Extensible and Executable Stochastic Models of Fatty Acid and Lipid Metabolism

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Understanding lipid metabolism and its regulation is essential in metabolic disorders and diabetes-related diseases. Many of the metabolites and transformation reactions involved are still poorly characterised. Because of the low numbers of carbons flowing through the lipid pathways, the effect of the inherent probabilistic nature of chemical events is amplified. These two factors make lipid pathways difficult to analyse with current modelling approaches used for metabolic processes, such as Flux Balance Analysis (FBA) [1], which is focused on deterministic average-case behaviour (of population growth). Here, we use an alternative stochastic and reaction-centric view to capture these pathways. In particular, we focused on Fatty Acid (FA) synthesis and elongation which is a central process in lipid metabolism. FAs are the core building blocks, modified for more complex lipids within the cell and tissues. FA synthesis and elongation pathways in particular display some characteristics that make models benefit from this alternative view: local iterative processes, probabilistic decisions at different levels and between pathway control mechanisms that affect decision making.

We modelled the iterative FA elongation process as the combined effect of synthesis and elongation pathways, which we reduced down to a series of binary decisions or Bernoulli trials. We also modelled the Acetyl-CoA flow decision between the Krebs cycle and FA synthesis, which is controlled by the immediate energy requirements of the cell.

Real output data from a lipid metabolomics study was used to tune the models. The data represented different metabolic states and treatment conditions. This adds an interesting dimension to the study as we can observe changes in the model parameters over different conditions. By observing changes in the parameters across conditions we can identify areas or topological structures that show behavioural changes and possible mechanistic explanations.

Another important aspect of this work was to assess possible languages for capturing this stochastic behaviour in a reaction-centric projection. Recently, there has been a general trend towards constructing executable models, from the distributed systems world [2]. Here, we use Petri Nets [3] mainly and pi-

calculus (SPiM [4] variant in particular) which is an example of a Process Algebra [5]. Petri Nets provide a vivid and intuitive graphical notation with a natural correspondence to chemical reactions and they have been used before for other metabolic pathways [6]. The main unit of definition for Petri Nets is the transition. The main unit of definition for Process Algebra is the species but the operational semantics are in terms of interactions, which again make them suitable for our reaction-centric view. Since these languages have been designed to handle distributed systems and therefore concurrency, non-determinism representing decisions is inherent in the structure of Petri Nets and in the syntax of pi-calculus.

Metabolic processes such as degradation of FAs and the anabolism and catabolism of more complex lipids can be added as extension modules to our core models. New extensions will remain biochemically valid with the new posteriors taken from experimental lipid and metabolomic data. It is important that phenomenological-statistical models retain essential mechanistic descriptions that allow them to discriminate between metabolic states in health and disease.

References

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