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REVIEW of the dissertation in the discipline of Mathematics and Computer Science

"Some aspects of the molecular mechanisms of cell cycle and diauxtic growth from a mathematical perspective"

by Mateusz Dębowski, M.Sc.

The doctoral thesis of Mateusz Dębowski, M.Sc., is devoted to mathematical modelling and analysis of the cell proliferation. In particular, the thesis focuses on modelling the dynamics of proteins responsible for the transition of the cell into the mitosis phase and the mathematical description of the diauxtic growth process containing two different growth phases. An example of the latter is the logistic growth used in literature to describe many cell population growth processes.

Proliferation is among the most important processes of cell biology. It is a complex process precisely controlled by signalling systems, the disruption of which can lead to uncontrolled growth and tumours. The dissertation is not only biologically motivated, but the mathematics involved provides important insights into biological mechanisms. The publication of the results of the work in journals such as the *International Journal of Developmental Biology* or *Cells* shows their biological relevance.

The dissertation is well written. It consists of an abstract, an introduction and, four additional chapters and a conclusion. In the introductory section, the author shortly explains the main aspects of the cell cycle and summarises previous mathematical approaches to its description. He then defines diauxic dynamics and explains the role of the description of such multi-phase growth in the study of cell proliferation. Chapters 2 – 5 present different results of the thesis.

The main achievement of this work is building and analysing a mathematical model which explains the dynamics of proteins that regulate the cell cycle. Specifically, it shows that one of these systems results in an increase in the CDK1/CYCBA complex via diauxtic growth. The model is based on ordinary differential equations and its analysis uses classical stability analysis methods and numerical simulations, supported by a technically involved error analysis using the Runge-Kutta algorithm. Parallel to this, the author is mathematically investigating various aspects of the diauxtic dynamics. The aim of this study is to develop a consistent mathematical framework for analysis of such dynamics. Mr Dębowski introduces its mathematical definition in one-dimensional setting and analytically characterises its basic properties, such as the number of different growth phases and their connection to the properties of the growth function. Mathematical analysis is illustrated by numerical computations. Next, the author examines a two-dimensional model that has two time-scales and investigates its dynamics using small-parameter methods. Applying the Tikhonov-Vasilyeva theorem allows to reduce the model to the slow dynamics. The reduced model is shown to describe the diauxtic dynamics if the original model does. The analysis has important implications for modelling. It shows that complex nonlinearities responsible for the system's dynamics may be a natural effect of its multi-scale nature, and can be analysed in terms of fast-slow dynamics. Derivation of models with diauxtic growth is also discussed in the context of the dynamics of the populations choosing a particular strategy in population games. Finally, Mr Dębowski looks at the problem from the mesoscopic perspective using a kinetic model in the form of an integro-differential equation. By analysing the distributant obtained from the solution of such a model, Mr Dębowski shows the possibility of the diauxtic growth in different classes of mesoscopic models. The paper concludes with a reference to microscopic models such as the DNA dentaurisation model proposed and studied by Mr Dębowski in a separate paper.

The results of the work have been published in five papers in international journals in the fields of biology or applied mathematics, in which Mr Dębowski is either the first or independent author.

The challenge in this work, and its major achievement, was on the one hand to build a mathematical model of a biological process in order to analyse a specific hypothesis proposed by biologists based on experimental evidence, and on the other hand to select diverse mathematical tools and apply them to the analysis of a complex phenomenon. This was achieved by combining a mathematical understanding of the various approaches to modelling and model analysis with an understanding of biology and, not unappreciated, the integration of available experimental data and their translation into the language of mathematics.

A certain weakness of the work is some lack of coherence between the chapters, both concerning the analysed models and the applied approaches. For example, the benefit of referring to the model in the language of game theory is not clear to me. Also, the assumptions about the dimensionality of the models and the analysed quantities change quite arbitrarily. Interesting in the context of the results in Chapter 4, for example, is the question of to what extent the different growth curves require more factors to be involved in the control process. Can we extend the analysis of slow-fast dynamics to more equations describing slow dynamics? Or perhaps a larger number of equations describing fast dynamics would allow explaining the nonlinearity of the macroscopic growth function through simple interactions in a higher-dimensional system?

In summary, the dissertation of Mr Dębowski is self-contained and clearly structured. It shows the author’s ability to translate between the languages of mathematics and biology. The thesis provides original models that fulfil their task in providing answers to biological questions but also proposes mathematical approaches to study the diauxtic dynamics at different levels of mathematical description. Approaching such problems required combination and integration of different mathematical and computational techniques. Mr Dębowski has mastered this interdisciplinary toolbox and in my opinion the thesis meets the requirements for a doctoral dissertation in mathematics. I request that the dissertation be admitted to public defence.

With best regards

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