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# Mathematical Modelling of Cellular Ageing : a Multi-Scale Perspective

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# Mathematical Modelling of Cellular Ageing : a Multi-Scale Perspective

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## Abstract

In a growing and increasingly older population, we are progressively challenged by the impact of ageing on individuals and society. The UN declared the years 2021-2030 as the Decade of Healthy Ageing, highlighting the efforts to minimise the burden of ageing and age-related diseases. A crucial step towards this goal is to elucidate basic underlying mechanisms on a molecular and cellular level. While much is known about individual hallmarks of cellular ageing, their interactive and multi-scale nature hinders the progress in gaining deeper insights into the emergent effects on an organism.

In the five papers underlying this thesis, we aimed to study protein damage accumulation over successive cell divisions (replicative ageing), as one emergent factor defining ageing. We combined experimental data in the unicellular model organism yeast *Saccharomyces cerevisiae* with mathematical modelling, which offers systematic and formal ways of analysing the complexity that arises from the interplay between processes on different time and length scales. In that way, we showed how interconnections in the cellular signalling network are essential to ensure a robust adaption to stress on a short time scale, being crucial for preventing and handling protein damage. By linking different models for cellular signalling, metabolism and protein damage accumulation, we provided one of the most comprehensive mathematical models of replicative ageing to date. The model allowed us to map metabolic changes during ageing to a dynamic trade-off between protein availability and energy demand, and to investigate global metabolic strategies underlying cellular ageing. Going beyond single-cell models, we examined the synergy between processes that create, retain and repair protein damage, balancing the health of individual cells with the viability of the cell population. Taken together, by constructing, validating and using mathematical models, we unified different scales of protein damage accumulation and explored its causes and consequences. Thus, this thesis contributes to a more comprehensive understanding of cellular ageing, taking a step further towards healthy ageing.

**Keywords:** replicative ageing, healthy ageing, yeast, complexity, multi-scale model, hybrid model, flux balance analysis, ordinary differential equations, Boolean modelling.