Improving in silico predictions in Metabolic Engineering problems

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The field of Metabolic Engineering (ME) has gained a major importance, since it allows the design of improved microorganisms for industrial applications, starting with wild-type strains that usually have low production capabilities in terms of the target compounds. The ultimate aim of ME is to identify genetic manipulations in silico leading to improved microbial strains, that can be implemented using novel molecular biology techniques. This task, however, is a complex one, requiring the existence of reliable metabolic models for strain simulation and robust optimization algorithms for target identification.

Strain simulation is usually performed by using Linear or Quadratic Programming methods that assume a steady state over the intracellular metabolites. However, most of the available genome-scale models do not allow to make good predictions on flux distributions, ultimately leading to ineffective ME strategies.

Another important aspect associated with model predictions is the influence of the biomass equation added to the model. Since most simulation tools require directly or indirectly the computation of maximal biomass formation, this composition has a great impact in the predictive power of these models. Moreover, biomass composition is intrinsically related with essentiality predictions.

In this talk, a detailed analysis will be presented on the present prediction power of genome-scale metabolic models and simulation tools and on the impact of having accurate experimental measurements for model validation. Moreover, improved simulation and optimization tools based on different optimization formulations and on the concept of control effective fluxes will be introduced that allow to perform metabolic engineering tasks in a more reliable fashion.

Relevant Literature:

Moduless in Metabolic Networks

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Flux balance analysis (FBA) is one of the most often applied methods on genome-scale metabolic networks. Although FBA uniquely determines the optimal yield, the pathway that achieves this is usually not unique. The analysis of the optimal-yield flux space has been an open challenge. Flux variability analysis is only capturing some properties of the flux space, while elementary mode analysis is intractable due to the enormous number of elementary modes. However, it has been found that the space of optimal-yield fluxes decomposes into modules [1]. These decompositions allow a much easier but still comprehensive analysis of the optimal-yield flux space.

We will present methods on how each module can be analyzed by itself. Together with visualization methods for the interplay of the modules, this gives an intuitive understanding of the optimal-yield flux space of genome-scale metabolic networks.

Using the mathematical definition of modules introduced by [2], we are now able to compute the decomposition into modules in a few seconds for genome-scale networks. Hence, we expect the new method to replace flux variability analysis in the pipelines for metabolic networks.

Literature

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