Remodeling oncolytic virotherapy

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Abstract

The potential of virotherapy cannot be understated. While there's many novel cancer treatments being researched and developed, virotherapy should definetly be considered one of the most important. The introduction of a specialised virus to tissue affected by cancerous cells shows different effects, all leading to cancer treatment without significant side-effets. Three diferent viruses were simulated using known data about tumour, cell and virus growth and their influence on eachother. All these viruses eventually lead to a partial, majority or even complete extermination of cancer cells in tumour affected tissue. With that being said, the parameters and virus used are of great importance in the effectiveness of the treatment. The viruses vary in their infection and destruction rates of the cells. Simulations have also shown that the competitiveness of both the cell types are significant in determining the effectiveness of treatment. It is important for both the cell types to be infected. Absence of competition could eventually lead to a premature end to the treatment. This concept of competition is substantiated by various observations throughout community ecology studies. In this case, the normal and tumour cells represent prey populations, who share a common predator, the virus. Regardless of the potential points of discussion and debate, the implication of virus mediated killing of cancer cells will surely serve as a groundwork for future research. Virotherapy will potentially lead to a relatively less destructive and more effective treatment.

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1 Introduction

Viruses and cancer are both considered to be very destructive and harmful. But what if one of these could be used to combat the other? Viruses infect cells. These cells do not have to be healthy ones. By introduction of specific viruses into tumor affected tissue, the tumor may be repressed and eventually entirely eliminated. The field known as oncolytic virotherapy is still developing. there is still many uncertainties, but also possibilities. This paper aims to reproduce and possibly revise another paper published in the journal of theoretical biology. The paper demonstrated extensive modelling relevant to exploring the effects of varying amounts of normal and tumor cells.

Oncolytic virotherapy has a lot of potential. With that comes many things to consider. Before diving deeper and challenging some of these considerations in more mathematical detail, let's ask some general important questions. What is the desired balance of infection? Viruses used in these treatments don't exclusively infect tumor cells. This could either be beneficial or a hindrance. At which amount of infection does one group start to suffer? And what are the ideal ratios when it comes to tumor to normal cell infection? As the amount of tumor cells declines, it becomes harder for the virus in the system to find and infect tumor cells before the immune system eliminates the virus completely. This could result in stray tumor cells being left behind, only delaying the growth until it propagates significantly again. This is also only addressing the use of viruses which lyses the tumor cells. Some viral infections may cause the cells to be more susceptible to other forms of treatment, such as chemotherapy. This brings in a whole other amount of variables to consider.

In any case, the immune response is of great importance. The immune response may vary from person to person and tissue to tissue. Whether the person had been exposed to a virus before, or the immune system engages an unknown pathogen mediates different responses too. it is important to be aware of those factors in treatment. Time is of the essence in all instances of virotherapy. It usually takes 5 to 7 days for the immune response to completely halt production rate of the virus. As mentioned earlier, it is important that the treatment, in the case of the lysation approach, destroys all of the tumor cells. Having to accomplish this in the time frame of only 5 to 7 days is quite a feat. This swift approach is referred to as one shot virotherapy. This is why it is so important for the initial values to be right, further solidifying the significance of researching and being absolutely certain about the relevant mathematical models, due to there only being one shot at the initial treatment with a specific virus.

2 Methods

Since the ambition of this paper is to reproduce the results found in Okamoto et al. [2014], our objectives are the same as described in that article:
"We model the dynamics of an oncolytic virus within the context of its interactions with the populations of tumor cells and normal cells. We integrate key ecological processes, such as the growth of normal cells and tumor cells and an adaptive immune response, with an explicit treatment of how viruses differentialy exploit the two cell types."

