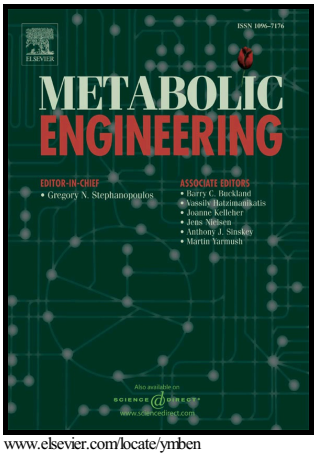

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Model-Based Metabolic Engineering Enables High Yield Itaconic Acid Production by *Escherichia coli*

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Abstract

Itaconic acid is a high potential platform chemical which is currently industrially produced by *Aspergillus terreus*. Heterologous production of itaconic acid with *Escherichia coli* could help to overcome limitations of *A. terreus* regarding slow growth and high sensitivity to oxygen supply. However, the performance achieved so far with *E. coli* strains is still low.

We introduced a plasmid (pCadCS) carrying genes for itaconic acid production into *E. coli* and applied a model-based approach to construct a high yield producer strain. Based on the concept of minimal cut sets, we identified intervention strategies that guarantee high itaconic acid yield while still allowing growth. One cut set was selected and the corresponding genes were iteratively knocked-out. As a conceptual novelty, we pursued an adaptive approach allowing changes in the model and initially calculated intervention strategy if a genetic modification induces changes in byproduct formation. Using this approach, we iteratively implemented five interventions leading to high yield itaconic acid production in minimal medium with glucose as substrate supplemented with small amounts of