# SBMLsqueezer 2: a context-sensitive rate law generator for biochemical networks with access to SABIO-RK

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## Dear Editor and Reviewers,

Thank you for giving us the chance to take up position on the criticisms of the reviewers. The software presented in this article is by far not just an update note for an original program. We here describe significantly upgraded software. In the publication from 2008, SBMLsqueezer was described as a pure plug-in for CellDesigner that was only able to interpret the CellDesigner-specific nomenclature and to suggest a limited set rate equations based on this information without caring about units or annotation of elements.

The new release presented here describes a totally new program with a large amount of improvements:

- **Several new built-in rate laws:** The selection of rate equations has been drastically extended. The now included five modular rate laws by Liebermeister *et al*. were proposed in 2010, i.e., 2 years after the first paper and not available in the first version, and belong to the most recent developments in the field of kinetic equations. Ten specific rate laws for gene-regulatory processes have been added:
  - Hill-Hinze equation
  - Hill-Radde equation
  - Linear additive network models (general form and Net*Gene*rator form)
  - Non-linear additive network models (general form, Net*Gene*rator form, Vorhradský's equation, Weaver's equation)
  - S-systems
  - H-systems
  
  None of those was provided in the original publication.
- **Experimental rate law download:** The connection to the rate law database SABIO-RK has been added and allows users to directly insert experimentally obtained rate laws from this database instead of deriving generic equations.
- **Unit derivation capability:** In contrast to the original program, SBMLsqueezer now derives units for all new parameters. This feature belongs to the most complex capabilities of the program, because numerous aspects of the model need to be taken into account in order to ensure unit consistency. This comprises, for instance, the

diverse fallback units in the model (depending on level/version combination of the SBML file), if the species involved are declared in concentration or amount units together with size and unit of their compartment, if reaction participants reside in different compartments etc. The program needs to set units off against each other in order to cancel out terms, which is not trivial.

- **Annotation:** The program is now entirely based on Systems Biology Ontology (SBO) annotations rather than on CellDesigner-specific information. This massive change was necessary in order to create a stand-alone version of the program. SBMLsqueezer now does not only understand annotations, it also annotates created objects (parameters, kinetic equations, units etc.) with SBO terms and where possible also with MIRIAM (Minimal Information Required in the Annotation of Models) controlled vocabulary terms. Once again, this new feature significantly increases quality and reusability of models.

- **Program usage:** The CellDesigner plug-in mode is now only one of many ways to use the program. SBMLsqueezer is probably one of very few scientific programs that run in so many diverse use-case scenarios and can therefore be inspiring for other tool developers. The program can be used as a command-line tool (with full access to all functions), as a stand-alone GUI program, through a web service, as a Garuda gadget, as a Java™ Web Start program, and also as plug-in for CellDesigner, and through its fully documented application programing interface (API) even as a software library for rate law creation. The comprehensive Users' Guide gives code examples and details how to benefit from all program features in each described environment.

- **Improved SBML support:** Since it is no longer just a plug-in for CellDesigner, SBMLsqueezer can now deal with all levels and versions of the SBML format, including Level 1 Version 1 and Level 3, whereas CellDesigner is restricted from SBML Level 1 Version 2 up to Level 2 Version 4.

- **Inspiring data structure:** The internal data structure of SBMLsqueezer has become a separate large-scale community effort and led to the development of JSBML, which is now an NIH-funded project and used by numerous other research groups.

Summarizing, with this new version of SBMLsqueezer, it is possible to create high-quality large-scale kinetic models with minimal human interaction. In particular, the access to SABIO-RK now enables the program to contribute to bottom-up knowledge-based model development as a complementary feature to the extended top-down rate law generation. The capability to derive units further enhances preciseness and usability of its results. The large number of ways to use the program allows researchers to benefit from the program's functionality in diverse potential use-case scenarios. Bug fixes and updates are only a small fraction of the improvements that are described in this article.

