An Integrated Analysis of the Metabolic and Regulatory Networks of *Escherichia coli* K12

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Objective: The major goal of this work is the integrated analysis of metabolic and genetic networks of *Escherichia coli* K12, by performing network topology analysis, motif finding and the simulation of cell behaviour. Here we use a novel logic framework, which provides users with a powerful language to query information using both first and second order predicates.

Results: The overall network integrates data from publicly available repositories, namely EcoCyc, BRENDA and RegulonDB, and Palsson's manually-curated stoichiometric model (Feist *et al.*, 2007). The metabolic level comprises all known chemical reactions catalyzed by enzymes, with the corresponding reactants and products, which may also act as metabolic regulators (inhibitors and activators). Genes, promoters, transcription factors, transcriptional inducers and sigma factors, constitute the elements of the gene regulation level.

Results from topological analysis confirmed previous studies on *E. coli* models, highlighting the importance of several biomolecules in the cellular metabolism. As expected, sigma factor σ_{70}, CRP transcriptional factor and metabolic cofactors, such as ATP, NADH and others, are major network hubs.

The integration of both metabolic and genetic regulation in the same network, allowed to perform a novel integrated analysis and to reach interesting results, namely the identification of the pathways in which one or the other type of regulation is dominant.. Additionally, it was possible to observe that in several pathways those regulation mechanisms are used together to provide a range of metabolic responses, e.g. in citric acid cycle and glycolysis.

Furthermore, results revealed the intrinsic complexity of reaction networks, involving several structural motifs. The uncovering motifs illustrated a tight control of metabolism.

Conclusions: An integrated view of the metabolic and regulatory networks is of paramount importance in the elucidation of the mechanisms of regulation in different cellular processes. Moreover, *in silico* strain improvement procedures through metabolic engineering design may benefit by considering simultaneously this different types of cellular regulations.

Feist, A. M. et al. *Mol Syst Biol* **3,** 121, 2008