Application of Standard Gibbs Free Energy Changes of Reactions to metabolic pathway computation

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1 Introduction

When metabolic reconstruction is performed to elucidate the biological function of a complete genome, it is essential to explore biosynthesis and biodegradation pathways by using the organism specific enzyme reactions. The KEGG(Kyoto Encyclopedia of Genes and Genomes) system provides a tool to compute possible pathways between two compounds [1]. However, it sometimes produces a large number of paths including the ones that are not working in actual biological pathways, because it adopts a simple graph search algorithm based on breadth first search. Therefore we need to consider other biological properties to extract biologically meaningful paths. In this work, we computed the standard Gibbs free energy changes of the reactions registered in the KEGG/LIGAND database [2] by utilizing an automatic compound structure comparison method, and used them to evaluate the output of the path computation tool.

2 Method and Results

In the COMPOUND section of the LIGAND database [2], there are about 10,000 biochemical compounds, including substrates, cofactors and inhibitors of enzymes as well as drugs. We calculated the standard Gibbs free energies of 8,689 compounds, which had 2-D structure data, using the group contribution method [3], where a compound was divided into functional groups and its standard Gibbs free energy was the sum of Gibbs free energy of each group and a constant origin. We then calculated the standard Gibbs free energy changes of 4,900 biochemical reactions using the method.

Also, we developed a scoring system using the calculated standard Gibbs free energy changes for screening the result of path computation, in order to provide a method for selecting feasible paths among all possible computed paths. We calculated two values for a path between two compounds. One is the largest free energy change in the reaction steps forming a path and the other is the summation of all the values in the reaction steps. As an example, we searched possible pathways from D-glucose to pyruvate consisting of 8 reaction steps(Fig. 1). The result of the path computation from D-glucose to pyruvate is shown in Fig. 2. We obtained 211 paths, among which we could calculate the standard Gibbs free energy changes for 200 paths. The generally known path(Fig. 1) ranked the 61th(-24kcal/mol) in the summation method and 121th(38kcal/mol) in the maximum value method. The reactions assigned to Pentose-phosphate-pathway frequentry appeared in the higher ranked paths.

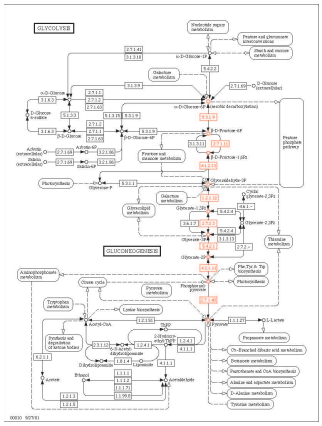

Figure 1: Pathway from alpha-D-glucose to pyruvate in the KEGG map glycolysis

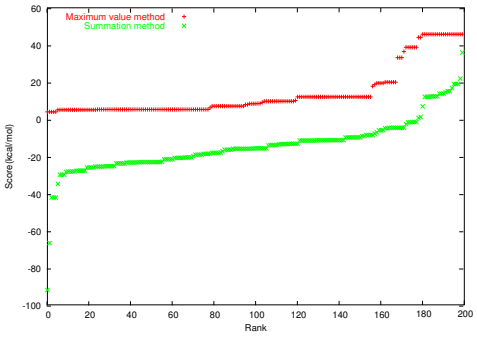

Figure 2: Score distribution of the path computation based on summation and maximum value method

3 Discussions

The result using the maximum value method shows that at least one reaction with the positive free energy change was included in all of the computed paths. A large positive free energy change could be a barrier of a biochemical reaction and the reaction with such a value is considered as a biochemically infeasible one. However, under the physiological conditions each reaction can not have large positive energy changes. Consequently, we have to consider some factors which make reaction feasible. As an example, the physiological concentration of substrate or product is not taken into consideration when we computed Gibbs energies of reactions. Physiological concentration for EMP pathway in erythrocytes [4] or cardiac muscle cell [5] was uncoverd, hence we can caluclate scores of the compounds considering metabolite concentration. When we caluclate Gibbs energy changes of reactions with consideration of concentrations for intermediate metabolites in human erythrocyte, the score for the reaction catalyzed by aldorase decreases from 23.97kcal/mol to 0.7kcal/mol, and so this reaction was able to evaluated for thermodynamic feasibility. In most cases, metabolite concentrations are unknown. However, because we can assume the permissible ranges of concentrations of metabolites, the future direction of this study will be how the ranges of concentration is treated. Another direction would be a consideration of stochiomeric information.

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