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Short Communication

Kinetic Models with Default Enzyme Kinetics from Genome-scale Models

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Abstract

Many genome-scale models of metabolism [GSMs] have been constructed to study the effects of changing native gene expression on its metabolism. Kinetic models of metabolism [KMs] can be a useful tool to study the effects of transgenes and regulations on the time-course metabolic profile of the host. However, the availability of KMs is substantially lesser with smaller scope than GSMs. A possibility is to generate KMs from GSMs but such tool is not available. Here, we present a converter to convert substrate-product pairs in GSM rate laws to enzyme kinetic equations in KM using default enzyme kinetics. Our testing results suggests that simulatable KMs can be successfully generated from GSMs to generate time-course metabolic profiles.

Keywords: Genome-scale Metabolic Models; Kinetic Models; Automated Model Conversion

Introduction

Mathematical modelling and simulation is an important tool to understand the behaviour of biological systems for metabolic engineering [1], systems biology [2,3], and synthetic biology [4-7]. Genome-scale models [GSMs, also known as constraint-based models] and kinetic models [KMs] are the two main modelling approaches [8,9]. GSMs are steady-state stoichiometric models which lacks enzymatic regulation [10] and difficult to add genes [transgenes] into the system as its original purpose is to evaluate changes in native gene expression on its metabolism [11,12]. However, there are many GSMs. On the other hand, kinetic models [KMs] can have regulation and is much easier to add transgenes. Since, the first GSM was for *Haemophilus influenzae* RD [13], GSMs have been reconstructed for 6239 organisms [5897 bacteria, 127 archaea, and 215 eukaryotes] with numerous applications by February 2019 [11]. However, the number of KMs available is much smaller and simpler than GSMs [9]. Hence, the metabolic engineering industry is calling for whole cell KMs of metabolism [10,14].

One of the ways to implement draft KMs is by converting the substrate and products of each rate law [15] in GSMs to enzyme kinetic equations in KMs but such tool is not available. In this study, we present a tool to convert reactions in GSMs to KM using default enzyme kinetics and incorporated this tool into AdvanceSyn Toolkit [8]. Tested on GSM models; e_coli_core [16], iAF1260 [17] and Recon3D [18]; we achieved the conversion of simulatable GSMs to simulatable KMs.

Implementation

Cameo [19] is utilised via AdvanceSyn Toolkit [8] to read and extract individual reaction string of the target GSM into Python pandas dataframe [20], where the reaction string is processed into reactants, products and enzyme, before converting into an AdvanceSyn Model [ASM] specification is based on Antimony language [21], which is both modular and compatible with AdvanceSyn Toolkit [8]. The set of reactants and products form the metabolite list, which is converted into the objects section of ASM specification. The initials section of ASM specification consists of the initial

concentrations of metabolites, which were defaulted to 10 uM. The variables section of the ASM specification defines the concentrations, k_{cat} [turnover number] and K_m [Michaelis-Menten constant] of the enzymes, which were defaulted to 1 uM, 13.7 per second and 130 uM respectively. The default k_{cat} and K_m values were median values from a survey of more than 1000 enzymes by Bar-Even., *et al*. [22]. All four default values [concentrations of metabolites and enzymes, and k_{cat} and K_m of enzymes] could be changed by the user during model conversion. The reaction section of the ASM specification consists of a list of reaction steps where each reaction step is then represented by Michaelis-Menten type rate law [23] extended for multiple substrates in the form of $\frac{k_{cat}(enzyme)\sum(substrate)}{K_m+(enzyme)\sum(substrate)}$. Michaelis-Menten type rate law [23] had been used for many kinetic models of biochemical reactions [24-28], which had been shown to be a suitable approximation for biochemical system modelling [15,29,30] and was used for all reactions in a whole-cell kinetic model of *Saccharomyces cerevisiae* [31]; hence, considered to be a suitable default choice for biochemical rate laws [32]. This enables subsequent generation simulatable ordinary differential equations where the concentration of each metabolite over time is modelled as $\frac{d(metabolite)}{dt} = \sum_{i=1}^{N} production_i - \sum_{i=1}^{N} usage_i$ and each production and usage term represent a reaction step.

