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Editorial

Special Issue on “Frontiers in Connecting Steady-State and Dynamic Approaches for Modelling Cell Metabolic Behavior”

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Understanding the behaviour of cell metabolism is the crucial key in bioprocess development and optimization, as well as in the development of efficient therapies. Indeed, it is established that a cell's behaviour relies on its genetics, and more practically on gene expression, and thus on metabolic pathways' activity. There are currently two fundamental trends in the analysis of metabolic networks: the constraint-based modelling (CBM) approach for large-size networks, which is used to determine a space for a feasible metabolic steady-state flux solution, and the kinetic metabolic modelling approach for relatively small-size networks, which is used to study the dynamic behaviour of a regulated metabolic system.

This Special Issue on “Frontiers in Connecting Steady-State and Dynamic Approaches for Modelling Cell Metabolic Behavior” covers a variety of theoretical studies which bring together the steady-state and the kinetic communities into a coherent set of contributions, drawing the synergistic capacity of both approaches. In Yasemi et al. [1], a general review of approaches at steady state and dynamic state is presented, while Moulin et al. [2] review recent efforts to draw both frameworks closer by adding temporal features (regulatory, dynamic, . . .) in CBM and present proposed techniques which combine the two approaches to reduce flux cone and to explain pathway shift.

Although kinetic models consider reaction network stoichiometry and flux regulation mechanisms, their resolution is not trivial, because it relies on the determination of a high number of kinetic parameters. Furthermore, extensive experimental data are required for extra and intracellular concentrations in metabolites to enable kinetic parameter value estimation. In the paper written by Kunna et al. [3], an Enhanced Segment Particle Swarm Optimization algorithm (ESe-PSO) is proposed for kinetic parameters estimation in *E. coli*. Meanwhile, Fu Yap et al. [4] combine kinetic and genetic algorithms, while integrating proteomics data, to elucidate the regulatory effect of heat stress on trehalose production in *S. cerevisiae*.

Such kinetic models allow real-time simulation of metabolic fluxes and of cell behavior. Indeed, methods are now emerging using the advantages of constraints-based modelling to analyse the time evolution of some interesting variables, integrating or not integrating kinetic descriptions. In Mazat et al. [5], the authors used elementary flux modes (EFMs) to decompose the steady state obtained by kinetic modelling to study the ATP/O ratio on the cell central energy production site, the mitochondria. Gibart et al. [6] extend “René Thomas” formalism, traditionally applied to a regulatory network, to represent regulation between metabolic pathways. They apply this to eukaryotic cells, proving that currently known regulating signals within the main components of central carbon metabolism are sufficient to create the Warburg/Crabtree effect. The integration of regulatory constraints can also be integrated in CBM. In Mahout et al. [7], they combine logic and linear programming to compute constraint EFMs which integrate transcriptomic regulatory networks, thermodynamics, environment and operating costs. Their methods allow the computation of a



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reduced set of EFMs for large metabolic network in a short period of time and identify efficient phenotypes in *E. coli* that have been observed experimentally. The EFMs have also been used to compute the optimal metabolic pathways for different carbon substrate combinations for *A. acidocaldarius* in Beck et al. [8]. The author used dFBA to generate time-resolved simulations of growth on phenol and xylose and demonstrate the versatility of the bacteria for lignocellulosic biomass.

Overall, this Special Issue offers a clear view of the potential of connecting steady-state and dynamic approaches in regard to modelling cell metabolic behavior. Here, the reader will find a condensed set of thoughts and practical examples as starting points for synergistic applications of such combined approaches.

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