Treating cancerous cells with a continuous release of virus particles

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Abstract

We investigate a model for the treatment of a tumour through the application of a virus. In the original model it was assumed that the virus particles are released only at one time. Such a treatment strategy cannot eliminate a tumour, as the tumour-free steady-state solution is unstable except for pathological circumstances in which the tumour does not grow and/or the virus does not die. We extend the model by allowing the tumour to be treated by a continuous release of virus particles. We show that the scaled delivery rate has two threshold values: below the lower threshold the system evolves to a stable periodic solution; above the higher threshold the tumour is eradicated.

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Contents

1 Introduction

Oncoloytic virotherapy is the treatment of a tumour using a virus that targets cancer cells without harming normal healthy cells. The virus infects cancer cells producing infected cancer cells. Once inside a tumour cell the virus replicates. Eventually the virus particles cause the infected tumour cell to break down and die. This releases a 'burst' of new virus particles. As virus particles do not harm healthy cells, this offers a mechanism to specifically target cancer cells. Figure 1 illustrates the biological processes in the model.

Many naturally occurring viruses are being investigated for their use as virotherapy agents. Advances in genetic technology offer the possibility of 'tuning' these viruses so that they only attack uninfected tumour cells. Engeland et al. [1] recently reviewed oncolytic virotherapy and combined oncolytic virotherapy and immunotherapy from both biological and mathematical perspectives.

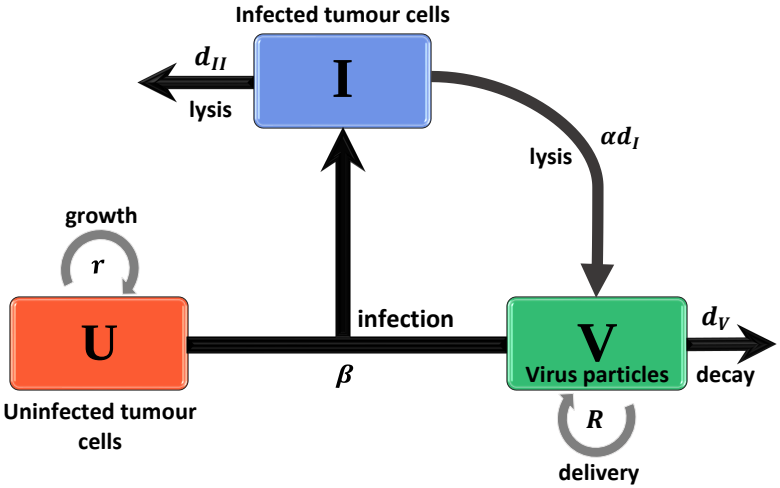

Figure 1: The biological processes included in the model. State-variables: U represents uninfected tumour cells, I represents infected tumour cells, and V represents virus particles.

We extend an existing model [2] by replacing a one-off release of virus particles by a continuous release. Experimentalists and clinicians are turning to continuous release protocols because they result in the most effective long-term therapy as the presence of the virus at the tumour site is extended for longer; this has a larger impact on the tumour. Controlled release of virus particles can be performed in *vivo* through the use of injectable gels or polymer matrix systems. Jenner et al. [3] provide details on hydrogels which release virus particles continuously over time. We show that there are two threshold values for the release rate. If the release rate is above the threshold, then the tumor is eradicated. If the release rate is above the lower threshold value, but below the second, then the system evolves to a stable steady-state solution. If the release rate is below the lower threshold value then the system evolves to a stable oscillatory state.

1.1 Literature review

Oncolytic virotherapy is a very appealing strategy for the treatment of tumours. Tian [4] proposed a basic model for oncolytic virotherapy which describes rates of change of uninfected tumour cells, infected tumour cells and infected virus particles, respectively,

$$\begin{aligned}\frac{du}{dt} &= ru\left(1-\frac{u+i}{K}\right)-\beta uv,\\ \frac{di}{dt} &= \beta uv - d_I i,\\ \frac{dv}{dt} &= \alpha d_I i - \beta uv - d_V v.\end{aligned}$$

Here, u, i and v are the uninfected tumour cell population, the infected tumour cell population, and the free virus population, respectively. The tumour load is $T(t) = u(t) + i(t)$. The parameters in the model are: the carrying capacity for tumour cells K; the per-capita decay rate of infected tumour cells and virus particles, d_I and d_V, respectively; the maximum per-capita growth rate of uninfected tumour cells r; the 'burst size' or average number of virus particles released from one infected tumour cell α; and a rate constant β.

