

Standard Gibbs Free Energy Changes of Enzyme Reactions in Metabolic Pathway Computation

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Abstract

Standard Gibbs free energies of formation of biochemical compounds in aqueous solution are calculated and applied to determining the direction of enzyme reactions. Although we need more analysis, a large positive free energy change could be a barrier of an enzyme reaction and could be used to suppress biochemically infeasible reactions in the computed pathways. The values of free energy changes can also be used to select the most feasible candidate from several reactions that use the same substrate.

1 Introduction

As whole genome sequences of several organisms have become available, they present computational problems to analyze how biological components are connected to form a functional unit, such as a metabolic pathway and a signal transduction pathway. The KEGG project aims to computerize current knowledge of the information pathway of genes and gene products, which may be considered as wiring diagrams of biological systems[1]. Computation of biological pathways from a collection of interactions or relations is one of the chief objectives of the KEGG project. Currently, our focus of the pathway computation is on a reconstruction of metabolic pathways from the database of enzyme reactions and the list of enzymes for a specific organism, such as *Haemophilus influenzae*.

When computing metabolic pathways, how to determine biochemically feasible pathways from a number of calculated (potential) pathways is a challenging problem. We exploit standard Gibbs free energy changes in enzyme reactions as a measure of the feasibility of metabolic pathways. The standard Gibbs free energies of selected biochemical compounds and the free energy changes associated with enzyme reactions are calculated for the LIGAND database[2], based on the method described in [3, 4].

2 Method and Results

In the COMPOUND section of the LIGAND database, there are about 5,000 biochemical compounds, including substrates, products, cofactors and inhibitors, that are related to enzyme reactions. We compiled standard Gibbs free energies of 251 compounds among them (185 from [3] and 66 from our calculation). The calculation was based on the group-contribution method, in which a compound was divided into functional groups and its standard Gibbs free energy was the sum of the Gibbs free energy of each group and a constant origin. The values of the Gibbs free energies of functional groups in aqueous solution were also taken from [3]. According to Mavrovouniotis's method[4], we then calculated the standard Gibbs free energy changes of 215 enzyme reactions taken from the ENZYME section of the LIGAND database, using the Gibbs free energies of the 251 compounds.

We then applied the calculated standard Gibbs free energy changes of enzyme reactions to the pathway computation. Using the *H. influenzae* data, the pathway from D-glucose to pyruvate in glycolysis produced 27 pathways. Among them there were seven pathways containing the reaction from phosphoenolpyruvate to pyruvate with a large negative free energy change (-18.7 kcal/mol), and a pathway containing the reaction from oxaloacetate to phosphoenolpyruvate with a large positive free energy change (34.4 kcal/mol).

Although we need more analysis, a large positive free energy change could be a barrier of an enzyme reaction and hence could be considered as a biochemically infeasible reaction. A large negative free energy change may mean that the reaction is virtually irreversible, which can also be used to suppress the backward reaction. Another possibility of using the standard Gibbs free energy changes is to select the most feasible candidate from several reactions that start from the same substrate, for example, at the branching point of several pathways. Thus, the scoring system using the Gibbs free energy change could be useful to select biochemically feasible pathways and refine the results of pathway computations.

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