On a three-dimensional and two four-dimensional oncolytic viro-therapy models

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Abstract
We revisit and carry out further computations on tumor-virotherapy compartmental models of Tian (Math Biosci Eng 8(3):841, 2011), Wang et al. (Appl Math Model 37(8):5962–5978, 2013), Phan and Tian (Comput Math Methods Med 2017, 2017), Guo et al. (J Biol Dyn 13(1):733–748, 2019). The results of these papers are pushed further. In particular, we resolve a problem left open from [1], and we illustrate numerically the existence of a bi-stability regime, in which a stable endemic point is also surrounded by a stable limit cycle—see Sect. 5.3.2. We also make public our electronic notebooks, absent for the papers cited, since we believe that electronic reproducibility has become crucial in an era in which software has increased immensely the limits of human computations.

Keywords Oncolytic viro-therapy · Immune response · Stability · Compartmental models · Bifurcation analysis · Electronic reproducibility
1 Introduction

Compartmental models became famous first in mathematical epidemiology, following the pioneering work of Kermack and McKendrick [6] on the SIR model; see [7] for other domains of application, and for some general theory. In the last 30 years, they have also penetrated in mathematical virology [8–11] and in mathematical oncolytic viro-therapy, i.e., the modeling of the use of viruses for treating tumors [12–14].

We may distinguish between at least two main directions of work in these fields:

1. Part of the literature is dedicated to creating models to fit specific viruses and therapies—see for example [15–26]. The proposed models are high-dimensional, and hence only analyzable numerically, for particular instances of the parameters.

2. Another part, which is our concern here, focuses on applying sophisticated mathematical tools, notably the theory of bifurcations for dynamical systems, to “lower-dimensional caricatures” of more complex models. This requires the use of both symbolic software like Mathematica, Maple, or Sagemath, and also of sophisticated numeric continuation and bifurcation packages, such as MatCont (written in Matlab), PyDSTool (Python), XPPAuto (C) and BifurcationsKit (written in Julia)—see [27] for a recent review.

In our work below, we combined the use of MatCont (see [28]) with that of Mathematica (see [29]), and in particular the package EcoEvo. The notebooks (interactive
documents created with Mathematica) we offer on GitHub are an important part of our work, and we attempted to achieve a roughly one-to-one correspondence between the equations numbered in the text and those displayed in Mathematica.

The origins of the glioma viro-therapy four-compartment \((x, y, v, z)\) model considered here, where untreated and infected tumor cells are denoted respectively by \(x, y\), virus cells by \(v\), and innate immune cell by \(z\), are in \([30, 31]\).\(^1\) Subsequent papers of Tian \([3, 4]\) tackled symbolically the two particular cases \(z_0 = \infty, z_0 = 0\). For further developments and further outstanding questions in the field, see \([33–35]\).

We propose to study a unification of the four-compartment systems studied in \([3, 4]\):

\[
\begin{align*}
\frac{dx}{dt} &= \lambda x \left( 1 - \frac{x + y}{K} \right) - \beta xv \\
\frac{dy}{dt} &= \beta xv - \gamma y - \beta_y yz \\
\frac{dv}{dt} &= b \gamma y - \beta xv - \delta v - \beta_v vz \\
\frac{dz}{dt} &= \rho \beta_y yz - cz^{\epsilon+1}, \quad \epsilon \in \{0, 1\},
\end{align*}
\]

(1)

where \(x, y, v\) and \(z\) represent the populations of uninfected (untreated) tumor cell population, infected tumor cell population, free virus and innate immune cells, respectively.

**Remark 1** The invariance of the first quadrant (also called “essential non-negativity”) is immediate since each component \(f_i(X)\) of the dynamics may be decomposed as

\[f_i(X) = g_i(X) - x_i h_i(X),\]

where \(g_i, h_i\) are polynomials with nonnegative coefficients, and \(x_i\) is the variable whose rate is given by \(f_i(X)\). In fact, under this absence of “negative cross-effects”, even more is true: the model admits a “mass-action representation” by the so-called “Hungarian lemma” \([7, 36]\), \([37, \text{Thm. 6.27}]\)\(^2\)

**Remark 2** Scaling all the variables by \(x = K \tilde{x}, y = K \tilde{y},...\) has the effect of multiplying all the quadratic terms by \(K\), and one may finally assume \(K = 1\), at the price of renaming some other parameters. Also, scaling time by a constant allows choosing another parameter as 1. Below, we will follow occasionally \([1, 3]\) in choosing \(K = \gamma = 1\), which simplifies a bit the results.