Burst size α is a bifurcation parameter with two threshold values [4]. Below the lower threshold, $\alpha < \alpha_1 = 1 + d_v/(\beta K)$, virotherapy always fails as the tumour goes to its carrying capacity. Between the lower and upper threshold virotherapy is partially successful; there is a stable steady-state with a reduced tumour load. The second threshold value is a Hopf bifurcation. (The value for the burst size at the Hopf bifurcation is not "algebraically expressible" [4, page 855].) As the burst size increases the tumour load can reach very small values, which may correspond to the eradication of the tumour. There may be additional Hopf bifurcations at even higher values of the burst size.

Jenner et al. [2] analysed a minimal model for oncolytic virotherapy (1)–(3) which "complements other oncolytic models." Using steady-state analysis

they deduced that "oncolytic viruses can reduce growing tumours into a stable oscillatory state, but are insufficient to completely eradicate them": a tumour is eradicated only if it does not grow and/or the virus does not decay. They therefore proposed that the eradication of a tumour requires combining an oncolytic virus with the use of additional anti-cancer agents.

2 Model equations

2.1 Dimensional model equations

Here we use a slightly different model to that of Jenner et al. [2] discussed in Section 1.1:

$$\frac{du}{d\tau} = ru - \beta uv\,. \tag{1}$$

$$\frac{di}{d\tau} = \beta uv - d_I i\,, \tag{2}$$

$$\frac{dv}{d\tau} = R - d_V v + \alpha d_I i\,. \tag{3}$$

Parameters have the same meaning as in Section 1.1, and we have added a 'virus delivery term' R to the rate of change of the infected virus particles.

2.2 Dimensionless model equations

We scale the dimensional model (1)–(3) by introducing the dimensionless variables scaled as $U = (\alpha\beta/d_I)\,u$, $I = (\alpha\beta/d_I)\,i$, $V = (\beta/d_I)\,v$, and $t = d_I\tau$. The scaled rate of change of uninfected tumour cells is

$$\frac{dU}{dt} = \xi U - UV\,n\,, \tag{4}$$

the scaled rate of change of (scaled) infected tumour cells is

$$\frac{dI}{dt} = UV - I\,, \tag{5}$$

and the scaled rate of change of virus particles is

$$\frac{dV}{dt} = R^* - mV + I\,, \tag{6}$$

where the bifurcation parameter is the scaled delivery rate $R^* = \left(\beta/d_I^2\right) R$. The other scaled parameters are $m = d_V/d_I$ and $\xi = r/d_I$.

3 Results

3.1 Steady-state solutions

For positive delivery rates $R^* > 0$ there are two steady-state solutions.

The eradicated steady-state solution is

$$(U, I, V) = (0, 0, V_e)\,, \quad V_e = \frac{R^*}{m}\,. \tag{7}$$

The eradicated steady-state represents elimination of the tumour.

The coexistence steady-state solution is

$$(U, I, V) = (U_c, I_c, V_c)\,, \qquad U_c = m - \frac{R^*}{\xi}\,, \tag{8}$$
$$I_c = m\xi - R^*\,, \qquad V_c = \xi\,.$$

The co-existence steady-state represents a partial eradication of the tumour and a non-zero viral load within the remaining tumour. This steady-state is not stable in one-off release models [2, 4].

By inspection, a transcritical bifurcation occurs when $R^* = m\xi$.