2.1 Variables

Variable	Explanation	Unit
t	Time	hr^{-1}
H	Normal (Healthy) cell type	-
C	Tumour (Cancerous) cell type	-
H_S	Normal cell that is susceptible	-
H_I	Normal cell that is infected	-
C_S	Tumour cell that is susceptible	-
C_I	Tumour cell that is infected	-
K_H	Carrying capacity of normal cells	cells
K_C	Carrying capacity of tumour cells	cells
β_H	Infection rate of normal cells	viruses $cell^{-1}$ hr^{-1}
β_C	Infection rate of tumour cells	viruses $cell^{-1}$ hr^{-1}
λ_H	Lysing rate of normal cells	$cell^{-1}$ hr^{-1}
λ_C	Lysing rate of tumour cells	$cell^{-1}$ hr^{-1}
b_H	Burst size of normal cells	-
b_C	Burst size of tumour cells	-
r_H	Per-capita growth rate of normal cells	hr^{-1}
r_C	Per-capita growth rate of tumour cells	hr^{-1}
ω	Rate of neutralisation by innate immune response	$virus^{-1}$ hr^{-1}
v	Virions	-

Table 1: All variables and their respective explanations

2.2 Equations

This model is a direct replica of the one presented in Okamoto et al. [2014], since that is the process we are trying to replicate. The model seeks to incorporate the effects of an oncolytic virus on the growth and maintenance of normal cells along with it is effects on tumour cells, thereby extending the work of Wu et al. [2004] which only aims to formulate the latter: characterising an oncolytic virus infecting a population of tumour cells. Wu et al. [2004] is itself an extension of previous models of virus-host interactions, further references to which van be found in Okamoto et al. [2014].

We start out with two separate cell populations both of which are divided into two sub populations: tumour cells (C) and normal cells (H), each having a susceptible (C_S & H_S) and an infected (C_I & H_I) sub population. All other parameter definitions can be found in table 1

2.2.1 Normal susceptible cell count

This first differential equation models the change in the number of normal cells that are still susceptible to an infection by virus particles.

$$\frac{dH_S}{dt} = r_H H_S(1 - \frac{(H_S + H_I)}{K_H}) - H_S \beta_H v \tag{1}$$

2.2.2 Tumour susceptible cell count

This second differential equation is very similar to equation (1), since it represents the same change in susceptible cells except it models tumour cells instead of normal ones.

$$\frac{dC_S}{dt} = r_C C_S(1 - \frac{(C_S + C_I)}{K_C}) - C_S \beta_C v \tag{2}$$

2.2.3 Normal infected cell count

This third differential equation is again similar to equation (1) in that it models normal cells, but in this case we're looking at the change in infected cells instead of susceptible ones.

$$\frac{dH_I}{dt} = \beta_H H_S v - \lambda_H H_I \tag{3}$$

2.2.4 Tumour infected cell count

This fourth differential equation relates to equation (3) in the same way as equation (2) relates to equation (1): This equation again models infected cells, but regards tumour cells instead of the normal cells found in equation (3)

$$\frac{dC_I}{dt} = \beta_C C_S v - \lambda_C C_I \tag{4}$$

2.2.5 Virion count

This fifth and final differential equation is a bit different from all of the other ones that came before, since it models virions instead of cell populations.

$$\frac{dv}{dt} = b_C \lambda_C C_I + b_H b_C \lambda_H H_I - \beta_H H_S v - \beta_C C_S - \omega v \tag{5}$$

2.3 Equation modeling

The results of the differential equations and their plots are made by an R program, utilizing the desolve and ggplot packages. By defining the parameters, variables and equations, analysis of results was made convenient. Changing and observing the effect of certain parameter values were easily done this way. The equations remained unchanged, stored as functions.

The goal in this process was to simulate the effects the three viruses in particular would have on tumour affected tissue. To further determine the most important elements of the equations, different values were changed according to what would logically be most influential, to confirm their importance. The specific values will be mentioned when discussing the equations themselves.

Starting out with the equation execution required distinction between parameters and state variables. The state variables are universal, and not specific to any virus. They are rather bodily constants, which were exposed to the effects of the different viruses. The amount of virus particles introduced to a system is a state variable, and initially remains the same for all viruses when t = 0. it is however worth noting that the amount of free virus particles are ever changing, and don't just reach 0 after they have infected cells. The virus replication rate differs. It is because of the complex interactions such as these that the virus types are important. There are 4 additional variables to the state variable mentioned above. These account for the susceptible and infected cells, both healthy and cancerous.

