Evaluation of fermentation processes using a mathematical model for metabolic reactions including metabolic bottleneck and product inhibition on cell growth

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1. Introduction
A number of recent research work has been focused on investigation of bottlenecks in metabolic reaction networks in order to enhance product yields in fermentation processes. However, when a toxic product strongly inhibits cell growth or executes cells, it is unknown whether removal of the bottleneck is meaningful. In this work, therefore, we constructed a mathematical model including a metabolic bottleneck and a product inhibition on cell growth and investigated how much product yield is enhanced when the bottleneck is removed under different conditions of product inhibition.

2. Theory
Figure 1 shows a generalized metabolic pathway model, which includes both bottleneck and inhibition components. The model was expressed in terms of S-system representation. In this model, the bottleneck parameter \( \gamma_1 \) is given by \( 1 - v_1 / (v_1 + v_2) \), while the inhibition parameter \( \gamma_2 \) is by \( h_{54} \), the exponent to the toxic product.

\[
Y_1 = \text{Extracellular substrate} \\
X_1 = \text{Intracellular substrate} \\
X_2 = \text{Intermediate metabolite} \\
X_3 = \text{Intermediate metabolite} \\
X_4 = \text{Toxic product} \\
X_5 = \text{Cell concentration}
\]

Fig.1 A generalized metabolic pathway model

3. Results and Discussion
Figure 2 illustrates the time courses of metabolite, product, and cell concentrations. All metabolite concentrations quickly increase and then keep constant, while the extracellular product concentration constantly increases throughout the period of time. The cell concentration increases and then decreases as a result of inhibition by the product. Figure 3 illustrates the time courses of product concentrations at different \( \gamma_1 \) and \( \gamma_2 \) values. When the degree of metabolic bottleneck is higher, the product concentration is lower. Also, as the inhibition parameter increases, the product concentration is significantly lowered. However, the extent of an increase in the product concentration by enhancing the flux at the bottleneck may be significantly reduced in the present of strong product inhibition. The product concentration, in turn, becomes high with the decrease of inhibition parameter.

Case examples for ethanol and penicillin fermentations were also considered to validate the generalized model. The obtained results suggest that finding a metabolic bottleneck and then genetically manipulating may be less meaningful under a condition of high product inhibition.

References

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