3.2 Stability calculations

The Jacobian matrix evaluated at the *eradicated solution* (7) is

$$J(0, 0, V_e) = \begin{pmatrix} \xi - V_e & 0 & 0 \\ V_e & -1 & 0 \\ 0 & 1 & -m \end{pmatrix}.$$

The eigenvalues of this matrix are

$$\lambda_1 = \xi - V_e\,, \quad \lambda_2 = -1\,, \quad \lambda_3 = -m\,.$$

Hence the eradicated steady-state is stable when

$$R^* > m\xi\,. \tag{9}$$

The interpretation of equation (9) is that a tumour can be eradicated by a constant supply of a virus, provided that the supply rate is sufficiently large.

The Jacobian matrix evaluated at the *co-existence solution* (8) is

$$J\,(U_c, I_c, V_c) = \begin{pmatrix} 0 & 0 & -U_c \\ V_c & -1 & U_c \\ 0 & 1 & -m \end{pmatrix}.$$

The characteristic polynomial is

$$\mathcal{P} = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0\,,$$

where

$$a_2 = 1 + m\,, \qquad a_1 = m - U_c\,, \qquad a_0 = U_c V_c\,.$$

The eigenvalues of the Jacobian have negative real parts if and only if $a_2 > 0$, $a_0 > 0$ and $a_2 a_1 > a_0$ (the Routh–Hurwitz criterion). The condition $a_2 > 0$ holds since $m > 0$. Since $V_c = \xi > 0$ the inequality $a_0 = U_c V_c > 0$ boils down to $U_c = m - R^*/\xi > 0$. Hence the coexistence steady-state is unstable when $m\xi < R^*$. Thus a necessary condition for the coexistence steady-state to be stable is

$$m\xi > R^*.$$

We now consider the final condition of the Routh-Hurwitz criterion. We find that

$$a_2 a_1 - a_0 > 0 \quad \Rightarrow \quad R^* > \frac{m\xi^2}{1 + m + \xi}\,.$$

Thus the co-existence steady-state is stable if

$$R_1^* < R^* < R_2^*,$$

where

$$R_1^* = \frac{m\xi^2}{1+m+\xi} \quad \text{and} \quad R_2^* = m\xi.$$

A Hopf bifurcation occurs at $R^* = R_1^*$. The significance of the Hopf bifurcation is that it acts as a 'centre' at which limit cycles are either destroyed or created.

4 Discussion

Figure 2 shows a bifurcation diagram for $\xi, m = 0.5$ which plots the scaled concentration of uninfected tumour cells as a function of the scaled delivery rate R^*. For sufficiently small values of the delivery rate, both steady-state solutions are unstable and solutions converge to a stable periodic solution. As the delivery rate is increased, the periodic solutions are terminated at the Hopf bifurcation $R^* = R_1^* = 0.0625$. As the delivery rate is increased through the Hopf bifurcation, the coexistence steady-state solution is now stable. As the value of the delivery rate is increased further there is a transcritical bifurcation at $R^* = R_2^* = 0.25$, also call the branch point. As the delivery rate is increased further the eradicated steady-state solution becomes stable and the coexistence steady-state solution is no longer physically meaningful.

Figure 2 marks four points (a–d) on the periodic solution branch. Figure 3 plots the solutions in the uninfected-infected tumour cell phase plane at these four points. Figure 2 shows that the maximum value for the scaled uninfected tumour cells increases as the delivery rate decreases towards zero. However, focusing on the maximum value of the solution component along the periodic solution does not show the full picture: the maximum value is increasing, but what is happening to the minimum value?

Curve (d) in Figure 3 shows that both the scaled uninfected tumour U and the scaled infected tumour I can become very small. The minimum values

