Bioinformatics Advance Access published July 30, 2012

# A MATLAB toolbox for structural kinetic modeling

Dorothee Girbig [1,*] Joachim Selbig [1,2] and Sergio Grimbs [2]

[1]Max-Planck Institute for Molecular Plant Physiology, Potsdam, Germany
[2]Institute of Biochemistry and Biology, University of Potsdam, Potsdam, Germany

Associate Editor: Prof. Martin Bishop

**ABSTRACT**

**Summary:** Structural kinetic modeling (SKM) enables the analysis of dynamical properties of metabolic networks solely based on topological information and experimental data. Current SKM-based experiments are hampered by the time-intensive process of assigning model parameters and choosing appropriate sampling intervals for Monte-Carlo experiments. We introduce a toolbox for the automatic and efficient construction and evaluation of structural kinetic models (SK-models). Quantitative and qualitative analysis of network stability properties is performed in an automated manner. We illustrate the model building and analysis process in detailed example scripts that provide toolbox-implementations of previously published literature models.

**Availability:** The source code is freely available for download at http://bioinformatics.uni-potsdam.de/projects/skm.

**Contact:** girbig@mpimp-golm.mpg.de

## 1 INTRODUCTION

SKM enables the analysis of dynamical features of metabolic systems in steady states, without requiring the knowledge necessary for the construction of kinetic models, such as kinetic parameters and reaction rates. Instead, these properties are derived solely from topological information and experimentally measurable steady state data. In doing so, the SKM algorithm derives a 'parameterized' version of the system's Jacobian matrix, in which model parameters encode the partial derivatives of the reaction rates around the steady state (Steuer *et al.*, 2006). Once the Jacobian matrix is computed for a given set of parameters, the evaluation of its eigenvalues indicates whether the steady state is stable. Here, a simple normalization step enables the restriction of the parameter values to predefined sampling intervals (for example, $[0, 1]$ for classical enzyme kinetics). This enables the combination of SKM with a Monte-Carlo approach (Steuer *et al.*, 2006) in which large numbers of SK-models are created using randomly sampled parameters. The resulting Jacobian matrices can then be evaluated quantitatively (by counting the proportions of stable and unstable models) or qualitatively (by analyzing the conditions that lead to such stability or instability). Qualitative SKM-analysis can be performed by pairwise comparisons of the model parameters leading to stable or unstable states (Grimbs *et al.*, 2007) or by machine learning approaches that search for patterns in the parameter space (Girbig *et al.*, 2012).

*to whom correspondence should be addressed

The SKM-experiments presented so far used customized algorithms in which the SK-models had been constructed manually 'from scratch' for each pathway (Steuer *et al.*, 2006; Grimbs *et al.*, 2007; Steuer *et al.*, 2007; Reznik and Segrè, 2010). While this might be sufficient for small systems like in the mentioned examples, the construction of SK-models for larger systems, or even systems of genomic scale is not feasible manually. However its potential to be applied to large-scale systems is a major advantage of SKM compared to kinetic modeling. Because it does not rely on detailed kinetic knowledge, it is well-suited for the investigation of large metabolic systems for which only limited or uncertain information about the individual reaction mechanisms is available.

Here we present a MATLAB toolbox that enables the automated construction and evaluation of SK-models. Models can be constructed from a minimal input consisting only of the stoichiometric matrix $\mathbf{N}$, steady state concentrations $\mathbf{S}^0$ and the steady state fluxes $\mathbf{v}^0$, with the experimental data being obtained from metabolomics and isotope tracing experiments. Model parameters can be derived automatically based on the information in $\mathbf{N}$. The user can also assign additional model parameters (for example to describe regulatory interactions) or manually manipulate the suggested parameter positions and intervals.

We illustrate the model building and analysis process in example scripts which demonstrate the construction of previously published literature models (Steuer *et al.*, 2006; Girbig *et al.*, 2012) using the toolbox.

## 2 FEATURES

The key functionalities of the toolbox can be summarized as follows:

- SK-models can be constructed from a minimum required input which consists only of $\mathbf{N}$, $\mathbf{S}^0$ and $\mathbf{v}^0$.
- Information about the model components and their stoichiometries can be efficiently imported from SBML files.
- The program is flexible to modifications of the model parameters. This can be achieved by either manually modifying the automatically determined parameters, or by building parameter matrices 'from scratch'.
- MATLAB functions for the quantitative and qualitative analysis of the resulting models are provided.