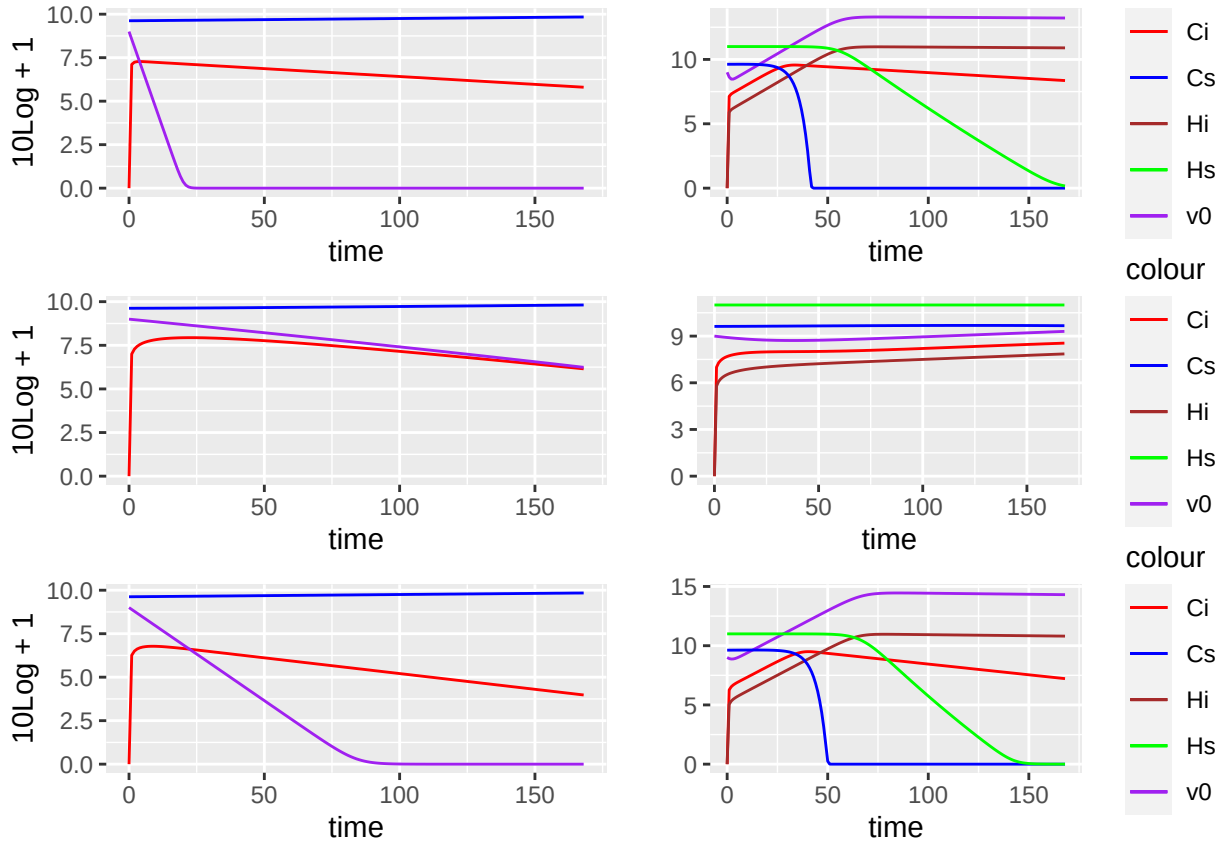
By letting desolve run the equations over 168 hours, three different datasets were created. One for every type of virus. By 10log transforming the data, comparing the differing effects was now possible. By plotting the three datsets, using ggplot, there seemed to be significant difference between the virus effects. To deduce what contributed to the different effects, the virus specific variables were compared next to the plotted results.

After simply observing the plot lines and making a rough estimation, it seemed that the main contributing differentiators are related to cell death and cell infcetion specificity. Lysing and burst rates being the main culpritswhen it comes to cell death The infection rate of healthy cells, betaH, being very relevant to specicifity. To further analyse this, the values were changed from the original values, which can be found in the sections above.

To reaffirm the previous suspicion, new plots were made with both lowered and increased values. Analysis of these findings are under the results section.