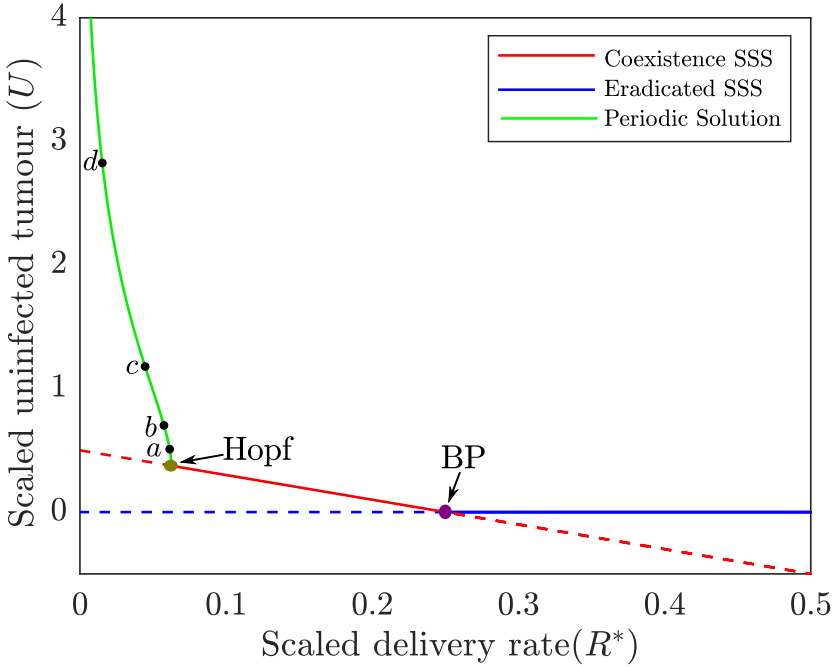

Figure 2: Steady-state diagram for parameter values $\xi = m = 0.5$. The location of the branch point is denoted by BP. Solid and dashed lines represent stable and unstable branches of solutions, respectively. For the periodic solution we only plot the maximum value of the solution. Phase-plane diagrams corresponding to the points (a–d) are shown in Figure 3.

of these variables could be so low that they correspond to less than a single uninfected/infected tumour cell. Depending upon which (unscaled) state variable reduces to less than one cell first, such a periodic solution would correspond to either eradication of the tumour (less than one uninfected tumour cell), or the absence of infected tumour cells (less than one infected tumour cell). Thus in practical terms such oscillations can represent tumour eradication. (Although these periodic solutions are a correct solution to the mathematical model, they are not a correct solution to the underlying physical

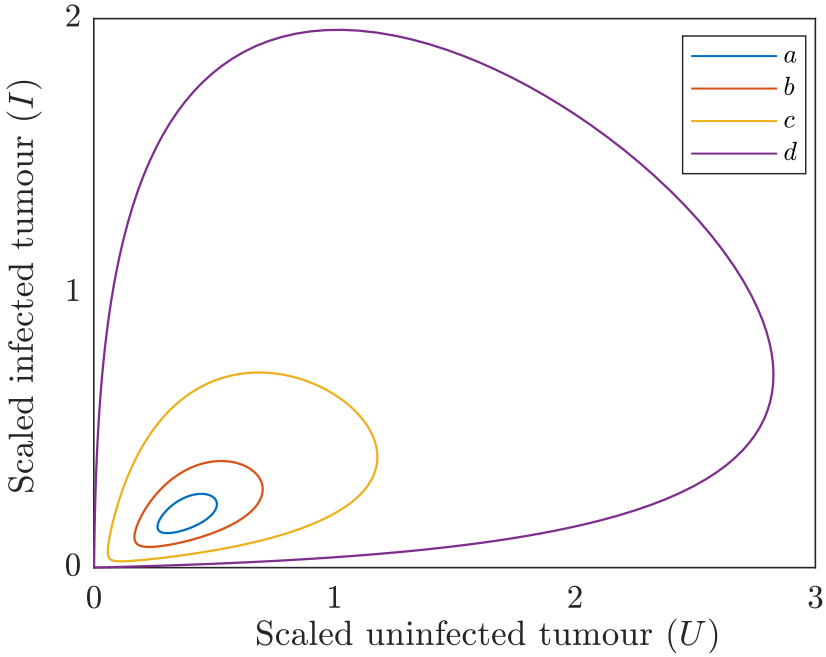

Figure 3: Phase-plane diagram of the four periodic solutions (a–d) identified in Figure 2 for parameter values $\xi = m = 0.5$. Delivery rates are (a) $R^* = 0.0614$, (b) $R^* = 0.0575$, (c) $R^* = 0.0446$ and (d) $R^* = 0.0153$.

problem.) A similar observation has been made by Tian [4, Sec. 4.1]. This leads to an unintuitive interpretation of the model: sometimes lower delivery rates are more dangerous to a tumour than higher delivery rates.

