Data, Parameters & Nonlinearities: Development and Applications of Large-scale Dynamic Models of Metabolism
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Abstract
Dynamic nonlinear models of metabolism offer a significant advantage as compared to constraint-based stoichiometric descriptions. However, progress in the development of large-scale nonlinear models has been hindered by both structural and quantitative uncertainties. In particular, the knowledge about kinetic rate laws and their parameters is till today still very limited when compared to the number of stoichiometric reactions known to be present in a large-scale metabolic model. In addition, strategies to systematically identify and implement large-scale dynamic models for metabolism are still lacking. In this contribution, we propose a novel methodology for development of dynamic nonlinear models for metabolism. Using the ORACLE\textsuperscript{3} (Optimization and Risk Analysis of Complex Living Entities) framework, we integrate thermodynamics and available omics and kinetic data into a large-scale stoichiometric model. The resulting set of log-linear kinetic models is used to compute kinetic parameters of the involved enzymatic reactions such as the maximal velocities and Michaelis constants. These kinetic parameters are in turn used to compute populations of stable, nonlinear, dynamic models sharing the same steady-state as the log-linear ones. The computed models offer unprecedented possibilities for system analysis, e.g., to study the responses of metabolism upon large perturbations; to investigate time course evolutions in and around the steady state; and to identify multiple steady-states and their basins of attraction. We illustrate the features of the generated models in the case of optimally grown \textit{E. coli}, where our analysis of the estimated maximal reaction rates highlights the significance of network thermodynamics in constraining the variability of these quantities.

Figure 1: Flowchart of the computational procedure for uncertainty analysis of metabolic networks within the ORACLE framework. The schematic application of computational procedures integrates biological information from different levels and sources thus refining kinetic models and providing a novel approach for metabolic engineering. ORACLE\textsuperscript{3} used to assemble the key aspects defining a non-linear model: thermodynamics, rate laws, metabolite concentrations and kinetic parameters, and coupling with partial/complete data.

Consistently reduced \textit{E. coli} model
Derived from a genome scale \textit{E. coli} reconstruction. Consists of 133 reactions and 77 metabolites. Used to demonstrate the strategy for developing large scale dynamic models.

Estimated kinetic parameters, e.g. $K_m$ values, are comparable to experimental measurements in databases like BRENDA. We use this partial data whenever available, to prune/refine our parametric estimates.

Model analysis using dynamic models of metabolic networks
The non-linear estimations about the stable state can be used to analyze diverse properties of the system upon large perturbations and investigate time course evolutions in and around this steady state.

Conclusion
\begin{itemize}
  \item The estimated parameters are consistent with BRENDA and other databases.
  \item These parametric estimates are used to investigate correlative/co-regulated properties of the system.
  \item The partial kinetic data is incorporated to further refine/constrain the kinetic parameter estimates.
  \item The kinetic parameters used to systematically develop populations of stable dynamic models having the same steady-state as the log-linear ones.
  \item These non-linear estimations around the stable state are used to analyze diverse properties of the system upon large perturbations and investigate time course evolutions in and around this steady state.
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References