

SigNetSim

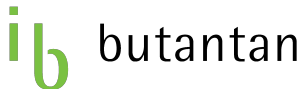
A web-based framework for designing kinetic models of molecular signaling networks

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Introduction

› Instituto Butantan

- › Biomedical center founded in 1901
- › Research and production center (anti-venoms, vaccines)
- › Large collection of snakes, spiders, scorpions, ...
- › Chosen by the OMS as a center to develop vaccines for Zika



Introduction



- › Need for a web tool
 - › Easy to use for biologist/students
 - › Able to do math
 - › Use a parallel simulated annealing algorithm
 - › Able to do model reduction
 - › Something to do waiting for experimental data

Introduction



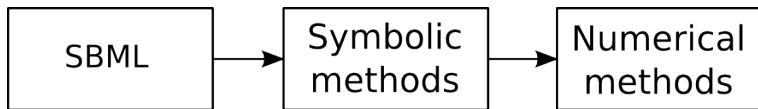
- › Structure

The SigNetSim framework is divided into two main components :

- › libSigNetSim, the core library
- › SigNetSim, the web interface

Both are coded in Python 2.7, with some part of the library in C

› Pipeline

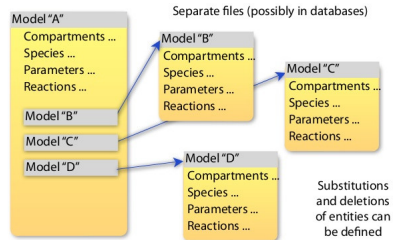


- › Sbm1 Model is read
- › Symbolic math model is built (SymPy)
- › Math is written as C files

› SBML Compatibility



- › Compatible with SBML version up to L3V1 (except CSymbolDelay)
- › Also support the Hierarchical Model Composition package (comp)



› Simulation

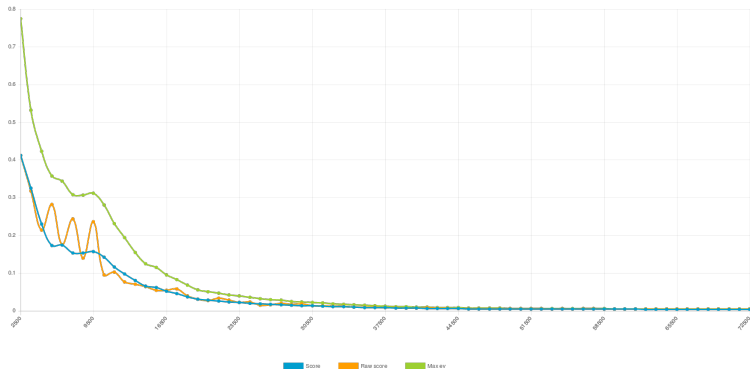
The integrations are performed using C-generated code, which can be executed in parallel.

To perform numerical integration for systems of differential equations (ODEs or DAEs), libSigNetSim uses the Sundials library (CVODE or IDA).

Before building the C code, the model is reduced to minimize the computational resources.

› Optimization

To perform model fitting, libSigNetSim uses parallel simulated annealing [1].



[1] Chu, K. W., Deng, Y., Reinitz, J. (1999). Parallel simulated annealing by mixing of states. Journal of Computational Physics, 148(2), 646-662.

› Analysis

$$\frac{d}{dt}E(t) = -E(t) \cdot S(t) \cdot k_f + ES(t) \cdot k_r + ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}ES(t) = E(t) \cdot S(t) \cdot k_f - ES(t) \cdot k_r - ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}P(t) = ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}S(t) = -E(t) \cdot S(t) \cdot k_f + ES(t) \cdot k_r$$

› Analysis

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$$\frac{d}{dt}P(t) = ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}S(t) = -E(t) \cdot S(t) \cdot k_f + ES(t) \cdot k_r$$

⇒ Continuation techniques don't like that

› Analysis

$$\frac{d}{dt}E(t) = -E(t) \cdot S(t) \cdot k_f + ES(t) \cdot k_r + ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}ES(t) = E(t) \cdot S(t) \cdot k_f - ES(t) \cdot k_r - ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}P(t) = ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}S(t) = -E(t) \cdot S(t) \cdot k_f + ES(t) \cdot k_r$$

$$\Rightarrow E(t) + ES(t) = 1.0$$

$$\Rightarrow ES(t) + P(t) + S(t) = 15.0$$

› Analysis

$$\frac{d}{dt}ES(t) = k_f \cdot E(t) \cdot S(t) - ES(t) \cdot k_r - ES(t) \cdot k_{cat}$$