Testing the converter

Three GSM models; e_coli_core [16], iAF1260 [17], and Recon3D [18]; were used to test the implemented converter. Model e_coli_core [16], is a subset of iAF1260 [17], which containing only the central metabolism of *E. coli* [16], is often used for tool testing [33-35] as it is the smallest GSM model in BiGG database [36] in terms of number of metabolites, reactions, or genes. Hence, e_coli_core can be used to test the functionality of the implemented converter. On the other hand, iAF1260 [17] consisting 1668 metabolites, 2382 reactions, and 1261 genes and Recon3D [18], the largest GSM in BiGG database [36] in terms of number of metabolites, reactions and genes [5835 metabolites, 10600 reactions, 2248 genes], are substantially larger models and can be used to test the scalability of our implemented GSM to KM converter.

Tested on e_coli_core [16], our results suggest that a GSM model can be successfully converted into kinetic model [Figure 1], which is simulatable using AdvanceSyn Toolkit [8] as 67 of the 72 metabolites [93%] illustrated concentrations different from the initial concentration of 10 uM after 6 hours simulation time [Figure 2]. This suggests that the required functionality of our implemented GSM to KM converter is met. Our results also show that iAF1260 [17] can be converted and simulated to produce time-course metabolite concentrations [Figure 3], suggesting that our GSM to KM converter can be used to convert larger GSM models.

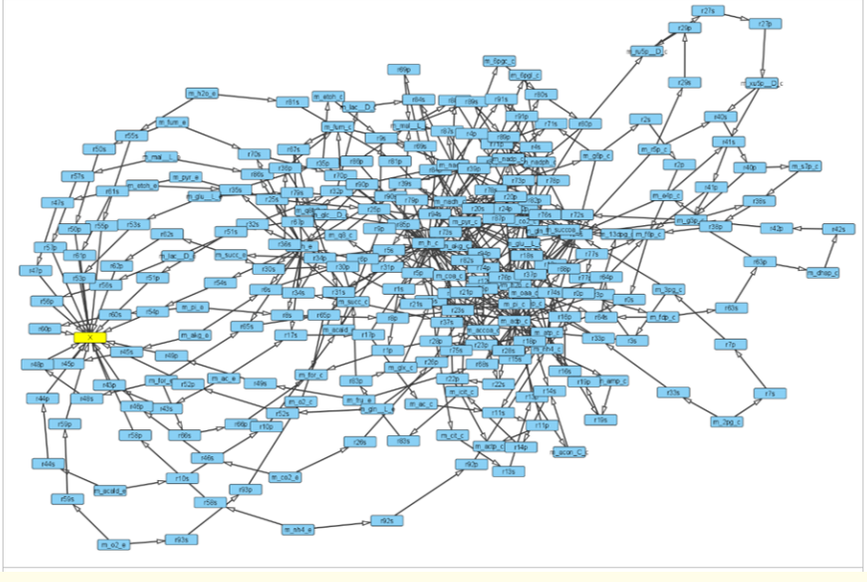

Figure 1: Reaction network for e_coli_core [16] model. Each reaction is modelled in Cytoscape [41] as a multi-step reaction where all reactants are aggregated into a reaction substrate complex (rNs) before metabolizing into a reaction product complex (rNp), which is used to form the products. The "N" in rNs and rNp refers to reaction number. Metabolite X (labelled yellow) represents the product of pseudo-reactions [42] in GSMs (for example, reactions with substrate but without product), such as fumarate exchange (EX_fum_e) which is coded as "fum_e ⇌".

