**Small is Beautiful. Reduced Model(s) of Metabolism.**

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The knowledge of genomes leads to the construction of genome-scale models (GSM) involving all the enzymes possibly encoded in the genome. The best example of such a model is Recon2 involving 7,440 reactions and 5,063 metabolites. Due to their big sizes, it is difficult to study these models and the only possible approach is Flux Balance Analysis looking for flux values able, at steady-state, to optimize some objective function. The calculation of all the Elementary Flux Modes (EFMs), i.e. the minimal pathways inside the metabolic network at steady-state are out of the possibilities of our computers. Similarly, the lack of knowledge of the amount of most of the enzymes and their kinetic properties prevent to develop large representative dynamical systems. Furthermore it is difficult on such big systems to understand their functioning in special situations normal or pathological and even to be sure that the results obtained are not artefactual or biased.

For all these raisons we decided to develop simpler models still representing the main architecture of the whole metabolism but with fewer reactions which are aggregations of the actual reactions (keeping the stoichiometries). Typically, such reduced models involve between 50 to 100 reactions and metabolites to describe the central carbon metabolism. The advantage of such models is to be more easily tractable and more understandable. Furthermore they can be approached with a greater panel of methods such as analysis of EFMs, FBA and FVA. Their dynamical behavior can be studied with some reasonable hypotheses on their kinetic laws and Metabolic Control Analysis (MCA) is possible leading to the determination of good targets for therapeutic or biotechnology purposes.

With such a simple metabolic model we have determined the different ways to synthesize serine from glutamine in cancer cells. We were also able to simulate Crabtree and Warburg effects and the metabolic changes accompanying mitochondrial diseases. We also specified the objective functions able to characterize different metabolism associated to different cell types.

However, it is obvious that a simple model cannot retain all the complexity of a GSM. Furthermore in the construction of the simple model some reactions may have been discarded without consequence in most of the conditions but which could play an essential role in some peculiar conditions. For this reason, it is important to compare the behavior of the reduced models to the genome scale models as often as possible with the only method applicable to both type of models, i.e. FBA

To sum it up, we propose the following general method to study metabolic networks:

* The study of reduced models with several complementary methods.
* The comparison of different models of various sizes with FBA approach.

The aim will be to look for the consistency between the results obtained on the one hand from the different approaches on a reduced model and on the other hand with FBA on different models of various complexity.