

# Dynamic flux balance analysis for metabolic modeling

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## ABSTRACT

There are a number of approaches to quantitatively model regulatory mechanisms which allow the prediction of dynamic metabolite responses. Some of the quantitative analysis approaches include Metabolic Control Analysis (MCA) (Fell [2]), cybernetic modeling (Varner and Ramkrishna [7]), and Flux Balance Analysis (FBA) (Varma and Palsson [5]). Both MCA and cybernetic models require detailed kinetic information, while FBA is based on steady state analysis and requires only the stoichiometric coefficients of the reactions. In this study, three different approaches to dynamic flux balance analysis are examined for the diauxic growth of *E. coli* on glucose and acetate.

Varma and Palsson [6] have extended the steady state FBA to model the dynamics of diauxic growth by solving the steady state problem at every time step followed by integration with the known fluxes over the time interval. The results from this approach matched the experimental data for glucose utilization. However, the dynamics of acetate utilization was not adequately described by this approach. van Riel *et al.* [4] have proposed a modified approach, where in addition to the stoichiometric constraints, constraints on the rate of change of metabolite levels were included in the programming problem. The overall approach of van Riel *et al.* [4] was to solve the programming problem at every time step followed by integration, similar to the Varma and Palsson approach. van Riel *et al.* [4] illustrated this approach on the central nitrogen metabolism in *S. cerevisiae*.

Another approach to dynamic flux balance analysis is the formulation of a nonlinear dynamic optimization problem, where the profiles of the fluxes are obtained as a solution to the optimization problem. The optimization problem is transformed into a nonlinear programming problem by parameterization of all the fluxes and metabolites as described in Cuthrell and Biegler [1]. Additional constraints on the rate of change of fluxes were incorporated into the optimization problem.

The nonlinear dynamic optimization approach is applied to a metabolic network for the analysis of diauxic growth of *E. coli* on glucose and acetate. The reduced metabolic pathway involving oxygen, glucose, acetate, and biomass is identified based on pathway analysis (Schillings *et al.* [3]) followed by simplification based on biomass yield. The objective function to be maximized is assumed to be the sum of the biomass concentrations over a time horizon of 10 *hr*.

The first case studied is the application of the Varma and Palsson approach to this simplified metabolic network. The approach of van Riel *et al.* [4] is also applied to this network after a modification where the rate of change of flux constraints instead of the metabolites is incorporated and is examined in the second case. The third case studied involved the formulation of a nonlinear dynamic optimization problem for the described metabolic network.

It is found that all the three approaches predicted the glucose utilization qualitatively; however acetate utilization in the absence of rate of change constraints occurred rapidly. The third case allows for the formulation of complex objective functions. However, the solution of the nonlinear dynamic optimization problem is computationally intensive for this case compared to the other approaches.

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