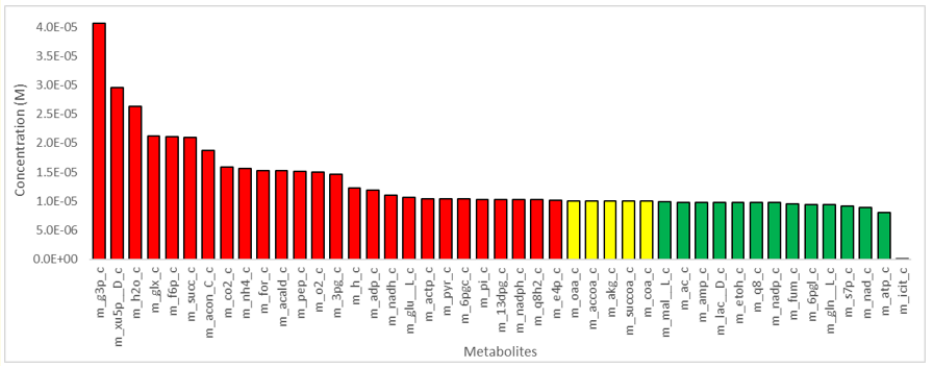

Figure 2: Concentrations of metabolites simulated from kinetic model converted from e_coli_core [16] model at 6 hours. Red bars represent metabolites with concentration higher than initial concentration of 10 uM while green bars represent metabolites with concentration lower than initial concentration of 10 uM. Yellow bars represent metabolites with no change in concentration after 6 hours.

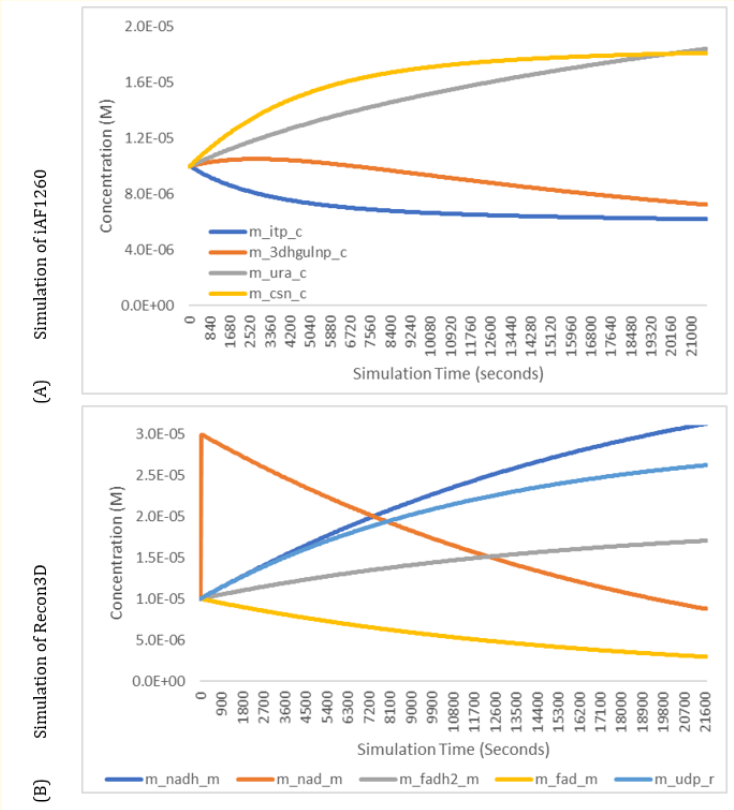

Figure 3: Sample of time-course metabolite concentrations simulated from kinetic models converted from iAF1260 [17] and Recon3D [18] models over 6 hours. Panels A and B shows a sample of metabolic profiles from simulating the kinetic models converted from iAF1260 and Recon3D, respectively.

Overall, our testing results suggests that our GSM to KM converter can automatically convert GSMs to KMs. This is similar to that of AutoKEGGRec [37], which generates draft GSM models from KEGG pathway maps [38,39], and CarveMe [40], which generates draft GSM models from annotated genomes. Thus, completing the toolchain from pathway maps or annotated genomes to KMs via GSMs.

Conclusion

We present a tool to convert reactions in GSMs to KMs by converting the substrate and products of each rate law [15] in GSMs to enzyme kinetic equations in KMs using default enzyme kinetics and incorporated this tool into AdvanceSyn Toolkit [8], and tested the conversion of simulatable GSMs to simulatable KMs.

Supplementary Materials

Data files for this study can be downloaded from http://bit.ly/GSM_to_KM.

Data Availability

The conversion tool presented in this manuscript is incorporated and can be found in AdvanceSyn Toolkit [https://github.com/mauriceling/advancesyntoolkit].

Conflict of Interest

Maurice Ling is a director of AdvanceSyn Private Limited and AdvanceSyn Toolkit is employed in consultancy services offered by the company. Nabil Amir-Hamzah, and Zhi Jue Kuan declare no conflict of interest.

Acknowledgement

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