3 Results

By finishing the simulations and plotting the results, multiple relations become clear. With the default values, there seems to be a clear indication that competition is important. it is important that there is relative balance between infection rates of healthy and tumor cells. The healthy cells can be slightly slower when it come to being infected, but not significantly, or else the aforementioned competition won't properly balance out the infections.

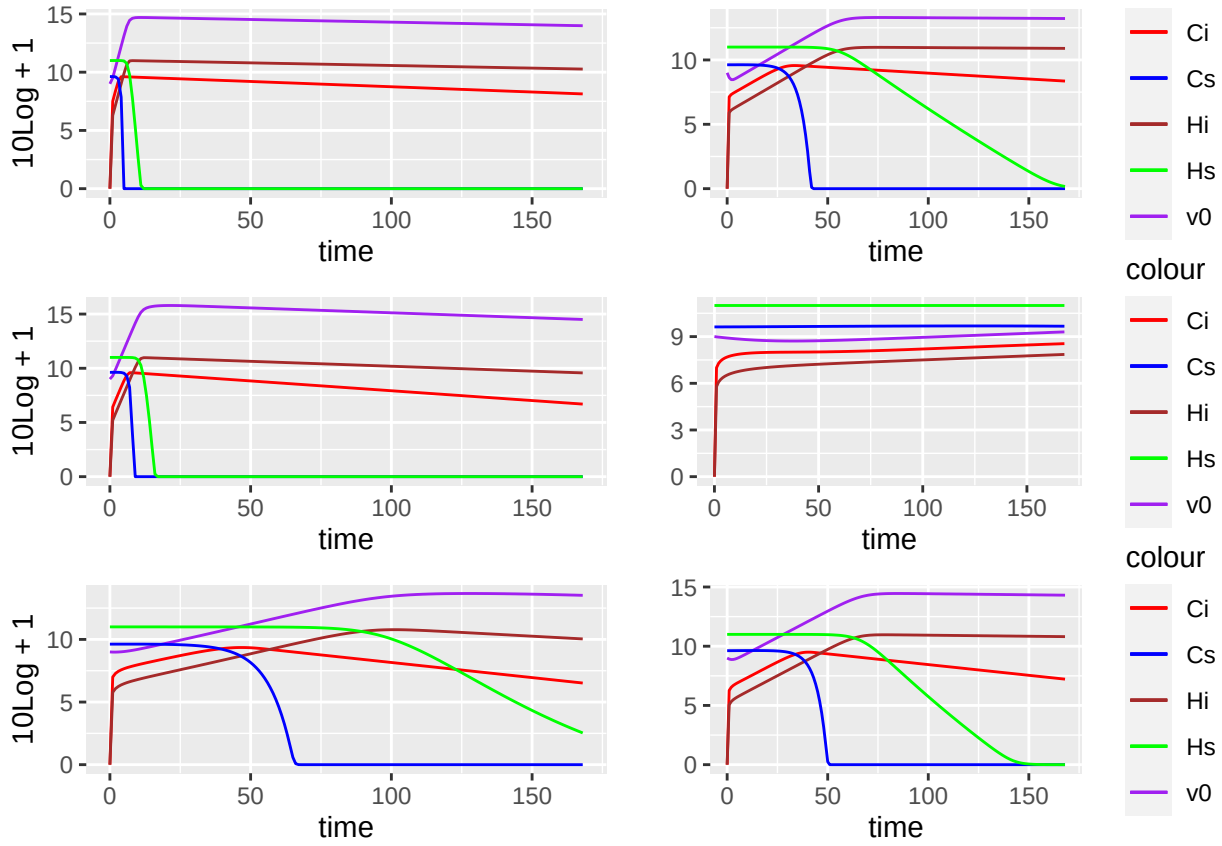


As can be seen in the plot above, when a virus only affects the cancerous cells, the results differ significantly. These and all proceeding plots are presented in the following order: Adeno, hsv and vsv with modified parameters, next to their default ranges. The differences can immediately be seen, but let us first examine the changes made.

