Project description: Master Thesis Lukas Rehfisch

The impact of parameter reparametrization on the efficiency of fitting ordinary differential equation models

Background:

Understanding of complex biochemical networks as they occur in living cells requires the combination of experimental work with mathematical modelling. Ordinary differential equation models (ODEs) can be used as mathematical representation for analyzing known biochemical interaction networks. A major goal is the calibration of such models, i.e. to estimate the parameters like initial concentrations or rate constants based on experimental data. Since the ordinary differential equations models are highly nonlinear and solutions of ODEs can only be calculated with limited numerical precision, optimization for finding optimal parameters is challenging.

State of the art:

In our group, a comprehensive implementation of the parameter estimation methodology is available [2,3]. The parameter estimation environment provides several optimization techniques as well as models and data from application settings.

It has been shown that reparametrization can have a beneficial impact on the performance of numerical optimization in the setting of dynamic pathway models [1]. However, up to now the impact has not been evaluated in details. Additionally, a clear strategy/algorithm for performing reparametrization is missing.

Method evaluations in general:

Alternative theoretical approaches are usually compared in a highly biased manner since they are typically performed to confirm the necessity of a new approach. In such circumstances, the evaluation setting is often tuned to highlight advantages of a certain approach compared to a standard method. In addition, the impact of hyper parameters of the methods (magic factors) is not considered.

To obtain an unbiased assessment of alternative computational methods, one has to design a method evaluation study for this purpose. In addition, the performance assessment and comparison should be performed using standard statistical models (like multivariate regression) to estimate and test the impact of potential effectors on the performance.

The specific evaluation:

In this master thesis, the impact of several strategies for reparametrization on the efficiency of the default optimization strategy in D2D is evaluated using several models and data setups. In addition, the impact of the log-transformation of the parameters is investigated.

To obtain results which hold in more general circumstances, the setting could be generalized, e.g. by using simulated data sets, changing the size of the parameter space (upper and lower boundaries) and using alternative optimization techniques.

In an ideal case, a strategy for selecting an appropriate reparametrization would be suggested, e.g. based on a decision tree.

[1] Raue A, Schilling M, Bachmann J, Matteson A, Schelker M, Kaschek D, Hug S, **Kreutz C**, Harms BD, Theis F, Klingmueller U and Timmer J. Lessons Learned from Quantitative Dynamical Modeling in Systems Biology. PLOS ONE 8(9), e74335, 2013

[2] A. Raue, et al. Data2Dynamics: a modeling environment tailored to parameter estimation in dynamical systems. *Bioinformatics* **31**, 2015, 3558-3560

[3] Data2Dynamics Software Website
https://bitbucket.org/d2d-development/d2d-software/wiki/Home