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Multi-objective shadow prices point at principles of metabolic regulation

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ABSTRACT

Perturbations in environmental and intracellular conditions often lead to changes across all cellular layers, from transcription to metabolism. Regulatory mechanisms are key to mediating these changes to maintain homeostasis and to ensure viability. Since changes in metabolic reaction rates are partly due to perturbations in metabolite concentrations, it is expected that metabolites with large effect on those reaction rates which govern metabolic functionality are tightly regulated. The extent of metabolic regulation has been quantified by the sensitivity of an individual metabolic function to changes in metabolite concentrations, in particular by shadow prices in the constraint-based modeling framework. However, the system-wide characterization of the extent to which metabolite concentrations are regulated in the more realistic scenario of multiple contending tasks remains elusive. Here we examine multi-objective shadow prices for the central carbon metabolism of *Escherichia coli* whose reaction rates are shaped by several contending metabolic functions. We determine shadow prices for sampled solutions of the Pareto front, which characterizes the space of multi-objective optima, for three contending metabolic functions that provide the best agreement with ^{13}C-labeling experiments. By analyzing the parts of the Pareto front closest to the experimentally determined flux phenotypes, we show that *E. coli* operates in the vicinity of an area of the Pareto front which facilitates robust and efficient regulation. In addition, we find significant associations between features of the transcriptional regulatory network and the sensitivity of *E. coli*'s metabolic functionality to changes in metabolite concentrations. We demonstrate that the structural constraints of the metabolic network together with data on condition-specific flux phenotypes can be effectively used to dissect metabolic regulation on a system-wide level.

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1. Introduction

Biological systems perpetually sense and respond to changes in environmental and intracellular conditions Kitano (2007). To ensure continuous functionality, maintain homeostasis, and to guarantee proliferation, cellular systems usually adapt to the perceived changes via an integrated response of their cellular networks. The system-wide response is ultimately reflected in the flux phenotype and levels of components (*e.g.*, transcripts, proteins, metabolites). The flux phenotype, which determines metabolic functionality, is characterized by the rates of the biochemical reactions in the underlying metabolic network and directly depends on the concentration of metabolites as well as the concentration and activity of enzymes. To ensure homeostasis on the level of fluxes, concentrations of metabolites with large effect on the flux phenotype are expected to be tightly regulated Fell (2005).

The molecular mechanisms by which metabolic regulation is exerted differ in timescale. A change of the metabolic state, *i.e.*, reaction fluxes and metabolite concentrations, is largely achieved by transcriptional regulation and takes place on the scale of minutes to hours Desvergne et al. (2006). In contrast, mechanisms relevant for correcting imbalances on shorter timescales are likely to involve post-translational modifications Helm (2006) and allosteric regulation Chubukov et al. (2014). Experimental *in vivo* study of the effects of allosteric regulation on the systems level is inherently difficult Motlagh et al. (2014), as it requires the arduous targeted manipulation of individual metabolite concentrations. An indirect way to learn about these short-term regulatory events, which aim at mitigating the effect of concentration fluctuations on the flux phenotype, is to determine how they relate to the topology of the underlying metabolic network.

To this end, shadow prices represent one means to derive and examine organization principles of metabolic regulation by

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employing the structure of the metabolic network. Shadow prices describe the sensitivity of the objective function of a linear program upon perturbation of individual constraints Bazaraa et al. (2010). In a cellular setting, shadow prices have been employed to analyze the change of the optimal flux phenotype upon imbalance of a given metabolite's concentration (*i.e.*, due to its accumulation or depletion) in the framework of flux balance analysis Varma and Palsson (1994), Savinell et al. (1992), Savinell and Palsson (1992). Specifically, shadow prices quantify the change in a metabolic objective (*e.g.*, maximization of biomass yield) upon increase/decrease in metabolic flux of individual reactions leading to a deviation from steady state.

It has recently been shown that shadow prices are suitable predictors of temporal variation of individual metabolite concentrations as well as indicators of their growth-limiting effects Reznik et al. (2013). As a result, shadow prices can be used to examine the requirement for regulating individual metabolite concentrations solely based on a stoichiometric model of the metabolic network and an assumed metabolic objective. If the absolute value of a shadow price is large, perturbations of the corresponding metabolite concentrations are expected to have large effect on metabolic function and should, therefore, be tightly regulated (*e.g.*, by high concentrations of the synthesizing and degrading enzymes).

