Proposal for a PhD thesis
MAPi doctoral program

Title:
Development of methods for in silico optimization of metabolic networks

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Background:

Most biological systems are **complex systems**[1] since they are composed of many parts which are coupled in a nonlinear fashion to form a highly connected interaction network. **Systems Biology** is a new field of science aiming to analyze complex biological systems by studying their emergent properties, which cannot be completely understood by investigation of individual components in isolation. This research field has received increasing attention in the last few years[2-5].
The ultimate aim of such an approach is to develop **models of biological systems** so that their response to any perturbation can be **predicted** and therefore used in custom **design** of such systems. It is expected that this new paradigm brings major benefits to several industrial and research efforts, namely in identifying the **function of unknown genes**[6], aiding **drug discovery** efforts[7] and in the development of **rational biotechnological production processes** of several chemicals[8].
Several model representation schemes exist that can be used to represent cellular behaviour, covering mainly metabolic and regulatory phenomena, and methodologies for the inference of model structure and parameters from experimental data are being developed. Metabolic models can be represented using notions from **graph theory**, where nodes and edges can represent enzymes and metabolites in a variety of ways. Topological analysis of these models allows raising some important conclusions regarding robustness and other features of the metabolic network.
Approaches related with this graph representation, also able to simulate cellular behaviour as discrete-event systems are the representation of kinetic models or gene regulatory networks with bipartite graphs called **Petri Nets**[9]. This representation is claimed to be a closer approximation to biological systems as compared to other approaches and methodologies have been described for the inference of pathways from experimental data using evolutionary computation.

Objectives:

This thesis has the following scientific/ technological objectives:

- To develop a **representation scheme** based on the paradigm of Petri Nets able to represent **metabolic networks topological and kinetic properties**. These models should be translated into standard languages (e.g. SBML, CellML).

- To develop appropriate **simulation tools and algorithms**, capable of predicting behaviour of microbial metabolism by using the above defined models.

- To develop **optimization methods,** based on the Evolutionary Computation paradigm, that allow the in silico competition of hypothetic models, given some defined objective function.

- To apply the developed methods to build and optimize specific biological models for a model micro-organisms: *Escherichia coli*.

- To develop tools for **metabolic engineering**, applied in the design of **cell factories** used for biotechnological production of pharmaceuticals, food ingredients, fuels and chemicals.

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