Dynamic modeling of *E. coli* central carbon metabolism combining different kinetic rate laws

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Abstract Detailed dynamic kinetic models at the network reaction level are traditionally constructed using mechanistic enzymatic rate equations and a large number of kinetic parameters have to be determined under non-physiological conditions *in vitro*. However, the validity of these parameters under *in vivo* conditions is doubtful and the rates equations are usually highly complex. Therefore, one of the major obstacles in building accurate kinetic models is the lack of detailed knowledge of the rate laws that describe the reaction mechanism and the absence of their associated parameters. There is an urgent need for alternative modelling approaches to fill this gap. In this study, we analyze four alternative hybrid modeling strategies to the reference large scale mechanistic *E. coli* central carbon metabolic network model based on the Michaelis-Menten equation only for the bimolecular reactions and the other reactions with different formats of approximative rate kinetics (Generalized Mass-Action, convenience equation, lin-log and power-law). These rate equations help to reduce the number of parameters that have to be estimated. The kinetic parameters optimization was performed through the combination of a global search evolutionary programming method followed by a local optimization method (Hooke and Jeeves) to refine the fitting. Predictions and stability analyses to test the viability of the alternative models were also performed. The good dynamic behaviour and powerful predictive power obtained by the mixed modeling composed on Michaelis-Menten kinetics and the approximate lin-log kinetics indicate that this as a suitable approach to complex large scale models where the exact rate laws are unknown.

Keywords: large-scale *E. coli* metabolic network, dynamic modeling, approximative enzyme kinetics, parameter estimation