UNIVERSIDAD ADOLFO IBÁÑEZ

DOCTORAL THESIS

Contributions to Metabolic Network Reconstructions

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Abstract

Cellular metabolism is a biological complex system made of many metabolites that interact through a large network of biochemical reactions catalyzed by cellular enzymes. To model these systems the first step is to have a good notion of which are its components and how they interact. The process of putting together a comprehensive representation of a cellular metabolic network is called genome-scale metabolic network reconstruction. These reconstructions aim to incorporate all available information regarding an organism's metabolism and usually result in networks with hundreds to thousands metabolites and reactions. The generation of these reconstructions is a valuable tool to understand the metabolism of specific organisms and also to gain knowledge on general properties inherent of this class of complex biological networks. The analysis of the dynamics of these systems is still a challenge because of the large number of reactions involved and their nonlinear behavior. As an alternative, genome-scale reconstructions are commonly accompanied with constraint-based analysis which allows to model the network's steady-state reaction flux distributions. This dissertation presents contributions to genome-scale reconstruction of metabolic networks and their constraint-based analysis. A brief overview of metabolic network modeling and reconstruction is presented in the first chapter. Chapter 2 presents a workflow aimed at assisting the genome-scale reconstruction of metabolic networks, ensuring the process is documented and reproducible. Chapter 3 describes the application of genome-scale network reconstruction and analysis in the study of *P. salmonis*, a fish pathogenic bacteria that is currently a major threat to the salmon farming industry. A comprehensive metabolic network reconstruction of *P. salmonis* is presented and compared with other pathogenic bacteria's networks revealing particularities of the fish pathogen's metabolism. Additionally, through the analysis of its network, essential metabolites required for its growth are identified, information that can guide its efficient culture and aid its study. In Chapter 4 the metabolic networks of two additional bacteria isolated from bioleaching environments are reconstructed. These networks are used to model the co-culture of these bacteria through a multi-objective optimization framework. Growth scenarios involving different energy sources are considered and the corresponding Pareto fronts are obtained to analyze the trade-offs between the growth of both organisms. Finally, Chapter 5 corresponds to another application of metabolic modeling that focuses on *N. salina*, a microalgae that has gained interest as a potential cell factory for lipid production. A first metabolic network reconstruction and model of the of this algae is presented and used to simulated growth in different conditions, results that are contrasted with experimental data. Furthermore, constraint-based analysis is used to propose gene-knockout strategies that result in modifications of this organism's metabolic network that could improve the production of triacylglycerols.

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