We believe that this applications note will have a high impact and is worth being published in Bioinformatics. The paper about the first CellDesigner plug-in version of SBMLsqueezer was downloaded almost 9,000 times and cited more than 40 times. It belongs to the 100 most viewed papers of BMC Syst. Biol. This new applications note about a significantly improved new version should therefore gain even higher attention.

# Reviewer: 1

## Comments to the Author

The work describes a piece of software with clear relevance to the system biology field. Furthermore, while I did not try the software myself, it seems to have many good features & ability to be run/interface with other programs in different ways. The paper is clearly written, with good motivation, discussion of related work, and some technical details of the program and its benefits. I have only a few small critiques:

(1) The figure quality might be improved. When I zoomed in, it looked quite pixelated.

**Thank you for pointing this out. The problem was the LaTeX compiler. We have now uploaded our original input files and this problem should no longer happen.**

(2) In section 3, "platform, for" should be just "platform for" -- i.e., no comma.

**Corrected.**

(3) In section 4, the last sentence "Based on SBMLsqueezer 2 complex..." is a bit confusing. I think the authors should put a comma after "(Drager, 2011)", so that "in which ... (Drager, 2011)," becomes a subordinate clause, with the main clause being "try-and-evaluate cycles now become possible". Assuming I understand well, that would clarify the grammar.

**Corrected.**

# Reviewer: 2

## Comments to the Author

### General Comments

This paper describes an update to the previously published SBMLsqueezer software that has already been used in a number of modelling studies (Pathak 2013, Dolan 2013, Autiero 2009). The software aims to generate parameterised kinetic equations in a semi-automated manner to allow for more rapid (and accurate) production of models derived from SBML. It has been delivered so as to be accessible to a range of expert and non-expert users though Galaxy, stand alone software, plug-in (CellDesigner) or Garuda gadget. It's entirely Java and in principle

platform independent. This new version offers direct connection to the kinetic rates database, SABIO-RK.

## Specific Comments
I have no additional comments.

**Thank you.**

**We like to point out that the paper is not just about an update of SBMLsqueezer. This new version comprises a large amount of new features, such as the access to SABIO-RK (as you describe), but also the ability to automatically derive units for parameters, the annotation of created elements, the improved support for SBML (no longer bound to CellDesigner's restrictions), a large variety of use-cases (command-line, graphical user interface, Galaxy web service, Garuda gadget, API library), and many other features. Since the original publication, SBMLsqueezer's internal data structure has inspired many other groups and developed to a separate, international, NIH funded software project, namely JSBML. Bug fixes und updates are only a small portion of the article.**

**The previous publication from 2008 only described the CellDesigner plug-in SBMLsqueezer. This is now only one small aspect of the current version. A new publication is required in order to describe all the new features and capabilities of the program and to give users an up-to-date reference to be cited.**

# Reviewer: 3

## Comments to the Author
This paper is well written and easy to understand. Authors present their new version of a tool to generate automatically some kinetic equation.
I think that authors have to choose if they want to present their method to do it and in this case to give the details of their algorithm or if they want to present some original results obtained with the help of the tool. In the paper we have nor algorithm nor concrete results. The  problem of finding the right rate law is a crucial one as the author told but they analyze this problem very roughly and just evoke generalities that are well-known - it could be interesting to develop an example of such automatic valuation of pathway reaction to show how they solve ambiguous cases or conflicts. To conclude, I suggest to the authors to review their paper in the way to give more details about the informatics developements or biological using.

**Thank you for this important comment. In this paper we intended to describe the application itself and the method behind it. Due to space limitations and the complexity of the algorithms, we have now thoroughly extended the Users' Guide. The completely new chapter 6 gives details about the**
- **architecture of the program**
- **algorithms for finding all applicable and the most relevant rate laws for a reaction**

- **matching of reactions to entries in SABIO-RK in order to find rate laws for all or selected reactions.**

**In the paper we refer to the Users' Guide, which is at the same time also supplementary material. We agree that the publication now gives much better insights about how the program works.**