Exploiting the Modular Topology of *E. coli* Genome Scale Reconstruction

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The topology of metabolic networks is recognisably modular with each module weakly connected to each other apart from sharing a common pool of currency metabolites. This structure provides a high degree of stability against perturbations. Modules can be used for model reduction and to simplify the study of network features. However, many definitions of modules have been proposed.

In this study, we were inspired by the classical definition of pathways and defined modules as sets of reversible reactions isolated from the rest of metabolism by irreversible reactions except for the exchange of currency metabolites. This approach creates thermodynamically isolated modules, in which the input and output are controlled by irreversible reactions commonly subject to allosteric regulation.

Using this approach to modularise *E. coli* iJO1366 created 103 modules, each with a defined metabolic function. Using this modularisation, we addressed a fundamental question about the flexibility conferred by reversible reactions: “Of all the potential directed topologies, how many (N) are in fact capable of carrying flux through all reactions?”

We define \( \log_2 N \) as "topological" degree of freedom of the network. A set of mass balance and loop-less rules that define the scenarios in which one or more reversible reactions are unable to carry flux were generated. Assuming that clusters are independent of each other the topological degree of freedom was determined to be 201, i.e., in average the direction of 201 irreversible reaction (79%) must be defined before all directions in the network are fixed. We conclude that - except in dependent of each other.

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