

Evolution of adaptive responses in metabolic networks: identifying feasible adaptive changes compatible with physiological constraints

**Albert Sorribas^{1,2}, Gonzalo Guillén-Gosálbez³, Ester Vilaprinyo⁴,
Rui Alves^{1,2}**

¹Departament de Ciències Mèdiques Bàsiques, Universitat de Lleida, Lleida, Spain

²Institut de Recerca Biomèdica de Lleida (IRBLLEIDA), Lleida, Spain

³Departament d'Enginyeria Química, Universitat Rovira i Virgili, Tarragona, Spain

⁴Fundació Dr Ferran per a la Investigació en Ciències de la Salut, Tortosa, Spain

Cells adapt metabolism to cope with environmental challenges. For each specific situation, evolution has selected a set of adaptive characteristics that range from gene expression changes to enzyme activity dependence on temperature and other physico-chemical conditions. Changes in enzyme activity either caused by modification of gene expression or by regulatory effects, ultimately lead to changes in metabolite levels and fluxes. Admissible changes in these activities are constrained by physiological requirements at different levels. For instance, economy in gene expression is an important constraint that acts as a selective pressure for the overall response.

Mathematical models can be used to evaluate different functional constraints. Models based on the power-law formalism, either in its Generalized Mass Action (GMA) or S-system forms, are specially suited for this task. Once a model of the target processes is defined, optimization methods could be used to evaluate the more appropriate changes. However, evolution of metabolic networks is not totally equivalent to optimization in biotechnological processes. From an evolutionary point of view, we shall develop a method that can be used for identifying feasible enzyme activity regions that are compatible, not necessarily reaching an optimum, with a set of physiological requirements.

We shall first discuss a new optimization method for GMA models and discuss their use in biotechnological applications. As in this situation changes in enzymes may be limited to few of them, we will discuss strategies for identifying the more relevant. Also, we shall briefly discuss the limitations of flux balance approaches and of the summation relationships in Metabolic Control Analysis.

Then, we will present a method for identifying feasibility regions in enzyme levels that are compatible with a set of physiological constraints. We will discuss the case of yeast adaptive response to heat shock to show the applicability of the suggested methodology. We shall show that the actual gene expression changes localize near the optimum for an economic response and for increasing trehalose production. Although the model can reach a higher production of ATP and NADPH, the adaptive response seems to be constrained by the economy in changing gene expression and for achieving an appropriate increase in trehalose synthesis.

References

- [1] Vilaprinyo E, Alves R, Sorribas A. Use of physiological constraints to identify quantitative design principles for gene expression in yeast adaptation to heat shock. *BMC Bioinformatics*. 7:184, 2006
- [2] Vilaprinyo E, Alves R, Sorribas A. Minimization of biosynthetic costs in adaptive gene expression responses of yeast to environmental changes, 2009 (submitted)
- [3] Guillén-Gosálbez G, Sorribas A. Identifying quantitative operation principles in metabolic pathways: a systematic method for searching feasible enzyme activity patterns leading to cellular adaptive responses, 2009 (submitted)