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To the editors of PLoS.

Publication “Precise generation of systems biology models from KEGG pathways”, submitted to PLoS Computational Biology

Dear Sir or Madam,

Attached, you can find our latest publication about the generation of systems biology models, based on pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG).

The development, implementation and publication of such a method was highly necessary: KEGG is a manually curated, high-quality source of data that contains pathways, which could vastly facilitate initial structural systems biology modeling. These models can be refined and used for many predictive biological and pharmaceutical systems (e.g., personalized medicine). Unfortunately, available applications for generating SBML or BioPAX models from KEGG pathways are simple one-to-one converters whose results are hard to use in further modeling steps (no annotations are included, reactions are almost never correct, no application adds stoichiometry to the reactions, and many more deficiencies. See Table 3 of the publication for more details).

In the beginning of 2011, we submitted a small two-paged applications note of KEGGtranslator¹, highlighting the availability of a new application that is able to convert KEGG pathways to, among others, SBML Level 2. The algorithm was only roughly outlined and, since then, we received a lot of feedback from the scientific community and inquiries regarding the method behind this tool. Today, the tool has more than 3,000 downloads and 70 registrations of researchers who want to get informed of any updates. To make sure that we obey all standards, suit most needs and facilitate the usage of those models as much as possible, substantial parts of the application have been rewritten and a lot of novel features are added. KEGGtranslator is now the first application with SBML Level 3 output that uses various extensions (qual, layout, groups) to generate correct and complete models, obeying all rules and standards in systems biology. It further can create BioPAX models and the entire methodology for creating initial models has been completely revised.

¹ KEGGtranslator: visualizing and converting the KEGG PATHWAY database to various formats. Wrzodek C, Dräger A, Zell A. *Bioinformatics*. 2011, **27**:2314-2315

In this manuscript, we present a detailed description how to precisely generate initial structural systems biology models from KEGG pathways. The described method goes far beyond a simple conversion from KEGG to other formats and builds optimal foundations to ease building subsequent models, which then may be tissue-specific models, kinetic models, flux-based models, or any other type. The aim of the method is to precisely automate initial model building steps to reduce the human effort for model creation to a minimum. All mentioned methods are included in the new version 2.0 of KEGGtranslator that is released along with the submission of this publication, but the key aspect of this publication are the algorithms behind their implementations.

The manuscript has been seen and approved by all listed authors.

Sincerely Yours,
The authors