UNIVERSITY OF GOTHENBURG

The construction, analysis and validation of mechanistic mathematical models of protein kinetics in the context of replicative ageing in budding yeast

JOHANNES BORGQVIST

The thesis for the Degree of Doctor of Philosophy is presented on
Friday the 12th of June 2020 at 10.15 a.m. in the lecture hall
"Gustaf Dalén-salen" with the address:
Department of Physics, Chalmers Tvärgata 5, SE-412 96 Gothenburg.
The presentation is given in English.

Opponent: Professor Ruth E Baker,
Mathematical Institute,
University of Oxford, United Kingdom

The construction, analysis and validation of mechanistic mathematical models of protein kinetics in the context of replicative ageing in budding yeast

Johannes Borgqvist

Division of Applied Mathematics and Statistics
Department of Mathematical Sciences
University of Gothenburg and Chalmers University of Technology

Abstract

Mathematical modelling constitutes a forceful tool for elucidating properties of biological systems. Using theoretical approaches in combination with experimental techniques it is possible to study specific molecular aspects of phenomena such as the ageing of human beings. In fact, as many processes are similar in simpler organisms such as the budding yeast *Saccharomyces cerevisiae* it is possible to experimentally investigate for instance the accumulation of damaged proteins due to ageing in these biological systems. The aim of this thesis is to construct, analyse and validate mathematical mechanistic models of protein kinetics consisting of both ordinary and partial differential equations in the context of ageing. This is done both on a large time scale corresponding to the entire life span of cells and a short time scale corresponding to an isolated part of the cell division. The focus of the work on the large time scale is twofold, firstly the life span of individual yeast cells is modelled (Paper II) and secondly the life spans of vast numbers of cells in numerous populations are simulated (Paper III). Using a model of the accumulation of damage involving the forces cell growth, formation and repair of damage as well as the cell division, the impact of these individual parts on the overall fitness of individual cells and entire populations is investigated. On the short time scale, a more detailed model of a single protein called Cdc42 involved in the cell division is presented (Paper IV) and this theoretical framework has a high level of detail as it describes the spatial movement of the protein of interest within the cell over time. Given this precise description of the geometry of an individual cell, the mathematical properties of the model is analysed and these theoretical results are used to conduct numerical simulations of the activity of this protein. Lastly, an overall theme of the thesis is the difficulty of validating mechanistic models even in the presence of data. More precisely, as numerous and sometimes mutually exclusive models can describe a system equally well it is currently very hard, even by calibrating the models to experimental data using statistical methods, to differentiate between various models. To this end, a mathematical tool called symmetry methods is introduced as a potential remedy to this problem, and using this methodology it is possible to extract information in the data as well as in the model that is not available using standard approaches. To showcase the power of symmetries, a minimal example of the usage of these methods in the context of enzyme kinetics is presented (Paper V). In conclusion, this work suggests that novel analytical tools such as symmetry methods could complement and assist the current standard approaches for modelling protein kinetics where the purpose is to deduce the underlying mechanisms of biological systems.

Keywords: Protein kinetics, replicative ageing, Cdc42, ordinary differential equations, reaction diffusion models, parameter estimation, model validation, model construction, symmetry methods.