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Editorial

A special issue of *Essays in Biochemistry* on computational biology

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Computational biology is a diverse research field that has gained increasing importance over the last two decades. Broadly, it aims to apply computational approaches to advance our understanding of biological systems. This can take place on multiple levels, for example, by creating computational models of specific biological systems, by developing algorithms that assist in the analysis of experimental data, or by investigating fundamental biological design principles through modelling. The articles in this special issue highlight and review four such distinct applications of computational biology.

The earliest applications of computation to biochemistry can be traced back to eighty years ago. In a remarkable paper published in 1943, Britton Chance demonstrated the validity of the Michaelis–Menten equation in the action of peroxidase using a combination of experimentation and simulation with a mechanical differential analyser, which can be viewed as a type of analogue computer [1]. The appearance of digital mainframe computers in the 1960s allowed such simulations to be performed on a larger scale [2]. As the capabilities of computers increased, so did the application of computation to biological problems. When personal computers became available in the 1980s, this technology became widely available. The rapid increase in computational power, evidenced by Moore's law (an empirical observation that the number of transistors on a microchip doubles every 2 years, yielding an order of magnitude increase every 6–7 years) has broadened and democratised access, and indeed modern biochemistry would be impossible without computers.

Nowadays, the field of computational biology is very broad, encompassing areas of bioinformatics and sequence analysis [3], structural biology simulations [4], algorithms assisting in analysis of high-dimensional data [5], and dynamic network simulations [6], to name a few. It is impossible to cover all these topics in depth in a special issue; rather, we focus on four specific examples: one paper dealing with analysis of high-throughput metabolomics data, two papers reviewing dynamic simulations of specific biochemical systems, and one contribution showing how computation can help us understand the regulatory design of genetic circuits.

Perez de Souza and Fernie [7] provide a review of computational methods for processing high-dimensional metabolomics data acquired with mass spectrometry. Omics technologies, notably metabolomics, play a pivotal role in unravelling the molecular intricacies of living systems because they measure a vast number of metabolites in a single run. However, the immense chemical diversity of metabolites, exceeding a million structures, poses challenges for comprehensive identification. Ultra-high-performance liquid chromatography (UHPLC) coupled with high-resolution mass spectrometry (LC-MS) emerges as a potent approach, offering sensitivity, dynamic range, resolving power, and flexibility. LC-MS generates complex multi-dimensional datasets, demanding advanced computational strategies, and in response various tools have been developed to automate mass feature detection, peak integration, and quantification. Nevertheless, automated processing requires careful curation to remove poorly integrated signals. Metabolite annotation involves spectral database searches but is limited by issues of isomer discrimination and database coverage. Novel approaches based on creating molecular networks related to similarity scores can help elucidate unknown compounds and contribute to their *in silico*

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structure prediction. Furthermore, recent advances in deep learning show promise for translating mass spectra into structures.

In their contribution, Van Niekerk et al. [8] review the kinetic modelling of glycolytic oscillations. While these oscillations have been investigated for more than 60 years, their precise mechanism of regulation and cellular function remain unknown. Glycolytic oscillations involve regular variations in the intermediates of the glycolytic pathway, driven by the allosteric regulation of phosphofructokinase (PFK) by ATP and AMP. These oscillations are not isolated events; they influence other metabolic processes, including mitochondrial membrane potential and ion concentrations. Two main mechanisms for driving these oscillations are reviewed: allosteric regulation of PFK and the autocatalytic character of glycolysis. Experiments with yeast glycolytic oscillations *in vitro* and in intact cells are also discussed, emphasising the role of PFK and the impact of external factors like acetaldehyde in mediating synchronisation. Oscillations are not limited to yeast glycolysis, but can occur in other cell types, including cancer cells and pancreatic β-cells. In multicellular organisms, one of the functions of glycolytic oscillations could be to drive coordinated organ responses. To further unravel the mechanisms of glycolytic oscillations, it will become increasingly important to study single cells, for example to investigate the effect of cellular differentiation or to quantify interactions between different cell types. Advanced technologies like micro-fluidic chambers and organ-on-a-chip systems open up new possibilities.

Pillay and Rohwer [9] provide a review of computational models for investigating cellular thiol redoxin systems. These systems play important roles in integrating cellular responses towards reactive oxygen species and are also involved in redox signalling. Computational modelling has been instrumental in reconciling discrepancies between *in vitro* and cellular descriptions of redoxin activity. In particular, computational approaches have demonstrated that systems like thioredoxin should be modelled with mass-action kinetics and not with Michaelis–Menten parameters, as was common practice in the literature. After providing a brief overview of kinetic modelling approaches, the authors show how computational models can be categorised into 'core' and realistic models, with the former comprising a limited set of ordinary differential equations that have been used, for example, in parameter estimation. In contrast, realistic models are built bottom-up from the properties of all the molecular components and can thus offer more detailed, mechanistic insights. Models will have to be updated continuously based on evolving knowledge, for example by addressing subcellular redox microdomains and integrating redoxin models with broader cellular processes.

The article by Berkvens et al. [10] reviews a number of computational models that have been used to study the regulation of fitness in microorganisms through changes in gene expression. They present ways to design gene regulatory networks that will lead to optimal states in metabolic pathways, defined as maximal flux for a given total enzyme pool (which can conversely be cast as minimising the total enzyme concentration for a given metabolic flux). Three examples are presented to illustrate the approach: a core model of a simple two-enzyme metabolic pathway, a model of the control of ribosomal gene expression in *Escherichia coli* (splitting of resource allocation between ribosomal protein synthesis and metabolic enzyme synthesis), and the design of an optimal gene circuit for a metabolic pathway with negative feedback based on bacterial amino acid biosynthesis pathways. The proposed 'qORAC' theory (Optimisation by Robust Adaptive Control) provides a framework for inferring or designing gene regulatory circuits that can steer a metabolic network to optimal states while remaining robust to environmental changes. The article emphasises the need for dynamic data and models, noting that many current metabolic modelling approaches are inadequate for understanding regulation because they are based on steady-state data, thus ignoring the dynamic responses of the system.

We hope that you enjoy reading this special issue of *Essays in Biochemistry*, and that it will spark your interest in how computational approaches can enhance our understanding of biochemical systems in diverse ways.

Competing Interests

The author declares that there are no competing interests associated with this manuscript.

Abbreviations

PFK, phosphofructokinase; UHPLC, ultra-high-performance liquid chromatography.

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