CABBI
CENTER FOR ADVANCED BIOENERGY AND BIOPRODUCTS INNOVATION

KETCHUP: Parameterizing of Large-Scale Kinetic Models Using Multiple Datasets with Different Reference States

Background/Objective

Large-scale kinetic models use physiological information, such as metabolite concentrations, enzyme levels, and regulatory information, to predict metabolic reaction rates of microbes. However, challenges in efficiently and robustly parameterizing these models hinder their broad application. Existing parameterization tools like K-FIT are limited to flux data alone. To address these challenges, we developed **K**inetic **E**stimation **T**ool **C**apturing **H**eterogeneous Datasets **U**sing **P**yomo (KETCHUP), a flexible kinetic parameter estimation tool that enables researchers to incorporate more data sets to improve model predictions.

Approach

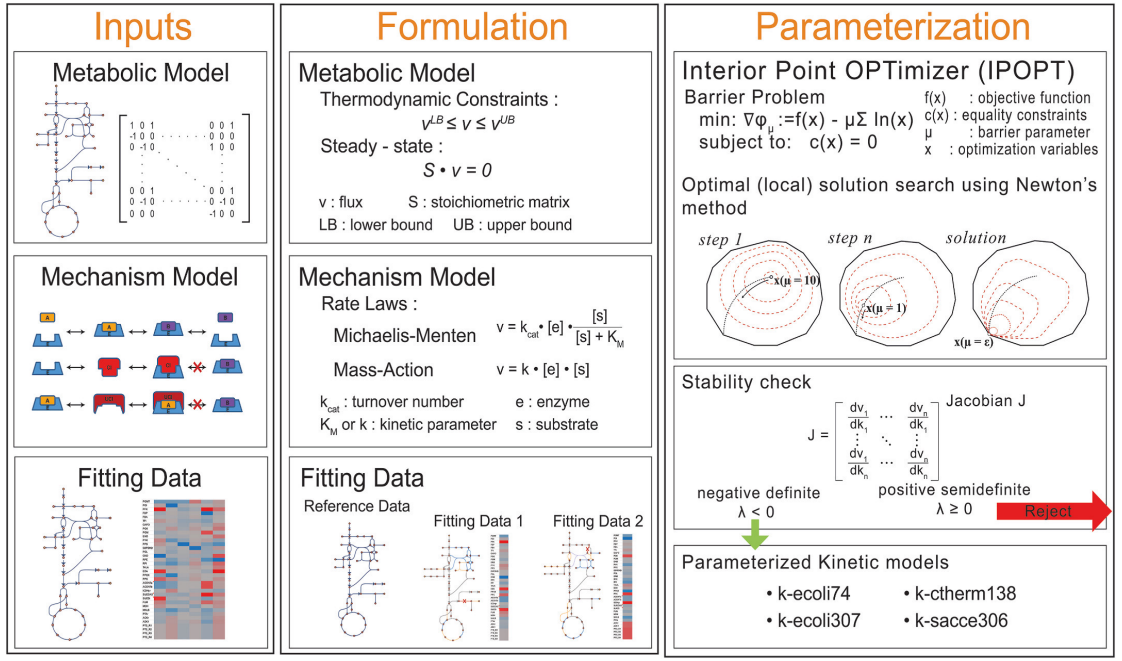
Developed KETCHUP to use interior point optimization methods and support Systems Biology Markup Language (SBML) and then expanded its supported mechanisms to include mass action elementary steps or Michaelis-Menten kinetics. Benchmarked KETCHUP on a large-scale kinetic *S. cerevisiae* model (k-sacce306) and evaluated its predictive abilities by comparing its target metabolite yields with strains not used as fitting datasets.

Results

KETCHUP outperformed K-FIT for all key metrics, was an order of magnitude faster at convergence, and attained better data fits. KETCHUP also predicted product yields for k-sacce306 better than flux balance analysis. It is also more flexible, accepting different kinetic descriptions, metabolic fluxes, enzyme levels, and metabolite concentrations, under either steady-state or nonstationary conditions, to enable robust kinetic model construction and parameterization.

Significance/Impacts

KETCHUP is a publicly available tool (github.com/maranasgroup/KETCHUP) that enables applying kinetic models to improve strain design predictions.



Overview of the KETCHUP workflow of required user inputs, automated formulation of rate laws and dataset incorporation, parameterization of kinetic model, and stability check.

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