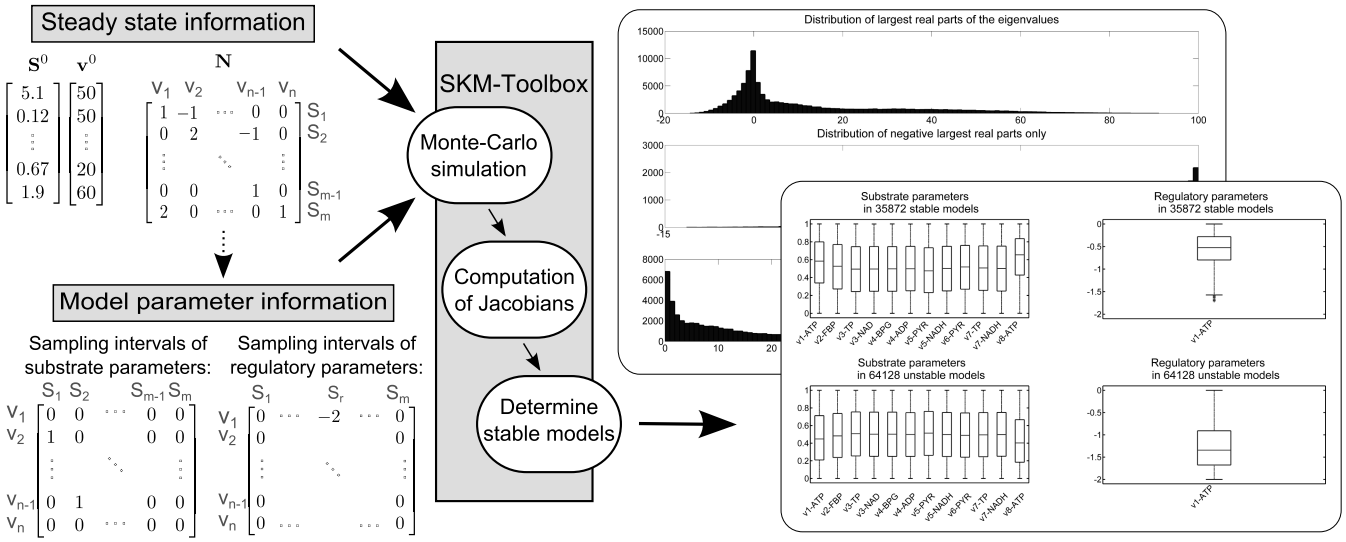


**Fig. 1.** SK-model building and evaluation using the SKM-toolbox. Required input arguments are the stoichiometric matrix $\mathbf{N}$, steady state concentrations $\mathbf{S}^0$, and the fluxes $\mathbf{v}^0$. Model parameters are assigned according to the information in $\mathbf{N}$. They can be manually adjusted (i.e. by adding allosteric regulators) before starting the Monte-Carlo-simulation. The resulting distributions of model parameters and eigenvalues for stable/unstable models are displayed automatically.

The most labor-intensive step in the construction of SK-models for Monte-Carlo experiments consists of choosing the model parameters' network positions, and assigning appropriate sampling intervals. The sampling intervals depend on the type of kinetic rate law assumed for the reactions. For example, the interval $[0, 1]$ serves for modeling enzyme-substrate interactions in enzymatic reactions while $[-n, 0]$ models the impact of an allosteric inhibitor with Hill coefficient $n$.

Internally, the toolbox uses a MATLAB `struct` object to store network positions of model parameters that describe different types of interactions. If not provided as an input argument for the toolbox, the `struct` will be automatically created based on the stoichiometric coefficients in $\mathbf{N}$. The toolbox also enables the generation of a template `struct` for manual modification by the user (for example by including regulatory interactions) prior to the start of the program.

After Monte-Carlo simulation, the eigenvalues of each Jacobian matrix, as well as an indicator of the stability of each underlying model are returned. This information can be further analyzed by additional toolbox functions, such as pairwise comparisons between stable and unstable models. It can also be converted into input for the decision tree algorithms `C4.5` or `C5.0` (Quinlan, 2012), or analyzed manually with respect to specific questions posed by the user. For instance, the example script for the simplified Glycolysis model of Steuer *et al.* (2006) demonstrates how to reproduce the results in the original publication with the toolbox. Using this system as an example, Figure 1 provides an overview of the model building and evaluation process.

## 3 AVAILABILITY AND IMPLEMENTATION

The SKM-toolbox was developed under MATLAB version 7.11 (release R2010b). The SBML import requires the freely available LibSBML package (Bornstein *et al.*, 2008).

## 4 SUMMARY

The proposed toolbox helps to overcome a major bottleneck of SKM-experiments, namely the time-intensive assignment of the model parameters. Furthermore, it provides a unifying framework for publishing and sharing SK-models. With the increasing availability of genome-scale reconstructions of metabolic networks, as well as the fast progress in experimental methods measuring concentrations and fluxes in these networks, our toolbox can assist in applying SKM to larger and more complex systems than attempted so far.

## ACKNOWLEDGEMENT

*Funding*: DG is supported by an International Max Planck Research School fellowship. JS and SG are supported by the Federal Ministry of Education and Research, Grant no. 0315417F.

*Conflict of Interest*: none declared.

## REFERENCES

Bornstein, B. J., Keating, S. M., Jouraku, A., and Hucka, M. (2008). Libsbml: An api library for sbml. *Bioinformatics*, **24**(6), 880–881.

Girbig, D., Grimbs, S., and Selbig, J. (2012). Systematic analysis of stability patterns in plant primary metabolism. *PLoS ONE*, **7**(4), e34686.

Grimbs, S., Selbig, J., Bulik, S., Holzhütter, H., and Steuer, R. (2007). The stability and robustness of metabolic states: identifying stabilizing sites in metabolic networks. *Molecular Systems Biology*, **3**, 146.

Quinlan, J. R. (2012). *Data Mining Tools See5 and C5.0*. Last accessed 2012 Mar 10.

Reznik, E. and Segrè, D. (2010). On the stability of metabolic cycles. *Journal of Theoretical Biology*, **266**(4), 536–549.

Steuer, R., Gross, T., Selbig, J., and Blasius, B. (2006). Structural kinetic modeling of metabolic networks. *Proceedings of the National Academy of Sciences of the United States of America*, **103**(32), 11868–11873.

Steuer, R., Nesi, A. N., Fernie, A. R., Gross, T., Blasius, B., and Selbig, J. (2007). From structure to dynamics of metabolic pathways: application to the plant mitochondrial TCA cycle. *Bioinformatics*, **23**(11), 1378–1385.