution

Results of the search

Results of the search

Results of the search

Results of the search

Results of the search

Conclusions

Thank you!