The rate of infection of normal cells has been changed to 0 here. Hs and Hi are hidden here, because they stay at a constant due to not being infected. Meaning that only tumor cells get infected and destroyed. Resulting in a premature ending of the treatment, with v0 hitting 0 and staying there. Further establishing that the competition is of great importance to the results. The balancing of healthy and cancerous cells being absent affects Ci and Cs. The Ci increases at first, as usual. But without healthy cells being infected too, it seems that Ci and V0 drop off swiftly. This means that Cs increases accordingly, which means cancerous cells grow faster than they are being eliminated.

The problem arising here is that the immune system doesn't allow for repeat exposure to the treatment. Immunity won't allow the treatment to work a second time, with the same virus atleast.

In addition to observing the specificity, the virus destructibility was also adjsuted and plotted below.An increase of 5 times the default of 0.1 for obth burst size and lysis rate seem to also rapidly decrease the Ci and Hi. These two seem to decrease significantly slower when using the default values. As the gradual increases kept stacking up, it became clear that the Cs and Hs also hit the 0 point earlier. This makes sense, because cells get lysed increasingly faster. It is also worth noting that V0 seems to decrease very slowly. Something that is different when observing the default values. This woud also explain why infections seem to happen quicker, because of the burst size being increased. Resulting in more virus particles in the system, at a faster rate.



Instead of increasing it five fold, other values were also tried. These essentialy ended up adhering to the same pattern seen above, just over different times. The healthy and cancerous cells eventually end up all being infected. While not unexpected, slight increases in burst size significantly increased infection rates. Even when increasing it by only 0.3 times the default value.

4 Discussion

The conclusions and discoveries made in this paper will surely be helpful for future studies. But there could be some points of discussion on a number of topics. The first ones relating to the accuracy of the variables involved. While this paper aimed to simulate the possibilities to the best of it is abilities, the process remains very complex, with a lot of parts involved. The point being that maybe not all influential parts have yet been taken into consideration. References were briefly made to the immune response and its relevance to ending the treatment in 7 days. The immunology aspect of this paper did not go into thorough detail in describing the underlying mechanisms which facilitate virus elimination. It is therefore entirely possible that something would've been missed in this consideration. But the immunology aspects this paper is based on come from reliable sources, such as Oxford university press. Nevertheless, it is probably useful to dive into the immunological relevance further in another paper.

While on the topic of the complexity, there is more to be remarked on this subject. Not all forms of cancer will respond in the same way to the viruses discussed. This paper lays a foundation, from which more specific forms of cancer may be modeled too. The same goes for the viruses mentioned. There are plethora of viruses out there, which would surely offer a world of opportunity when it comes to modeling of new responses.

The critiques mentioned above are worthy of being explored further. This doesn't trivialize the fact that the models created here are important. The results are very promising in finding new ways to treat cancer. The basis of the models are sound and could surely be used for future research. As mentioned before, the specificity of future papers may lead to actual trials of the treatments.

5 Conclusion

there is several conclusions which can be made on the basis of the models. As stated in the prior paper this one is based on, the competitiveness is once again reinforced as an important factor in virotherapy. The absence of such a mechanism surely inhibits the ability for the virus to help in treatment, as shown by the plots in results. The ability of the virus to also infect normal cells is detrimental in offering a proper treatment.

Many factors go into ensuring this competition between cells, viruses and immune system. Most of the important variables being controllable, like the specificity of the virus. This is because viruses already differ in their abilities. But for them to be modified in the lab is also a possibility. Although that might be worth further experimentation and examination.

The destructive capability has also been observed. The models indicate that the rate at which the virus reproduces, and lyses, is important. Changing this value makes it so that all the parameters change their in their slopes. This means that once again, the virus that is selected must be considered. Since viruses tend to vary in their replication and lysis rates. Whether a virus destroys the host too fast, too slow or just right for treatment, should be considered.

The spread ability of the virus was also observed with the plots mentioned earlier. It seems that an increasing spread ability should be kept around a balanced point, where not all the healthy cells get infected too fast. When the susceptible amount of healthy cells hits 0, it means that all the healthy tissue has been infected. This is a very vital side effect of increasing the burst size. The goal of hitting 0 susceptible cells in a treatment is still possible, but with a lower burst size. It would otherwise defeat the point of having a relatively side-effectless cancer treatment, which virotherapy aims to be.

6 Bibliography

References

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