Prediction uncertainty in the case of unidentifiability and single-cell data – new concepts and methods

Gunnar Cedersund*†[1]

[1]Department of Biomedical Engineering – Linköping University 58185 Linköping, Sweden, Sweden

Abstract

Mathematical modelling is an integral part of both systems and synthetic biology, because it can more accurately deal with the complexity of biological data. However, to be truly useful, the predictions of the model must be in the form of core predictions, i.e. they must come with a correct uncertainty. In the last few years, there have been important progress in this field, especially concerning the important situations of unidentifiable parameters and single-cell data. This presentation will give an overview of some of these developments.
In the case of unidentifiable parameters, it has become clear that traditional approaches based on sensitivity analyses, the Hessian of the cost function, and sampling-based Monte Carlo approaches all give inaccurate results. In such situations, one may instead use rediscovered and recently improved alternatives based on the conditional profile of the likelihood function. Importantly, these methods can now not only be used for assessing the uncertainty of parameter values, but for the uncertainty of arbitrary model predictions.

For the case of single-cell data, problems with unidentifiability are often more severe: it is often not possible to generate enough data from a single cell, and averages over many cells provide inaccurate results. In such cases, it is instead better to use methods from nonlinear mixed-effects modelling (NLME), which borrows information across the entire cell-population. Using simulated data where the truth is known, and real data from individual yeast cells, I will illustrate when, why, and how NLME is advantageous.
All in all, these new and improved concepts and methods provide important tools for a sound and correct model-based analysis of single-cell data.

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*Speaker
†Corresponding author: gunnar.cedersund@liu.se