$$\frac{d}{dt}P(t) = ES(t) \cdot k_{cat}$$

$$E(t) = -ES(t) + 1.0$$

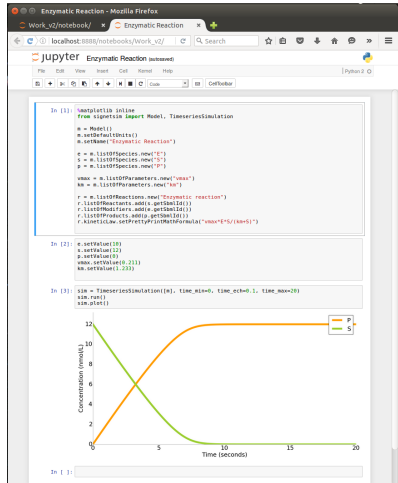
$$S(t) = -ES(t) - P(t) + 15.0$$

⇒ Cheaper to integrate, enable to use continuation techniques

⇒ All done automatically with symbolic math

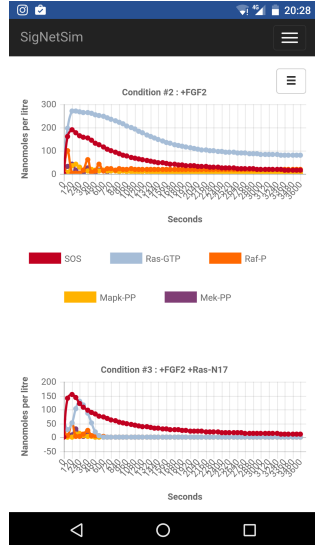
Jupyter

- Very basic compatibility with Jupyter
- Mainly to be able to play directly with the symbolic math model
- Still work in progress



- › Introduction

- › Using Django framework
- › Bootstrap as a front-end
- › Chart.js, MathJax, MPLD3, ...
- › Compatible



The screenshot displays the SigNetSim application interface. The top navigation bar includes tabs for 'SigNetSim', 'Models', 'Data', 'Edition', 'Simulation', 'Fitting', and 'Analysis'. The left sidebar contains a 'Selected model' dropdown set to 'Ras model' and a list of model components: Overview, Species, Parameters, Reactions, Compartments, Rules, Events, Submodels, and Units. The main workspace is titled 'Reactions' and lists several chemical reactions under the 'Description' section, such as $\text{SOS} + \text{Ras-GDP} \leftrightarrow \text{SOS-Ras-GDP}$ and $\text{Ras-GTP} + \text{GAP} \rightarrow \text{Ras-GDP} + \text{GAP}$. A 'Create new reaction' button is located at the bottom of this list. An 'Edit reaction' dialog box is open in the foreground, featuring four tabs: 'Summary' (selected), 'Species', 'Kinetic law', and 'Annotation'. The 'Summary' tab shows the reaction $\text{Ras-GDP} + \text{SOS-Ras-GTP} \rightarrow \text{SOS-Ras-GTP} + \text{Ras-GTP}$. Below this, the 'Reaction name' field contains 'SOS-Ras-GTP controlled Ras activation'. The 'Reaction identifier' field contains 'sosrasgtp_ras_activation', which is marked with a green checkmark. At the bottom of the dialog are 'Cancel' and 'Save changes' buttons.

Edit reaction

Summary Species Kinetic law Annotation

Summary

Ras-GDP + SOS-Ras-GTP \rightarrow SOS-Ras-GTP + Ras-GTP

Reaction name

SOS-Ras-GTP controlled Ras activation

Reaction identifier

sosrasgtp_ras_activation ✓

Cancel Save changes

SigNetSim

Models

Data

Editing

Simulation

Fitting

Analysis

SOS-Ras-MAPK c...

labstol

Help

Logout

Selected model

SOS-Ras-MAPK with N17

Selected submodel

model_0 (Main model)

model_0 (Main model)

MSOS

mras

mmmapk

Flatten model

Parameters

Reactions







Compartments

Rules

Events











Submodels

Submodels

Name	Type	
SOS model	External	 
Ras model	External	 
MAPK model	External	 

Create new submodel

Substitutions

Description	Type	
MSOS :: SOS <- SOS	Replacement	 
mras :: SOS <- SOS	Replacement	 
MSOS :: Ras-GTP <- Ras-GTP	Replacement	 
mras :: Ras-GTP <- Ras-GTP	Replacement	 
mmmapk :: Ras-GTP <- Ras-GTP	Replacement	 

