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**Small Molecule Regulation of Metabolic Networks**


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**Short Abstract:** We have used data from the KEGG and BRENDA databases to study the way in which small molecules regulate metabolism. We find a scale-free topology in the regulatory network that is conserved across several organisms, though the details of which compounds act as regulators is found to vary.

**Long Abstract:**
In addition to genetic regulation at the transcription and translation level, enzymes are also regulated by small molecule inhibitors and activators. The network properties of the genetic regulatory network have been well studied, but not so with small molecule regulation. Understanding the way in which cellular metabolism is regulated by small molecules, such as metabolites or drugs, is important for developing in silico models of cells, elucidating the evolution of pathways and enzymes and understanding the effects of drugs that modulate metabolic activity. We aim to establish the network properties of this regulatory system across a number of different organisms and identify common and varying regulatory motifs. <p> We extract data from the KEGG and BRENDA databases that describes the inhibition and activation of enzymes by small compounds. To improve coverage of poorly studied organisms, annotation is transferred from originally annotated enzymes to closely related orthologues in some cases. By analysing the resulting data in terms of a network of regulatory compounds and regulated enzymes, analogous to transcription factor/gene networks, we identify the global properties of the regulatory network and common regulatory motifs. By comparing networks from different organisms we also identify the different ways in which organisms regulate their metabolism. <p> We find that the topology of the regulatory network matches the commonly observed scale-free topology observed in many other biological networks. A few hub molecules, such as ATP, dominate the network, regulating many different enzymes, while most compounds only regulate one or two different enzymes. Similarly, most enzymes are only regulated by a few compounds while a few 'hot-spot' enzymes are regulated by many different compounds. Inhibition is found much more commonly than activation, accounting for ~80% of regulatory interactions. This reflects the fact that it is structurally easier to disrupt an enzyme active site, and thus inhibit an enzyme, than form a more effective one. <p> We find a surprisingly weak relationship between the propensity for a compound to be involved in enzyme reactions as a substrate or product, and the propensity for a compound to be involved in regulating reactions. This suggests that the use of a compound as a regulator is not simply determined by how often it is used in metabolism. For instance, ATP and NAD are both involved in many reactions as a substrate/product. However, we observe ATP acting as a regulatory molecule far more often than we do NAD. Clearly there are other factors besides metabolic importance, such as chemical properties, which determine a compounds `usefulness' as a metabolic regulator.

<p> Comparisons between the regulatory networks of different organisms such as E.Coli, S.Cerevisiae and H.Sapiens show that while the global properties of the regulatory networks are conserved, some important details change between organisms. In particular, we find differences in the importance of certain classes of molecules as regulators. Metabolites involved in glycolysis, amino acid metabolism and the citric acid cycle tend to be important enzyme regulators in both E.Coli and S.Cerevisiae, while they are less important in H.Sapiens. Pyruvate, for instance, regulates 25 different enzymes in E.Coli and only 4 in H.Sapiens. In contrast intra and inter-cellular signalling molecules such as NO, cAMP, and components of the phospholipid and glycan metabolic pathways such as CDP, phosphatidylserine and phosphatidylcholine are more important in H.Sapiens. This would seem to reflect the need for single celled organisms to regulate their metabolism based on the availability of basic nutrients, while for multi-cellular organisms it is more important to respond to signals from surrounding cells. <p> In conclusion, we have identified several important properties of small molecule regulation of metabolism. Many of these features are found to be common across different organisms, though we find important differences in the compounds used as regulators between different organisms.