

Regulation of Metabolic Networks By Small Molecule Metabolites

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1 Introduction

Cellular metabolism comprises all the chemical reactions that take place within a cell. Through these various reactions, the cell generates mass and energy, replicates itself, and can transmit information to its neighbours. A fundamental property of all organisms is their ability to adapt to changing environments by regulating their metabolism. Cells use a number of mechanisms to regulate their metabolism. Two of the most common and well studied are genetic regulation (repression or activation of enzyme gene transcription)[5], and enzyme inhibition/activation by small molecules (allosteric inhibition for example)[3]

Barrett *et al*[1] studied the genetic regulation of metabolism in *E.coli* using a genome-scale model of the known metabolic and genetic regulatory networks[2]. In contrast genome-scale analyses of enzyme inhibition and activation networks have been lacking to date. Here we present such an analysis. We aim to answer basic questions about how the enzyme inhibition and activation regulatory system is organised.

2 Method and Results

Inhibitory and activatory interactions between small molecules and enzymes were extracted from the BRENDA database[4] for *Escherichia coli*, *Homo sapiens*, and *Saccharomyces cerevisiae*. The regulatory interactions for each organism are represented by a directed bipartite network. An edge is drawn to connect a compound node to an enzyme node when the compound is known to regulate the enzyme. We compare the global properties of this regulatory network with the underlying metabolic network.

Figure 1 shows the degree (k) distribution and the relationship between the clustering coefficient (C) and k for the interactions taken from *E.coli*. In both cases the structure of the regulatory network appears similar to the metabolic network, with patterns characteristic of scale free hierarchical networks evident in each.

While it is clear that the regulatory network follows the metabolic network in many respects, there are also areas where it diverges. NAD and ATP, for instance, are involved in similar numbers of metabolic reactions, however ATP is observed acting as a regulator far more often than NAD. We propose that this is related to the chemical structure of the two compounds and their respective partners: NADH^+ and ADP. Since the change between NAD and NADH^+ is chemically so small (a single proton), we suggest that it is harder for enzymes to evolve binding sites capable of distinguishing between them, than it is for enzymes to evolve binding sites capable of distinguishing ATP and ADP which differ by a whole phosphate group.

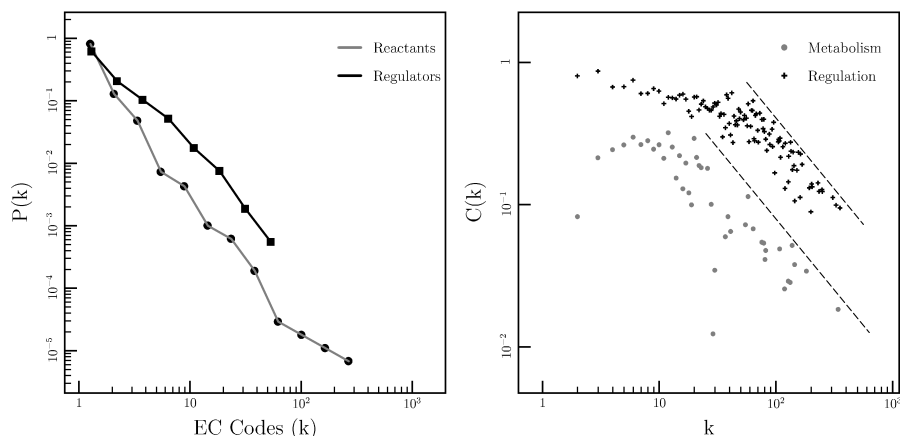


Figure 1: Log-log plots of the degree distribution (left) and clustering coefficient (right) for compound nodes in the regulatory and metabolic networks of *E.coli*.

The role of chemical structure in enzyme regulation is also of interest because of the way enzymes can evolve to bind sub-structures within compounds, rather than whole compounds. This allows groups of similar compounds to regulate the same enzyme(s) and for regulatory modules of compounds and enzymes to form. We show that there is a relationship between the chemical similarity of two compounds and their ‘regulatory similarity’, and that structurally and functionally related groups of compounds tend to form regulatory modules.

3 Discussion

The relationship between metabolism and its regulation is of importance in understanding basic biology. In the future, computer models of cellular processes will have to correctly account for this type of regulation, as well as genetic regulation and other forms. The role of chemical structure in performing this regulation is also of interest in medicine, particularly in designing drugs that may seek to regulate metabolism themselves.

References

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