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Improved kinetic model of *Escherichia coli* central carbon metabolism in batch and continuous cultures

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Many kinetic models of *Escherichia coli* central metabolism have been built, but few models accurately reproduced the dynamic behaviors of wild type and multiple genetic mutants. In 2016 our latest kinetic model improved problems of existing models to reproduce the cell growth and glucose uptake of wild type, Δ*pykA*:*pykF* and Δ*pgi* in a batch culture, while it overestimated the glucose uptake and cell growth rates of Δ*ppc* and hardly captured the typical characteristics of the glyoxylate and TCA cycle fluxes for Δ*pgi* and Δ*ppc*. Such discrepancies between the simulated and experimental data suggested biological complexity. In this study, we overcame these problems by assuming critical mechanisms regarding the OAA-regulated isocitrate dehydrogenase activity, *aceBAK* gene regulation and growth suppression. The present model accurately predicts the extracellular and intracellular dynamics of wild type and many gene knockout mutants in batch and continuous cultures. It is now the most accurate, detailed kinetic model of *E. coli* central carbon metabolism and will contribute to advances in mathematical modeling of cell factories.

[**Key words:** Kinetic model; Synthetic biology; Central carbon metabolism; Dynamic simulation; *Escherichia coli*]

Systems biology and synthetic biology aim to understand the mechanism by which a biochemical network yields dynamic behaviors in response to environmental stresses or genetic variations and to rationally design and engineer such networks. Mathematical modeling is a powerful method that simulates biological behaviors and characteristics under different culture and genetic conditions. Different types of mathematical equations are available. S-system and General Mass Action are suitable when there are few kinetic data. In the case of widely-used microbes such as *Escherichia coli*, detailed Michaelis–Menten type equations have been developed for enzyme reactions in biochemistry and biochemical engineering. Kinetic models of *E. coli* central metabolism, including glycolysis, the tricarboxylic acid (TCA) cycle, the pentose phosphate pathway, the glyoxylate cycle, and anaplerotic pathways, have been built in a batch culture (1–5). Since metabolite and enzyme concentrations vary over time and with a change in environmental and genetic conditions, the models needed to integrate transcription factors, enzyme modification and allosteric reactions into the central carbon metabolism (6–10).

However, few kinetic models accurately reproduced the dynamic behaviors of wild type (WT) and multiple genetic mutants due to biological complexity. In 2016 we employed extensive parameter optimization by a supercomputer to build a detailed, accurate kinetic model for the central carbon metabolism with four transcriptional factors of *E. coli* in a batch culture (6). This kinetic model more accurately reproduced the cell growth and glucose uptake of WT, *pykA*:*pykF* knockout mutant (Δ*pykA*:*pykF*) and *pgi* knockout mutant (Δ*pgi*) in a batch culture than the existing models (1,3,7–9), while it remains to be improved. It overestimated the glucose uptake and cell growth rates of *ppc* knockout mutant (Δ*ppc*) and hardly captured the typical characteristics of the glyoxylate and TCA cycle fluxes for Δ*pgi* and Δ*ppc*. Such discrepancies between the simulated and experimental data suggested biological complexity.

To reproduce the dynamics and typical characteristics of the *E. coli* cells under different genetic and culture conditions, we improved our previous model (6) by assuming some mechanisms regarding the OAA-regulated isocitrate dehydrogenase (Icdh) activity, *aceBAK* gene regulation and cell growth suppression. The present or improved model estimated not only the extracellular dynamics but also the intracellular characteristics of WT and many genetic mutants in batch and continuous cultures.

MATERIALS AND METHODS

Kinetic model To solve some problems of our previous (Jahan) model (6), we have developed a kinetic model of the central carbon metabolism of *E. coli*, including the glycolytic pathway, pentose phosphate pathway, Entner–Doudoroff (ED) pathway, anaplerotic pathway, TCA cycle, glyoxylate cycle and oxidative phosphorylation, together with transcription factors of catabolite repressor/activator (Cra), cAMP receptor protein (Crp), pyruvate dehydrogenase complex repressor (PdhR), and acetate operon repressor (IclR), as shown in Fig. 1.

