Extraction of a Thermodynamic Property for Biochemical Reactions in the Metabolic Pathway

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1 Introduction

When metabolic reconstruction is performed to elucidate the biological function of a complete genome, the path computation between two compounds is sometimes necessary. For example, if a missing enzyme is found in a biosynthesis pathway for a compound that is supposed to be synthesized, we need to search an alternative enzyme or a path for the enzyme reaction. Typically, the input of the path computation is a set of two compounds that correspond to a substrate and a product, and the output is a set of all possible paths that connect the two compounds. However, this set includes many paths that are not working in actual biological pathways.

Previously we have considered the standard Gibbs free energy changes in enzyme reactions and discussed about their applicability to the path computation [1]. In this work, we computed the standard Gibbs free energies of the compounds and the standard Gibbs free energy changes of the reactions registered in the LIGAND database [2]. We covered as many entries as possible with the advent of the automatic compound structure comparison method [3]. We also developed a new function to sort the result of path computation in consideration of the standard Gibbs free energy changes of the pathway. We report here a new addition to the pathway computation tool in the KEGG system and discuss about the distribution of the standard Gibbs free energy changes in the metabolic pathways for further evaluation.

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 [4], 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 described in [5]. Figure 1 shows the distribution of the standard Gibbs free energy changes for 4,900 biochemical reactions.

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. A large positive free energy changes could be a barrier of a biochemical

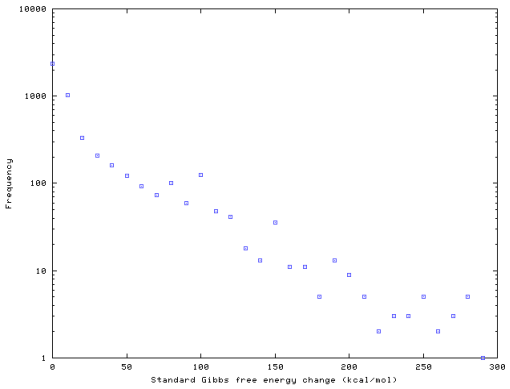

Figure 1: Distribution of the absolute standard Gibbs free energy change of 4,900 biochemical reactions.

Table1: The list of metabolic pathway with large Standard Gibbs free energy changes (over 100).

Metabolic pathway	Number
Starch and sucrose mtabolism	17
Flavonoids, stilbene and lignin biosynthresis	13
Benzoate degradation via CoA ligation	13
Tyrosine metabolism	12
Terpenoid biosynthesis	10
Alkaloid Biosynthesis I	9
Porphyrin and chlorophyll metabolism	8
Aminosugars metabolism	8
Tryptophan metabolism	8
Sterol biosynthesis	8

reaction and the reaction with such a value is considered as a biochemically infeasible reaction. 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 a-D-glucose to pyruvate consisting of 8 reaction steps, whose total free energy change is known to be -5 kcal/mol. We obtained 161 paths, among which we could calculate the standard Gibbs free energy changes for 142 paths. When these paths were ranked in the increasing order, the real 8-reaction pathway was not ranked among the best paths in our computation. When we used the summation or the largest value of 38 kcal/mol, we could not identify the real pathway either. Table 1 shows the list of metabolic pathways with the number of reactions with the standard Gibbs free energy change of 100 kcal/mol or higher.

3 Discussion

The current scoring system for identifying a potential pathway adopts the simple summation of energy changes or the largest energy changes in the pathway. Since neither of the scoring systems ranked well, a score representing other thermodynamic properties in the pathway should be investigated.

Figure 1 shows that the metabolic pathway is formed of many equilibrium reactions with small Gibbs energy changes and a small number of virtually nonequilibrium reactions with large Gibbs energy changes. The latter produces a flow or a bottleneck in the pathway. Table 1 suggests that nonequilibrium biochemical reactions with large degrees of standard Gibbs energy changes are localized in several pathways. In general, the flow in the pathway is strictly controlled by such nonequilibrium reactions. From this point we might go on to a more detailed analysis of the thermodynamics properties of the pathway.

References

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