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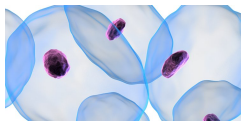

Computational limitations to modelling dynamic metabolic networks

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Type of thesis: Computational

Required competences: Knowledge of ordinary differential equations (ODEs), their analysis, and ability to simulate systems in MATLAB, Python or R, are desired skills.

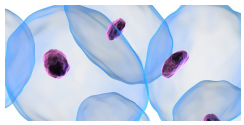
Acquired competences: Model analysis and reduction methods. Parameter sensitivity analysis.

Date: 27-11-2020

Description

A key aspect of Systems Biology is the ability to model biological systems accurately despite having incomplete or limited data. This is a model optimisation problem. Classically, a system of ODEs is iteratively simulated with different estimates for reaction rates and compared to datasets using a scoring function. The best-fitting model is then the set of reaction rates with the lowest associated score. By performing this analysis for multiple different models, one can find both the most likely model and best-fitting reaction rates from a predefined range of parameter values. However, all of this analysis assumes that our models are able to be simulated and that we have an initial idea of bounds within which feasible reaction rates exist!

In multiple previous projects, we have found that ODE models of metabolic pathways are unable to be numerically simulated. This is despite using common methods such as Michaelis-Menten functions and taking reaction rates close to their experimentally determined values. The failure of an ODE solver can be observed when a simulation stops before the defined final time-point. We would like to understand, in detail, why this is the case. One possibility is that we simply need to use a different solver or computer package (MATLAB, Python, R, or Julia) to simulate these systems. Another possibility is that placing



constraints on individual reaction rate parameters is not enough, and that we need to consider constraining reaction rates in a combinatorial manner (i.e. constraining the product of multiple reaction rates). Finally, it could be that complete reactions or fluxes in our models are incorrectly formulated using Michaelis-Menten kinetics. If we can find out what the rules of dynamic metabolism should be, we can then relate our analysis back to real systems through fitting of test cases.

This project fits together with another project testing model optimisation methods for metabolic models, and will provide valuable information to multiple ongoing projects in SSB.

References

Smith RW, van Rosmalen RP, et al. (2018) DMPy: a Python package for automated mathematical model construction of large-scale metabolic systems. BMC Systems Biology 12:72. Doi:10.1186/s12918-018-0584-8.