An Improved Framework for Parameterizing Large-scale Biological Kinetic Models Leads to Improved Fitting and Convergence

Background

- Kinetic models of microbial metabolism capture physiological information as a function of metabolite and enzyme concentrations and offer a mechanistic way of predicting metabolic reaction rates.
- Researchers need computationally tractable methods that recapitulate wild-type and perturbed networks and parameterize using experimentally determined fluxes along with metabolite concentrations and enzyme levels.

Approach

- We developed Kinetic Estimation Tool Capturing Heterogeneous Datasets Using Pyomo (KETCHUP), a kinetic parameterization tool that supports the interoperable Systems Biology Markup Language (SBML) (Fig. 1).
- KETCHUP is a Python package that reads kinetic model definitions (connectivity, allosteric interactions, and mechanism) and data files, defines the parameterization problem, and solves using an interior point optimizer.

Results

- We successfully applied KETCHUP for five different kinetic models ranging from 47 to 307 metabolic reactions using either elementary step mass action or Michaelis-Menten kinetics (*i.e.*, of *Escherichia coli*, *Clostridium thermocellum*, *Saccharomyces cerevisiae*, and *Clostridium autoethanogenum*).
- Dataset flexibility was demonstrated by parameterizing a large-scale *E. coli* model with 305 reactions, 259 metabolites, 39 substrate-level regulators by using both chemostat and batch datasets simultaneously.
- KETCHUP outperforms previous method K-FIT for all key metrics (Fig 2) and is available on GitHub: github.com/maranasgroup/KETCHUP.
- Kinetic models parameterized by KETCHUP predict product yields better than flux balance analysis.

Significance

- KETCHUP is a versatile tool impacting the way to generate, parameterize, and share kinetic models. Its application furthers CBI's goal of understanding drivers for cellulolytic strain phenotypes and responses to perturbations and thus allows better *in silico* design for strain optimization.

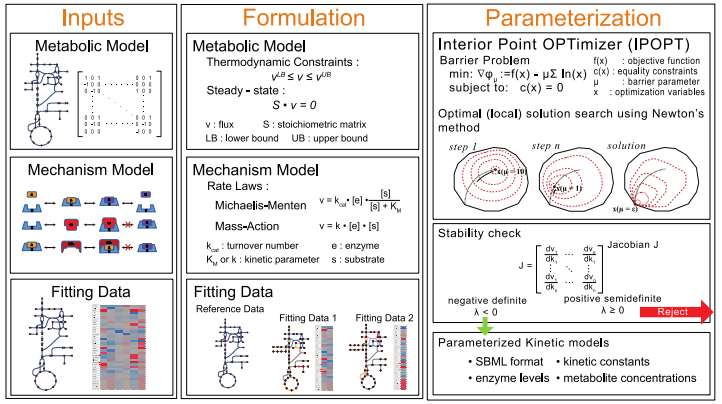

Fig. 1. KETCHUP's kinetic parameterization workflow. The framework is flexible in defining rate law mechanisms and can incorporate heterologous datasets as well as multiple-reference datasets, simultaneously.

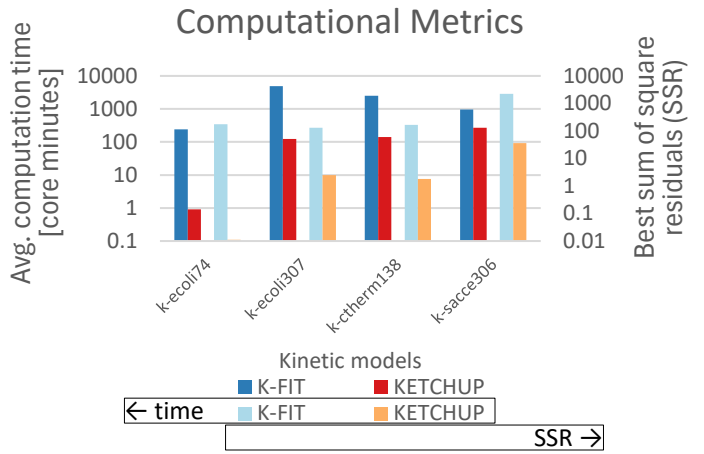

Fig. 2. Summary of comparison metrics on log-scales showing how KETCHUP outperforms K-FIT when parameterizing kinetic models of several microorganisms covering a range of model sizes and complexity.

Hu, M. et al. *Metab Eng* (2024) 82, 123-133. doi.org/10.1016/j.ymben.2024.02.002