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A scalable systems analysis approach for regulated metabolic networks

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Abstract—**High-throughput data such as genome sequencing and genome expression profiling have enabled the reconstruction of cellular networks. These networks have been represented in computational frameworks that can be used to make testable predictions concerning phenotypes under a variety of experimental conditions and multiple molecular perturbations. This presentation will detail several recent advances in the analysis of these networks as well as provide an outlook of remaining challenges.**

I. Introduction

The genomics revolution has led to the generation of an enormous amount of data on the composition, regulation, and physiology of cellular networks. There is a need to integrate this information into computational frameworks so that testable predictions can be made with an accounting of the complexity inherent in cellular systems. Work will be presented on the reconstruction and analysis of genome-scale networks of metabolism and regulation of important cellular systems. These genome-scale models have been used to predict gene essentiality, minimal medium composition, and cellular growth under specified environmental conditions with a high-level of accuracy. These methods have been used for a variety of applications, including the identification of drug targets and mechanisms of pathogenicity (e.g., see [1] and [2]). In particular, methods concerning the reconstruction and analysis of transcriptional regulatory networks will be discussed, in particular their integration with metabolic network analysis approaches.

II. Methods

A. Network Reconstruction

An annotated genome provides the parts list for what is included in a network reconstruction. The list of metabolic genes is manually curated and the associated chemical transformations catalyzed by metabolic enzymes are incorporated into a stoichiometric matrix, ***S***. The rows of the stoichiometric matrix correspond to the metabolites or network components. The columns correspond to the reactions catalyzed by the given metabolic enzymes. The elements of the matrix are the stoichiometric coefficients corresponding to the associated metabolites in the given reactions. This network reconstruction approach has been extensively reviewed [3].

B. Flux-Balance Analysis

Flux-balance analysis (FBA) is a computational technique to characterize properties of the reconstructed network [4]. FBA uses linear programming to determine the flux distribution through a stoichiometric network that optimizes the output of an objective reaction, a metabolic pathway hypothesized to be the evolutionary objective of the organisms (e.g. biomass production for bacterial growth).

C. The ***R*** matrix

An approach for reconstructing and analyzing transcriptional regulatory networks has been developed [5]. The ***R*** matrix uses a quasi-stoichiometric representation of a regulatory network to correlate protein production (a "product") with metabolite availability (the "reactants"). This matrix representation allows linear analysis techniques to be applied to regulatory networks.

III. Results

A. Analysis of the ***R*** matrix identifies key features of a transcriptional regulatory system

The singular value decomposition of the **R** matrix enables the calculation of key properties of the transcriptional regulatory program of a biochemical networks. The resulting characteristic modes can be used to identify key transcriptional regulators of the metabolic network.

B. A scalable mixed integer programming framework for a transcriptional regulatory network integrates with metabolic systems

A method for expressing a Boolean regulatory network as a system of integral inequalities will be presented. This formalism will be extended to FBA, allowing constraint-based optimization of both the metabolic and regulatory networks. Both the flux distribution and the set of metabolites can therefore be optimized, allowing a more complete analysis of metabolism.

C. The mixed integer programming approach is scalable and identifies key evolutionary principles of biochemical networks

Results will be presented that demonstrate the utility of an integrated metabolic/regulatory in calculating minimal media conditions, optimal growth environments for both wild type and mutant organisms, and differences among flux

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distributions under a series of environments.

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