174. Development of a core *Escherichia coli* inetic metabolic model using the E formalism

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Project Goals: The goal of this project is to explore the use of Ensemble odeling E concepts for constructing inetic models of metabolism consistent with available measurements metabolomics fluxomic and capable of guiding genetic interventions for overproduction. Here we describe the development of an E based inetic model of core *E. coli* metabolism.

Recent availability of fluxomic and metabolomics data has paved the way for large-scale kinetic modeling of metabolism. Challenges still remain on deriving meaningful kinetic descriptions and parameterizations that faithfully replicate metabolic responses to genetic and/or environmental perturbations. In this study we introduce a kinetic model of *E. coli* core metabolism that satisfies the fluxomic data for wild-type and seven mutant strains [1] by making use of the recently introduced Ensemble Modeling (EM) concepts. This model encompasses 138 reactions, 93 metabolites and 60 substrate-level regulatory interactions and accounts for glycolysis/gluconeogenesis, pentose phosphate pathway, TCA cycle, major pyruvate metabolism, anaplerotic reactions and a number of reactions in other parts of the metabolism (Figure 1). Parameterization is performed using a formal optimization approach that minimizes the uncertainty-scaled discrepancies between model predictions and flux measurements. The predicted fluxes by the model are within the uncertainty range of experimental flux data for 78% of the reactions (with measured fluxes) for both the reference (wild-type) and seven mutant strains. The remaining flux predictions fall within three standard deviations of measured values. Converting the EM-based parameters into a Michaelis-Menten equivalent formalism revealed that 80% of K_m and k_{cat} parameters are within one order of magnitude of the literature available values. The predicted metabolite concentrations by the model are also within uncertainty ranges of metabolomic data for 68% of the metabolites. A leave-one-out cross-validation test to evaluate the flux prediction performance of the model showed that metabolic fluxes for the mutants located in the proximity of mutations used for training the model are predicted more accurately. The constructed model and parameterization procedure provides the means for the construction of even larger-scale models as well as models with more narrowly distributed parameter values as new metabolomics/fluxomic data sets are becoming available for *E. coli* and other well studied organisms.

Reference

1. Ishii N, Nakahigashi K, Baba T, Robert M, Soga T, Kanai A, Hirasawa T, Naba M, Hirai K, Hoque A et al: Multiple high- throughput analyses monitor the response of E. coli to perturbations. Science 2007, 316(5824):593-597.

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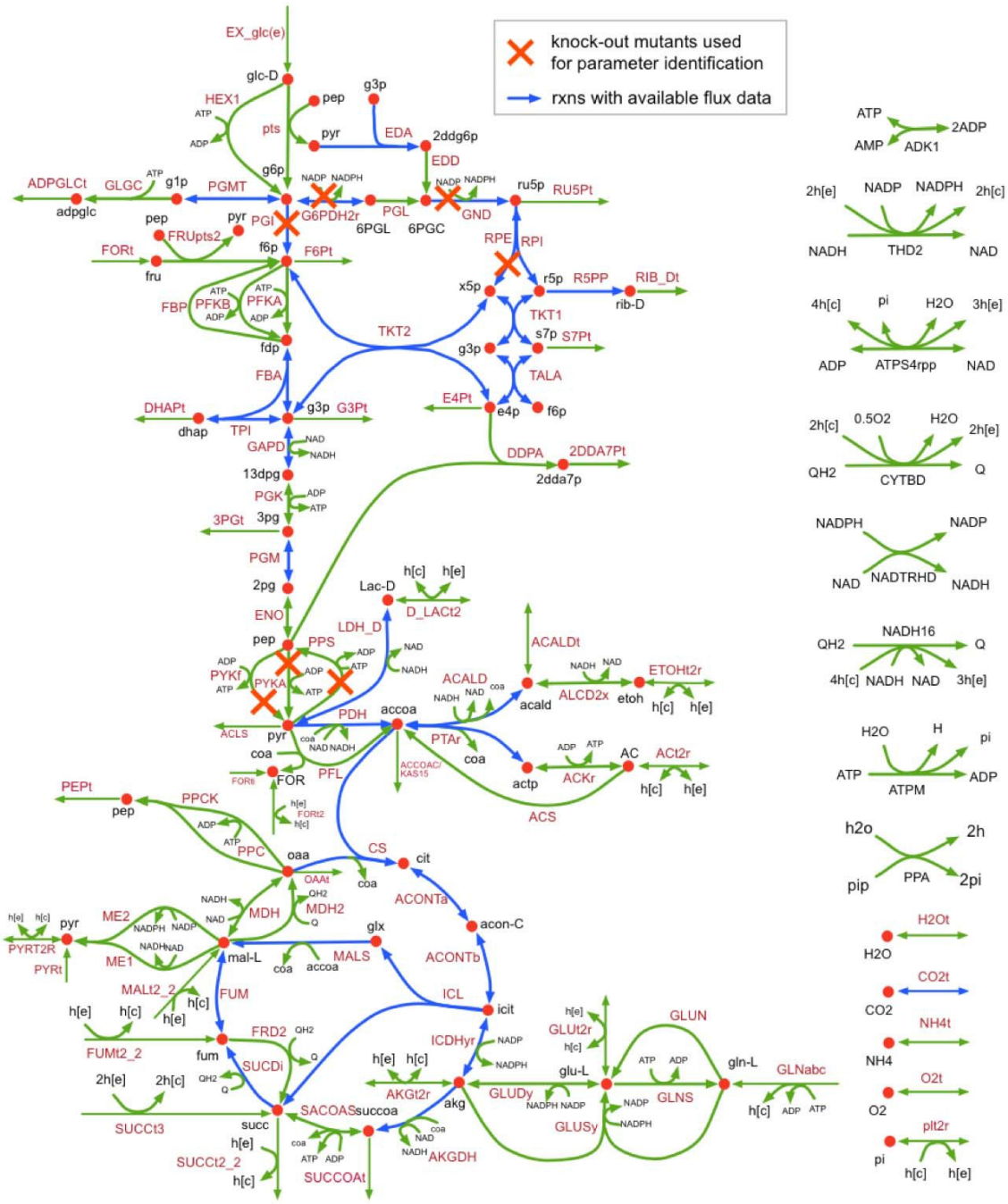

Figure 1. The constructed kinetic model of *E. coli* core metabolism**.** The red crosses represent the knockout mutants with available flux data, used for parameter estimation and cross-validation analysis. Reactions in blue represent those with available flux measurements for the wild-type and mutant strains.