The following kinetic models are employed for batch and continuous cultures:

$$\frac{dX}{dt} = \mu(\mathbf{x}_1, \mathbf{x}_2, \mathbf{y}, \mathbf{p})X - DX \quad (1)$$

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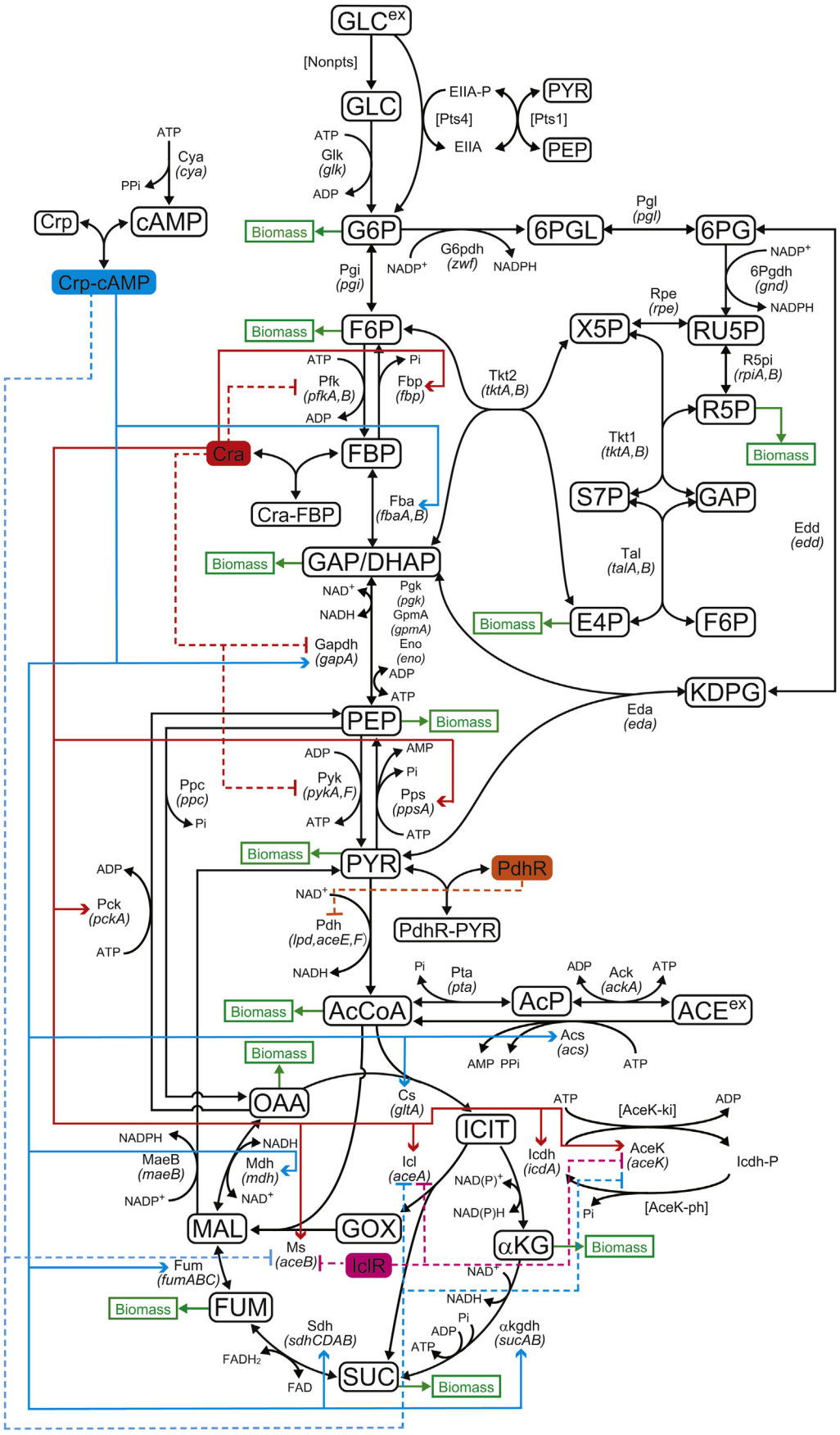

FIG. 1. An *E. coli* metabolic network map. The solid line indicates activation and the dotted line indicates repression.

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