The existing studies have concentrated only on shadow prices for a single objective function. However, it was shown that using a combination of multiple objective functions leads to higher accuracy of the predicted flux phenotypes Schuetz et al. (2007). For the case of *Escherichia coli*, a multi-objective analysis established that flux phenotypes determined under different environmental conditions could be best described by combining two efficiency objectives (maximization of biomass yield, maximization of ATP yield) and one optimal resource allocation objective (minimization of total flux) Schuetz et al. (2012). Moreover, it was found that flux phenotypes are in a close vicinity to the Pareto front describing the set of non-inferior solutions, i.e., flux phenotypes which can only improve one objective at the expense of reducing at least one other.

Here, following the work of Schuetz et al. (2012), we examine shadow prices with respect to multiple contending objectives in the central carbon metabolism of *E. coli* to obtain insights in metabolic regulation and its relation to the structure of the metabolic network. For representative solutions of the Pareto front, shadow prices of metabolites are determined individually for each of the three objective functions which were found to provide best agreement between experimentally determined and predicted flux distributions. By using ^{13}C flux estimates for non-limited as well as carbon- and nitrogen-limited aerobic conditions, we investigate shadow prices in the physiologically relevant section of the Pareto front in which the cell operates under these conditions.

2. Results

We examine sensitivity of the flux phenotype with respect to changes of metabolite concentrations in the multiple-objective scenario for the model of *E. coli*'s central carbon metabolism developed by Schuetz et al. (2007) (see Fig. S1 and Tables S1 & S2). A multi-objective optimization problem usually has no unique solution due to the trade-off between individual objectives. Here, we focus on Pareto-optimal solutions, *i.e.*, solutions which cannot be improved with respect to an individual objective without deteriorating the optimal achievable value of at least one of the other objectives. The entirety of such solutions forms the Pareto front. Each Pareto-optimal solution is associated with a set of shadow prices for every objective and each metabolite.

Here, we determine a representative set of the Pareto front solutions (for brevity, in the following we refer to the representative set as the Pareto front) emerging from three contending objectives: (i), maximizing biomass yield, (ii), maximizing ATP yield, and (iii), minimizing total flux. Schuetz et al. showed that these objectives yield flux phenotype predictions closest to *in vivo* ^{13}C flux estimates in the central carbon metabolism of *E. coli* for a range of environmental conditions Schuetz et al. (2012). The Pareto front together with the projection of the polyhedral cone of steady-state flux distributions on the three contending objectives alongside the experimentally determined flux distributions is shown in Fig. 1. Schuetz et al. demonstrated that, for the examined environments, *E. coli* exhibited flux phenotypes which were located in close

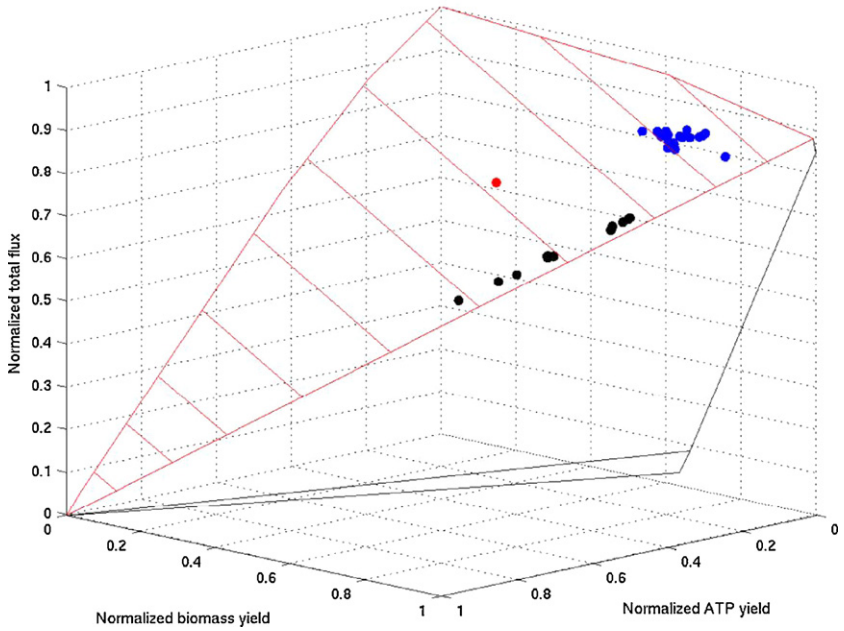

Fig. 1. Visualization of the Pareto front. The flux cone (solution space of flux balance analysis) is obtained via elementary flux mode analysis and is projected onto the three contending metabolic objectives. The Pareto front is highlighted in red. Parts of the flux cone corresponding to minimum total flux larger than the minimum observed for zero ATP and zero biomass yield are excluded. Experimentally determined flux distributions (aerobic conditions) are shown as dots: non-limited (blue), carbon-limited (black), nitrogen-limited (red).

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