Mathematical Models of Cell Cycle Progression: Applications to Breast Cancer Cell Lines

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Abstract

The aim of this thesis is to develop mathematical models of cell cycle progression which can be used in conjunction with biological experiments. The thesis focusses on modelling processes which have biological relevance, and uses mathematics to investigate biological hypotheses about mechanisms which drive experimental results.

In this thesis, we introduce a mathematical model of cell cycle progression and apply it to the MCF-7 breast cancer cell line. The model considers the three typical cell cycle phases, which we further break up into model phases in order to capture certain features such as cells remaining in phases for a minimum amount of time. This results in a unique system of delay differential equations which are solved numerically using MATLAB. The model is also able to capture a uniquely important part of the cell cycle, during which time cells are responsive to their environment. The model parameters are carefully chosen using data from various sources in the biological literature. The model is then validated against a variety of experiments, and the excellent fit with experimental results allows for insight into the mechanisms that influence observed biological phenomena. In particular, the model is used to question the common assumption that a 'slow cycling population' is necessary to explain some results. A model analysis is also performed, and used to discuss misconceptions in the literature regarding the average length of the cell cycle. An extension is developed, where cell death is included in order to accurately model the effects of tamoxifen, a common first line anticancer drug in breast cancer patients. We conclude that the model has strong potential to be used as an aid in future experiments to gain further insight into cell cycle progression and cell death.

The model is then applied to the T47D cell line, which has significantly different cell cycle kinetics to the MCF-7 cell line. The aim of modelling this cell line, which is naturally receptive to the effects of progestins, is to model the effects of progestins on cell cycle progression. It is important to understand the effects of this substance, as it has been used in hormone replacement therapies, and its effects on cell cycle progression are still not understood.

In order to understand how progestins influence cell cycle progression, a more detailed protein model is developed to get a better understanding of how progestin influences protein concentrations within a cell. We find that progestin effects on cell cycle progression

are complex, and that progestin can be considered to be both a proliferative hormone and an anti-proliferative hormone, depending on the cell's previous history of progestin exposure, and on the length of time the cells have been exposed to progestin. The fact that the timing of progestin exposure can have different effects on cell behaviour has profound implications for treatments that contain progestins, such as combined hormone replacement therapies.

In summary, this thesis develops mathematical models representing different aspects of the cell cycle, and uses a variety of sources in the literature to parameterise the models. The model results are used to give insight into mechanisms that play a role in cell cycle progression under different experimental conditions. The models have the potential to be used alongside experiments, giving further insight into the mechanisms that influence events, such as cell cycle progression in the presence of hormones, as well as cell death.