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Metabolic Regulation and Maximal Reaction Optimization in the Central Metabolism of A Yeast Cell

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Abstract. Regulation of fluxes in a metabolic system aims to enhance the production rates of biotechnologically important compounds. Regulation is held via modification the cellular activities of a metabolic system. In this study, we present a metabolic analysis of ethanol fermentation process of a yeast cell in terms of continuous culture scheme. The metabolic regulation is based on the kinetic formulation in combination with metabolic control analysis to indicate the key enzymes which can be modified to enhance ethanol production. The model is used to calculate the intracellular fluxes in the central metabolism of the yeast cell. Optimal control is then applied to the kinetic model to find the optimal regulation for the fermentation system. The sensitivity results show that there are external and internal control parameters which are adjusted in enhancing ethanol production. As an external control parameter, glucose supply should be chosen in appropriate way such that the optimal ethanol production can be achieved. For the internal control parameter, we find three enzymes as regulation targets namely acetaldehyde dehydrogenase, pyruvate decarboxylase, and alcohol dehydrogenase which reside in the acetaldehyde branch. Among the three enzymes, however, only acetaldehyde dehydrogenase has a significant effect to obtain optimal ethanol production efficiently.

Keywords: fermentation process, kinetic modelling, metabolic control analysis, Differential Evolutionary algorithm.


INTRODUCTION

Metabolic regulation of a microbial process has became a main concern in the recent of metabolic engineering study [1, 2, 3]. It is quantitative and qualitative tools for optimization the productivity of microorganism in producing a desired metabolic product. Regulation of cellular activities is conducted through regulation of chemical reactions in the metabolic pathways. Manipulation of enzymatic functions of the cell will improve cellular activities to achieve an optimal metabolism. Equipped with structural analysis of the metabolic networks, it will provide a relationship between metabolic variables based on the stoichiometric analysis of the network [1, 4]. The essential prerequisite to achieve a successful metabolic regulation is information about metabolic networks and enzymes underlying the process. Such information about metabolic networks and enzymes can be accessed freely from the number of database such as KEGG [5, 6], BREnda [7], and MetaCyc [8], which provide complete metabolic information derived from experimental results and from primary literatures. Combination of experimental data and theoretical approach will complete identification and analysis of metabolic networks for attaining the optimality of the cellular metabolism system.

One of the most important aspects in physiological study of metabolic process is quantification of metabolic fluxes. It becomes an optimality criterion in studying cellular reaction systems. Identification of fluxes will allow us to design some regulation rules to maximize the steady-state fluxes of the desired metabolite production. Obviously, quantification of metabolic fluxes requires a technique to determine relationship between steady-state properties of a biochemical network and the properties of its individual reactions. Metabolic control analysis is a powerful tool for theoretical and experimental analysis for quantifying how the control of steady-state fluxes and concentrations is shared between the different reactions in a metabolic pathway. This method was developed independently by two researcher groups, Kacser and Burns (1973) [9], and Heinrich and Rapoport (1974) [10] (for more detail about the method see for instance [11, 12, 13, 14]). The quantification was covered in term of a flux control coefficient which shows the percentage change in flux divided by the percentage change in activity of an enzyme that was responsible for that flux change. Once the fluxes are identified such regulations can be applied to the respective reactions to improve the production of the desired metabolite.