

Bridging the Gap between Constraint-based and Kinetic Modelling

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Abstract

In recent years, two major (and divergent) modelling methodologies have been adopted to increase our understanding of metabolism and its regulation. The first is constraint-based modelling [1,2], which uses physicochemical constraints such as mass balance, energy balance, and flux limitations to describe the potential behaviour of an organism. The biochemical structure of metabolic pathways is more or less well-known, and hence the stoichiometries of such a network may be deduced. In addition, the flux of each reaction through the system may be constrained through, knowledge of its V_{\max} , or irreversibility considerations. From the steady state solution space of all possible fluxes, a number of techniques have been proposed to deduce network behaviour, including flux balance and extreme pathway or elementary mode analysis. In particular, flux balance analysis (FBA) [3] highlights the most effective and efficient paths through the network in order to achieve a particular objective function, such as the maximization of biomass or ATP production. The key benefit of FBA lies in the minimal amount of biological knowledge and data required to make quantitative inferences about network behaviour. However, constraint-based modelling is concerned only with fluxes through the system and does not make any inferences nor any predictions about cellular metabolite concentrations. By contrast, kinetic modelling aims to characterize fully the mechanics of each enzymatic reaction, in terms of how changes in metabolite concentrations affect local reaction rates. However, a

considerable amount of data is required to parameterize a mechanistic model; if complex reactions like phosphofructokinase are involved, an enzyme kinetic formula may have ten or more kinetic parameters. The determination of such parameters is costly and time-consuming, and moreover many may be difficult or impossible to determine experimentally. The *in vivo* molecular kinetics of some important processes like oxidative phosphorylation and many transport mechanisms are almost completely unknown, so that modelling assumptions about these metabolic processes are necessarily highly speculative.

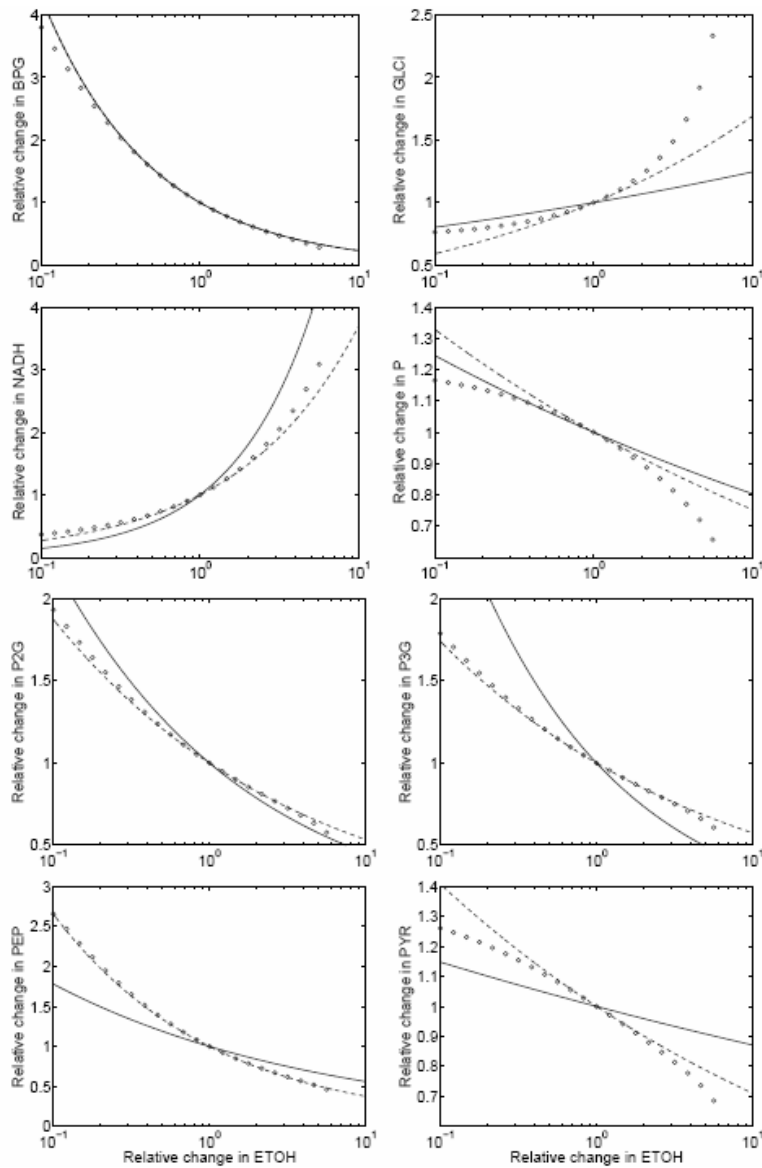


Figure 1. Variations in steady state intracellular metabolite concentrations with changes in ethanol concentration. Shown are the Teusink *et al.* model solutions (o), and the predictions of the linlog model with both estimated (solid line) and correct (dashed line) fluxes and elasticities.

Here, we define a novel method for the generation of kinetic models of cellular metabolism [4]. Like constraint-based approaches, the modelling framework requires little experimental data regarding variables and no knowledge of the underlying enzymatic mechanisms; nonetheless it allows inference of the dynamics of cellular metabolite concentrations. The fluxes found through FBA are allowed to vary dynamically according to linlog kinetics [5]. Elasticities are estimated from stoichiometric considerations, following the tendency modelling approach [6]. Figure 1 demonstrates that the predictions of the proposed model agree well with the original and mechanistic branched yeast glycolysis model of Teusink *et al.* [7]. Moreover, we show that a model framed within the linlog format affords analytical forms for steady state determination, stability analyses and studies of dynamical behaviour. As such, it does not suffer from the usual [8] computational scalability problems, and could therefore be applied to existing genome scale models of metabolism [2,9,10]. Such a model has powerful predictive power in determining cellular responses to environmental changes, and may be considered a stepping-stone to a full kinetic model of cell metabolism: a “virtual cell”.

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