

APPLICATIONS OF MATHEMATICAL MODELLING IN ONCOLYTIC VIROTHERAPY AND IMMUNOTHERAPY

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With more than 10 million new cases each year, cancer is one of the most devastating diseases worldwide. Developing curative treatments for this disease is slow and represents a highly complex, multidisciplinary problem requiring extensive research and creativity. Oncolytic virotherapy is an emerging cancer treatment that uses virus replication to destroy cancer cells. Competent and specific viruses which attack tumour cells but not healthy cells have been made with advances in the field of genetic engineering.

Oncolytic viruses are also investigated as immunotherapy agents for cancer treatment. Combined virotherapy and immunotherapy is a new approach that uses the ability of a virus to lyse tumour cells (leading to the release of soluble antigens and danger signals) to drive an antitumour immune response. This immune response then results in immune cell induced apoptosis (programmed cell death) of cancer cells. New strategies have been developed to maximise this immunotherapeutic potential through the addition of immunostimulatory cytokines to viral genes or combined injections of viruses and immune cells.

Unfortunately, there are still major challenges facing oncolytic virotherapy and combined virotherapy and immunotherapy. Firstly, determining which genetically engineered virus can maximise both viral spread and anticancer cytotoxicity is difficult due to the unknown correlation between the virus genomes and virus effectiveness. Additionally, optimal dosage protocols for these treatments (considering treatment length and administration protocol) are not yet universally established. Overall, significant characterisation of the virus infectivity and immune response is needed to improve future iterations of these treatments.

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Mathematical and computational biology is a growing field of research that is used to answer important questions in biology. Over the years, a diverse range of techniques from this field, varying from deterministic to agent-based modelling, have provided critical insight into cancer treatments. In this thesis, a range of mathematical and computational techniques are developed to advance the current baseline of oncolytic virotherapy and immunotherapy and answer two broad questions.

- (a) How can mathematical and computational tools be used to improve cancer therapies?
- (b) In what ways can oncolytic virotherapy and immunotherapy be improved?

Investigations into different oncolytic virotherapy derivatives are carried out at two physiological scales: intracellular and extracellular. An integro-differential system with distributed parameters is developed to model the intracellular dynamics of the virus–tumour interactions. By optimising the model parameters to *in vitro* virus titre measurements for gene attenuations of the E1B 19 and E1B 55 kDa proteins, specific viral characteristics and the dominant processes altered by the mutations are determined [6]. To consider how these processes act at the extracellular level, the sensitivity of therapy to individual tumour cell and viral heterogeneity using a system of coupled ordinary differential equations (ODEs) is investigated. Bifurcation and local stability analysis is used to establish dosage protocols that result in tumour extinction [1, 3].

Drawing on the results of the general investigation, the dynamics of specific virotherapies are then analysed. To overcome the rapid clearance of viral particles by the immune system, oncolytic adenoviruses can be conjugated with Herceptin. A system of coupled ODEs is used to represent the experimental data for this specific virus and predict the response of cancer growth to other treatment protocols beyond those in the experiments [4]. To contrast this investigation, the system of ODEs is then extended to consider a combined virotherapy and immunotherapy treatment: an oncolytic adenovirus modified with immunostimulatory cytokines interleukin-12 (IL-12) and granulocyte-macrophage colony-stimulating factor (GM-CSF). A sensitivity analysis of optimised parameter values is used to investigate the characteristics of the immune response to virotherapy and suggest treatment improvements. To begin to establish a universally optimal administration protocol, a degradable gel-release mechanism is modelled. Perturbations to the application protocol that achieve optimal treatment effectiveness are determined [5].

To account for the stochasticity in cancer development, a Voronoi cell-based model (VCBM) is developed to assess the sensitivity of treatment efficacy to tumour geometry. The VCBM captures the interaction between oncolytic virus particles and cancer cells in a two-dimensional setting by using an underlying agent-based framework, where agents are cells with edges from a Voronoi tessellation. Simulations show that delaying the infection of cancer cells, and thus allowing more time for intratumoural treatment dissemination, can improve the efficacy of oncolytic virotherapy [2]. Continuing in this way, an agent-based framework known as PhysiCell

is used to model an adenovirus expressing tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and predict optimal viral characteristics.

This thesis develops new mathematical models that can be applied to a range of cancer therapies and suggests engineered treatment designs that can significantly advance current therapies and improve treatments.

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