Mathematical modelling of oncolytic virotherapy: The effects of a PEG-modified adenovirus conjugated with herceptin

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Oncolytic virotherapy is an experimental cancer treatment which uses genetically engineered viruses to specifically target and kill cancer cells. One limitation of this treatment is that free virus particles are rapidly cleared by the immune system, preventing the virus from arriving at the tumour site. To improve virus survival and delivery, virus particles may be coated with polyethylene glycol (PEG) which is known to increase plasma retention. PEG-modification however, is also known to decrease viral infectivity. To overcome this, the virus may be conjugated with herceptin. Herceptin is a monoclonal antibody which recognises and binds to a protein over-expressed on 20%–30% of breast cancer cells. Experimental studies in Kim *et al.* [2] look at the effects of treating tumour cells with a PEG-modified virus conjugated with herceptin. In the study presented here, a mathematical model is derived to describe the interaction between an oncolytic virus, tumour cells and the immune system.

Oncolytic viruses have the ability to infect tumour cells, replicate, then burst out of the infected tumour cell, killing it and creating new viruses to infect nearby tumour cells. Once a virus enters the body, the immune system activates cells that can kill the invading virus particles. As oncolytic viruses only replicate within tumour cells, this local infection coordinates the immune response to the tumour site. Once there, the killer immune cells are assumed to not only cause apoptosis in virus infected cells, but also tumour cells. It is believed that infection of a tumour cell by a virus triggers the production of antiviral factors, [3]. These antiviral factors induce an antiviral state in neighbouring tumour cells which is assumed to reduce their susceptibility to infection, [1]. A diagram which represents these interactions is shown in Figure 1.

The mathematical model of this system is comprised of seven ordinary differential equations (ODEs). The model was optimised to the experimental data from [2] to obtain parameter estimates. A least-squares non-linear fitting algorithm was used

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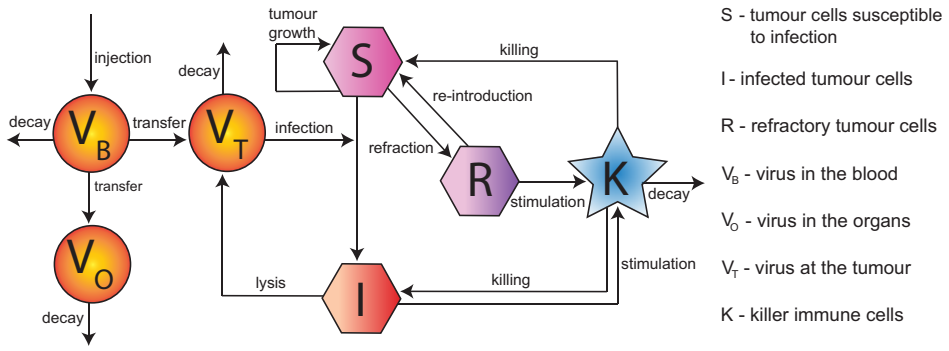
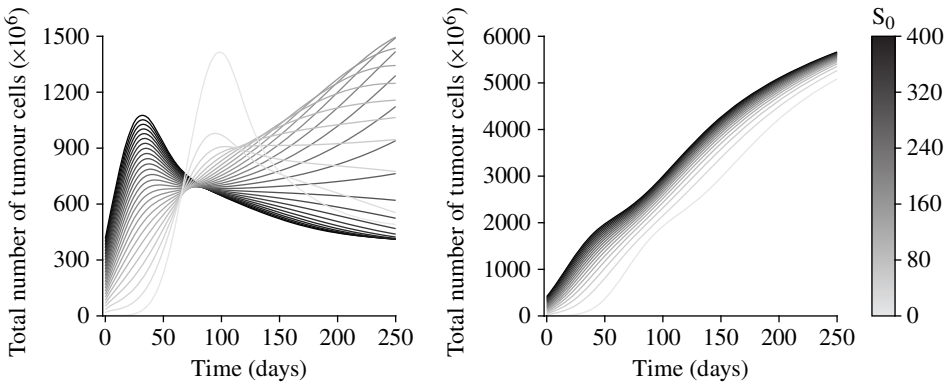


Figure 1. Compartmental diagram of the interaction between an intravenously injected oncolytic virus, tumour cells and the immune system.

to obtain estimates for all parameters. With these, the model provides a platform from which predictions can be made about the response of cancer growth to other modes and combinations of treatments. For example, when perturbations were made of the initial tumour volume prior to treatment, a counter-intuitive outcome of the treatment was observed, Figure 2.

From Figure 2(a) we see that the initial tumour volume can have an extensive effect on the overall treatment outcome. Those tumours starting with a typical (mid range) initial tumour volume tend to grow over time and do not respond to the treatment as well as those with a very small initial tumour or a very large initial tumour size. This illustrates that there is a window of tumour growth within which it would be be disadvantageous to start treatment. The model predicts



(a) Model with immune system (b) Model with no immune system

Figure 2. Predicted total tumour volume as a function of time, obtained using the model with parameter estimates obtained through optimisation to the experimental data of [2]. Figure (a) is obtained using the full model and Figure (b) is obtained by removing the immune system from the model. Different initial tumour sizes are shown.

that treatment should be postponed until the tumour leaves this intermediate size range.

One aim of this study was to determine whether or not the inclusion of an immune response was necessary to embody the observed experimental behaviour. A comparison was made between the predicted tumour volume of the complete model and that from the model with the killer immune cells removed, see Figure 2(b). It was found that the effect of the initial tumour size was negligible on the overall outcome as all tumour volumes tended to the same limiting volume in the absence of killer immune cells. Extremely different outcomes can be obtained depending on the behaviour of the subject's immune system, supporting the inclusion of the immune system into the model.

It is envisioned that refinements of the model could be used to tailor treatment regimes to optimise individual patient outcomes. If it was possible to quantify all the different possible outcomes of this treatment based on the possible stimulation and killing rates of a subject's immune system, then we could predict, depending on their initial tumour size, how likely a particular treatment was to succeed. It is widely known that every subject reacts to treatment differently and we could use this to our advantage to optimise the treatment regime.

We have shown that without the inclusion of the immune system in this interaction we would be missing some very interesting dynamics. This indicates that the immune system is a critical non-negligible part of the interaction between an oncolytic virus and a tumour. With this knowledge, viruses used to treat cancer may be better understood and the treatment of cancer be made more effective.

References

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