Title: *Modeling integrated biochemical networks: methods, advances and perspectives*

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Extended Abstract (~250 words):

Understanding how cellular systems build up integrated responses to their dynamically changing environment is one of the open questions in Systems Biology. Despite of their intertwinement, signaling networks, gene regulation and metabolism have been frequently modeled independently in the context of well-defined subsystems in model organisms. Several mathematical formalisms have been developed according to the features of each particular network. These range from fully qualitative to fully quantitative approaches, graph-based descriptions and stoichiometric models, discrete logical models, continuous kinetic models or stochastic models, which have been used thoroughly. Nonetheless, a deeper understanding of cellular behavior requires the integration of these various sub-networks into a model capable of capturing how they operate as ensemble.

With the recent advances in the 'omics' technologies, more data is becoming available and thus recent efforts have been driven towards this integrated modeling approach. Most attempts use either the above mentioned formalisms or some improved derivations.

We herein review and discuss these methodological frameworks currently available for modeling and analyzing integrated biochemical networks. These include some graph-based methods, extensions of Flux-Balance Analysis, logical modeling, Petri nets, traditional kinetic modeling and hybrid systems that couple continuous dynamics with discrete state transitions. Comparisons are also established regarding scalability with network size, required computational power and the biological problems each method is more adequate to address. The methods are illustrated with successful case-studies of large-scale genome models or some particular subsystems mainly in organisms such as the budding yeast or the bacteria *E. coli*.