

# A MATLAB toolbox for structural kinetic modeling

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## 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 analyses of network stability properties are 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>.

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## 1 INTRODUCTION

Structural kinetic modeling (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 (e.g. [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).

The SKM experiments presented so far used customized algorithms in which the SK models had been constructed manually ‘from scratch’ for each pathway (Grimbs *et al.*, 2007; Steuer *et al.*, 2007, 2006; 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 with 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  $N$ , steady-state concentrations  $S^0$  and the steady state fluxes  $v^0$ , with the experimental data being obtained from metabolomics and isotope tracing experiments. Model parameters can be derived automatically based on the information in  $N$ . 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 that demonstrate the construction of previously published literature models (Girbig *et al.*, 2012; Steuer *et al.*, 2006) using the toolbox.

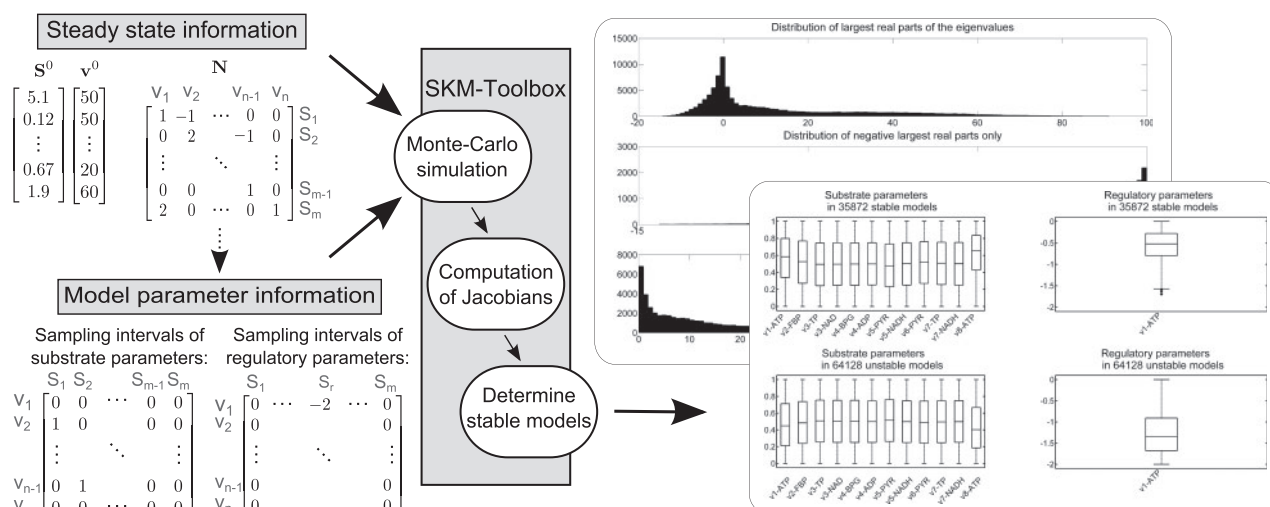
## 2 FEATURES

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  $N$ ,  $S^0$  and  $v^0$ .
- 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.

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

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**Fig. 1.** SK model building and evaluation using the SKM toolbox. Required input arguments are the stoichiometric matrix  $N$ , steady-state concentrations  $S^0$  and the fluxes  $v^0$ . Model parameters are assigned according to the information in  $N$ . 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.

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  $N$ . 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.

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**Conflict of Interest:** none declared.

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