

**THE SMALL WORLD IN BIOPHYSICAL SYSTEMS
STRUCTURAL PROPERTIES OF GLYCOLYSIS AND THE TCA
CYCLE IN *ESCHERICHIA COLI***

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Abstract: It has been shown that the central metabolic network of *Escherichia coli* is of the small-world type. In this paper, we present that the metabolic network of glycolysis and TCA cycle as a part of the *E. coli* metabolism is also a small-world network. We found that the hubs of the studied network are consistent with those found in the complete metabolic network. The evolutionary meaning of this finding is discussed.

Key Words: Small World Network, Glycolysis, TCA Cycle, *Escherichia Coli*

INTRODUCTION

It was recently shown that many biophysical systems, such as the neural network of the nematode worm *Caenorhabditis elegans* [1], and several metabolic networks, have the characteristics of small-world networks [2]. Here, we focus on the structural properties of the metabolic network of *Escherichia coli*, previously studied by Fell and Wagner [3, 4]. They found that the metabolic network of *E. coli* is of the small-world type. From a study of the most highly-connected metabolites (hubs), it was proposed that glycolysis and the TCA cycle are perhaps the most ancient metabolic pathways. Therefore, it is in our interest to study only glycolysis and the TCA cycle. We show that the metabolic network of glycolysis and the TCA cycle found in *E. coli* is a small-world network. Our results confirm our hypothesis that the hubs of the studied metabolic subsystem are consistent with those found in the complete central metabolic network of *E. coli* [3, 4]. A possible evolutionary meaning of this finding is discussed.

METHODS

For glycolysis and the TCA cycle of *E. coli*, we assembled 19 stoichiometric equations containing 32 key metabolites that represent the two important metabolic pathways. Using Herbert Sauro's software package Jarnac v1.19 (<http://www.sys-bio.org/>), we generated a stoichiometric matrix. From this matrix, a substrate graph was created. The substrate graph consists of all the chemical compounds (metabolites) found in glycolysis and the TCA cycle acting as vertices, linked together by a number of edges. Two metabolites are declared

as adjacent if they are found in the same stoichiometric equation. However, we discarded the direction of the edges. We consider that two metabolites are connected if a path exists from one to another.

To determine the small-world properties of the substrate graph, we calculated the characteristic path length of the graph (L) and the clustering coefficient of the graph (C) [1]. The path length (L) measures the typical separation between two vertices in the graph. It is calculated as a number of edges in the shortest path between two vertices, averaged over all the pairs of vertices. The clustering coefficient (C) represents the cliquishness of a typical neighbourhood. Consider all vertices adjacent to vertex v , and count the number of all possible edges among them (not including the edges connecting them to v). The fraction of all of these allowable edges that actually exist represents C_v . The clustering coefficient (C) is then defined as the average of C_v over all v . Additionally, in the analysis of the substrate graph, we took a closer look at the connectivity of each metabolite. The most connected metabolites were assigned as hubs.

RESULTS

In Table 1, we compare the quantities L and C for the substrate graph with the corresponding values for regular and random graphs, generated with the same number of vertices and the nearest possible number of edges. We found that the substrate graph has a path length L very close to the value obtained for the random graph, whereas C is very close to the value obtained for the regular graph. This indicates that the substrate graph of glycolysis and TCA cycle has a small-world character.

Tab. 1. Characteristic path lengths and clustering coefficients for the substrate graph and the corresponding regular and random graphs.

	Characteristic path length L	Clustering coefficient C
Regular graph	3.0	0.60
Substrate graph	2.3	0.77
Random graph	2.0	0.20

Another important aspect of this analysis is to check the connectivity of the metabolites involved in glycolysis and the TCA cycle. As Fell and Wagner [3, 4] suggested, the metabolic networks probably evolved over time and consequently networks expanded in size, adding new metabolites. Therefore the metabolites with the highest numbers of connections, the so-called hubs, are probably evolutionarily the oldest. If we omit the substrates ATP, ADP, NAD, etc. because of their universal presence, we find that HSCoA, SuccinylCoA, AcetylCoA, Pyruvate, Succinate and OxaloAcetate are the most highly connected metabolites, and probably belong to the core of the metabolism from

an evolutionary point of view. Here, we have to take into account that the small metabolic network of glycolysis and the TCA cycle cannot always adequately represent the global properties of the metabolism. However, our results concur well with those obtained for the complete core metabolism of *E. coli* [3, 4].

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