Figure 4 shows the scaled population numbers as a function of scaled time in the region where both steady-state solutions are unstable. The introduction of the virus has not eliminated the tumour, but it has restricted its growth. As commented by earlier authors [2, 4], when such behaviour occurs an additional treatment strategy should be employed. This figure suggests that for best effect the second treatment method should be deployed when the number of infected and uninfected tumour cells is minimised.

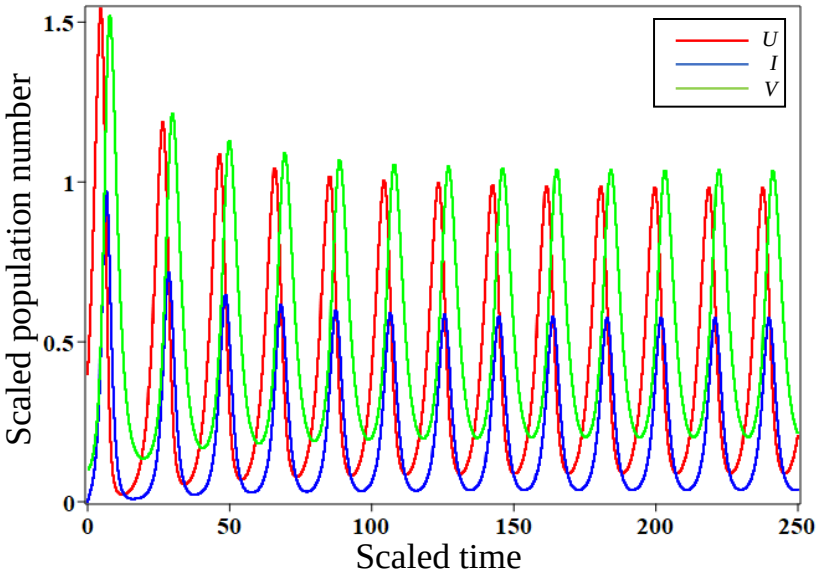

Figure 4: Variation in the scaled population numbers U, I and V with scaled time for parameter values $\xi = m = 0.5$, $R^* = 0.05$.

5 Conclusions

We have extended a model for oncolytic virology by allowing a continuous release of virus particles into a tumour. We showed that a virus can destroy a tumour, provided it is released at a sufficiently high rate. Release rates below this threshold value result in the tumour being partially eradicated, with either a stable steady-state solution or a stable oscillatory state. In the original model complete eradication only occurs when the tumour does not grow and/or the virus does not decay. Thus continuous release can eliminate a tumour without requiring a second treatment strategy.

Casting the condition for complete eradication of the tumour into dimensional

form we obtain the requirement that

$$R > R_{cr} = \frac{d_V r}{\beta}.$$

To reduce the critical value of the release rate R_{cr}, genetic modifications of the virus should either reduce the virus decay rate d_V or increase the rate of infection β. The critical value can also be reduced by combining virotherapy with a second treatment strategy that decreases the replication rate of uninfected tumour cells r.

Rather than considering protocols in which there is either a one-off release or a continuous release, it would be interesting to consider impulsive releases at times $t = t_1, t_2, t_3 \ldots$. When virus particles are delivered to solid tumours some cells may receive a much higher dosage, particularly if they are closer to the vasculature. This issue can be investigated by using partial differential equations with a non-uniform initial condition for the virus particles.

Finally, when the eradicated state is stable an interesting question to pose is 'how long does it take to eradicate the tumour?' We define the eradication time to be the time at which the *number* of tumour cells decreases below one, if this occurs in a finite time. Estimating this time scale is very relevant to treatment.

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