› Database

Very basic DB to store experimental data

- › Experiment : A list of conditions
- › Condition : A list of treatments associated to a list of observations

⇒ Treatments can be used to do multi-conditions simulations

⇒ Treatments and observations are used for model fitting

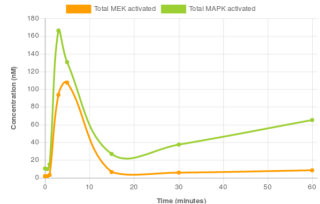
SigNetSim

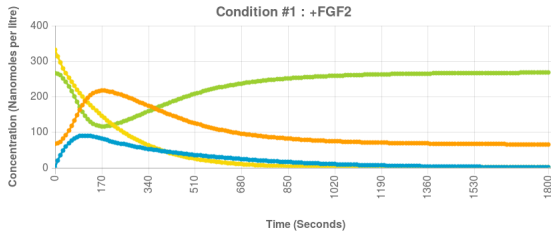
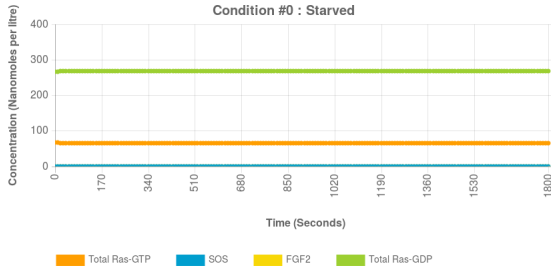
Treatments

Species	Time	Value
FGF2	0.0	333.0

+ New treatment

Observations





SigNetSim

Models

Data

Edition

Simulation

Fitting

Analysis

Michaelis reaction ▼

labestiol

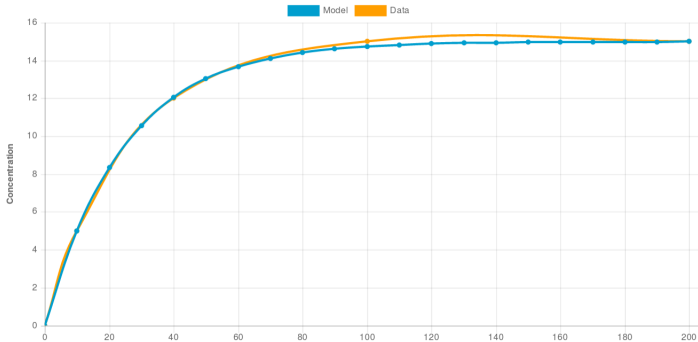
Help

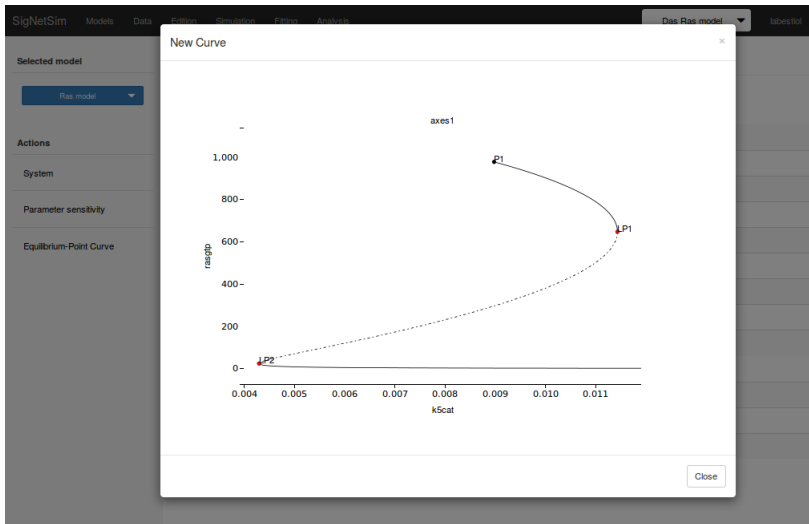
Logout

Fitting result

Experiment #0

Condition #0





Conclusion



- › Getting ready

- › "Core" nearly done

- › Soon to have a first version

- › The library and the web interface will be soon on GitHub

- › Paper should be submitted in the next months

Conclusion



- › Future work
 - › Performance improvements
 - › Annotations
 - › SED-ML
 - › Simple SBGN vizualization (SBGNViz ?)
 - › Distribution, Multi, Math ?

Conclusion

› Funding

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Conclusion

- › Live test version



cetics.butantan.gov.br/signetsim