Contextualization of Metabolic Network Models and their Application to Drug Repurposing

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Introduction

Mathematical modelling of metabolic networks is a powerful tool to study metabolism on a genome-scale level. It allows to discover the activity of pathways of interests, the amount of produced or exchanged metabolites, and to elucidate essential and specific metabolic genes amongst many other applications. The most widely employed constraint-based modelling approach uses linear programming on mass balance equations in steady state further enriched with thermodynamical constraints. Often the optimization of a reasonable objective function (like growth or ATP maintenance) is pursued thereby.

Material and methods

To increase the predictive power of such metabolic models, we develop fast and powerful large-scale data integration methods which enable the reconstruction of context-specific molecular networks, e.g., for a given disease, patient group or individual patient. The fastcore family of algorithms allows the integration of large-scale gene expression data and other data types with generic metabolic reconstructions for producing specific molecular metabolic networks [1]. This is powered by an efficient linear programming approach, which allows to obtain a close-to-optimal minimal network given a core set of metabolic reactions. Largely applied also by other teams, these algorithms have been included in a community-effort toolbox [2]. This has lately been extended with a novel dynamic Flux Balance Analysis approach for multi-tissue metabolic modelling and allows now also for simulating disease-specific metabolic blood level alterations [5]. And a recently released single cell version of the algorithm allows to study the metabolic activity of the different cell types captured with single cell-RNAseq data, as well as their putative metabolic crosstalk in terms of exchanged metabolites [4].

Results

Based on these and other state-of-the-art computational biology, data science and machine learning approaches, we developed a variety of fruitful collaborations, notably in cancer research. E.g., we employ the reconstructed cancer specific molecular networks for identifying promising specific targets and to suggest novel treatment strategies. Drug repurposing thereby aims at reorienting approved drugs to novel disease indications. In proof-of-concept studies we used fastcore to predict several non-cancer drugs to be effective in colorectal cancer [1], melanoma [3], or glioblastoma [under preparation], while less harming healthy control tissue. The experimental validation gave superior results compared to large-scale screening efforts. We could also show that synergistic effects of such metabolic drugs in combination with state-of-the-art targeted signalling drugs are possible [3].

Conclusion

In summary, large scale metabolic modelling combined with powerful data integration methods is an excellent tool to enhance the discovery of novel metabolites and pathways of interest, as well as of new drug candidates.

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Narrative CV :

I am Professor of **Systems Biology** and **Study Director** at the University of Luxembourg. My research focus is on computational systems biology, especially on model-based data integration and analysis of disease-specific networks. I am convinced that the language of mathematics and its methods are an essential necessity in modern biological research, as they help to **extract knowledge from the enormous amounts of data** being generated and to consolidate our understanding. A formalization of our biological knowledge will be of tremendous importance for many tailored treatments in medicine, similar to what has happened in physics during the last century. One key step is the capacity to integrate many different large-scale data sets into coherent and specific **computational models**. This key research activity of myself and my team builds the basis for many collaborations with experimentally oriented partners and for applications in drug target identification and drug repositioning.

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Including relevant information about my academic track record, publication list, history of organizational affiliations, list of funded research projects, and other.