Theoretical Analysis of Metabolic Networks: Attempt to Express Topological Position of Individual Atoms in a Given Network

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1 Introduction

Connectivity in metabolic networks is classified into metabolite-level connectivity through enzymatic reactions and atom-level connectivity. Atom-level connectivity is further classified into inter-metabolite connectivity through enzymatic reactions and intra-metabolite connectivity through chemical bonds. Intra-metabolite atom-level connectivity has been expressed in structural formulae of metabolites and considered separately from inter-metabolite atom-level connectivity. Evolutional co-emergence of a new metabolite and a new enzymatic reaction responsible for the metabolite is a reasonable idea, suggesting potential correlation and probably complicated relationship between inter- and intra-metabolite connectivities in the network structure. I have developed data format for describing inter- and intra-metabolite atom-level connectivities to contribute to complete understanding of metabolic networks including evolutional generation of metabolic networks and relationship between the capabilities of a metabolic network as an organic whole and its structure [1–3]. On the other hand, in order to understand function of each metabolite or atom in the context of structure-function relationship, it is important to develop the indices for expressing topological position of each metabolite or atom in a given metabolic network. The present study was conducted as an attempt to develop such indices.

Topological position of metabolites or atoms in a metabolic network is considered to closely relate to the set of possible paths or cycles connecting between metabolites or atoms. Therefore, in the present study, possible atom-level cycles through inter-metabolite atom-level connectivity were investigated in a model network of carbohydrate metabolism as the first step to develop topological indices of each atom in the network.

2 Method

2.1 The Model Network of Carbohydrate Metabolism

The model metabolic network used in the present study was composed of the reactions for glycolysis, oxidative decarboxylation of pyruvate, citric acid cycle, pentose phosphate pathway, and gluconeogenesis. In the model network, reactions in the cytosolic compartment are distinguished from those in the mitochondrial compartment.

2.2 Description of Inter-Metabolite Atom-Level Connectivity in the Model Network

Each atom in the network was expressed as a row vector composed of 4 integers indicating metabolite species, position of atom in the metabolite, atom species, and compartmentation. Information about connectivity itself was also expressed as a row vector composed of integers. A vector for inter-metabolite connectivity included 1 (connectivity-type number), reaction number, direction number, and stoichiometry number, which indicates how many times the connectivity, appears in the reaction. Thus, conversion of atom \textit{v}_{a_1} to atom \textit{v}_{a_2} through reaction \textit{v}_r is expressed as (\textit{v}_{a_1}, \textit{v}_{a_2}, \textit{v}_r), a row vector formed by the combination of
3 row vectors. Using this format, all the atom-level connectivities in the network were expressed as a matrix, connectivity matrix, each row of which corresponded to one connectivity [1–3]. Metabolite number and reaction number were from the LIGAND database [4].

2.3 Construction of Connectivity Matrix and Computation of Atom-Level Cycles in the Network

Construction of connectivity matrix from IMAC and computation of all the possible atom-level cycles in the network using information on the connectivity matrix were conducted on GNU Octave or Matlab by functions or scripts written for analysis of metabolic networks [1, 3, 5, 6].

3 Results and Discussion

The total number of carbon species in the model network of carbohydrate metabolism was 465, which included 324 carbons from currency metabolites. 153 atom-level cycles of carbon atoms were identified. The average length of the cycles as number of reactions was 32 (3–56). The number of carbon species on the cycles was 132.

The frequency of appearance of specific atoms in the cycles depends on the structure of the whole network. Therefore, it can be a candidate of indices of topological position of atom in the network. Table 1 shows the frequency of appearance of several specific atoms in the cycles, indicating the frequency was different among carbon species. As for pyruvate, C1, the -COOH carbon, which is directly metabolized to CO2 had low frequency in contrast to C2 and C3. As for glucose 6-P and fructose 6-P, C4, C5, and C6 had low frequency in contrast to C1, C2, and C3, which seems to correspond to cleavage of these hexose phosphate into triose phosphates. These findings show that frequency of appearance of specific atoms correlates to the biological fate of each of those atoms, indicating that analysis of the set of all the possible paths or cycles is a right approach to develop indices of topological position of atoms in the network.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Compartment</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyruvate</td>
<td>Cytosolic</td>
<td>3</td>
<td>66</td>
<td>62</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>Mitochondrial</td>
<td>3</td>
<td>66</td>
<td>62</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Glucose 6-P</td>
<td>Cytosolic</td>
<td>18</td>
<td>48</td>
<td>45</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fructose 6-P</td>
<td>Cytosolic</td>
<td>88</td>
<td>102</td>
<td>107</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 1: Number of atom-level cycles including the carbon atom indicated.

References