Figure 1 depicts a schematic diagram of this model. The interpretation of parameters can be seen in Table 1.

\(^1\) A considerably more complex four-dimensional model was proposed in \([32]\). Interestingly, these papers suggested a density dependent rate of immune cells, linear up to a threshold \(z_0\), and quadratic afterwards. “The first process occurs when \(z\) is small and yields a linear clearance; the second process occurs when \(z\) is large and yields a quadratic clearance” \([31, \text{p. 2}]\).

\(^2\) The previous virology literature does not seem to be aware of this result, and offers direct proofs instead.
Fig. 1 Schematic diagram of model (1). The compartments $x$, $y$, $v$ and $z$ denote uninfected tumor cells, infected tumor cells, free virus and innate immune cells, respectively. Continuous lines represent transfer between compartments. Dashed lines represent viral production or activation of immune cells.

Table 1 Interpretation of parameters for model (1)

| Symbol | Description |
|--------|-------------|
| $\lambda$ | Intrinsic growth rate of uninfected tumor cells |
| $K > 0$ | Carrying capacity of uninfected tumor cells |
| $\beta > 0$ | Viral infection rate |
| $\beta_y$ | Rate at which immune system removes infected tumor cells |
| $\gamma > 0$ | Lysis rate of infected cells |
| $b \geq 1$ | Virus burst size |
| $\delta$ | Clearance rate of viruses |
| $\beta_v$ | Rate at which immune system removes viruses |
| $\rho \beta_y := \beta_z > 0$ | Proliferation rate of immune cells due to the interaction with infected tumor cells |
| $c$ | Rate of clearance of immune cells |

Remark 3 The three-compartment viral model (2) of [1, 5] can be seen as a special case of the general model (1) when the variable $z$ is identically zero (the immune system is totally inefficient).

The fourth compartment for the immune system was subsequently modeled differently in [3, 4] (where $K = \infty$). We have unified these two papers by adding the parameter $\epsilon$, which equals 0 in [3] and 1 in [4].

The three-compartment model from [1] has been analyzed symbolically up to a point, and it ended with a list of open problems, which awoke our attention since they seemed to be still open. Other interesting open problems were raised by the two four-compartment model (for example, the local stability of certain points was only established in particular cases, numerically).

We point out now another important open problem, not mentioned in [1].

Q: Can chaos arise in model (1)?
Note that while we do have the right to hope for the absence of complicated dynamical behaviors, since we are dealing with a pseudo-linear, essentially non-negative system, this is by no means guaranteed. Indeed, complicated dynamics like multiple “concentric” cycles have been found in [38], and in the parallel ecology literature on three-dimensional food-chains, chaos is known to occur as well [39–46].

While very interesting and worthy of further investigation, the virology papers cited above suffer from the lack of providing supporting electronic notebooks. The importance of symbolic and numeric computing in mathematical biology cannot be overstated (see, for example, [47]).

**Electronic reproducibility.** As emphasized already 30 years ago, the opportunity we have nowadays of being able to accompany our pencil calculations with electronic notebooks “gives a new meaning to reproducible research” [48]. Following efforts of numerous people, for example [49, 50], lots of progress has been achieved, as witnessed by the existence of the platform GitHub. Unfortunately, the percentage of researchers who take the time to tidy their notebooks and make them available on GitHub is still infinitesimal in some fields.

Our main contribution below is in providing electronic notebooks, where the readers may recover the results of the previous works of [1–4], and then modify them as they please, for analyzing similar models. Note this is a non-trivial task, and it goes in a direction orthogonal to that of most of the current literature.

**Contents.** We start by revisiting in Sect. 2 the three-dimensional model of [1], which had been already essentially solved symbolically. However, with help from Mathematica, we resolve one of the problems left open in [1].

In Sect. 3, we introduce a “generalized virus” model, geared at unifying previous studies and initiating new directions of research (as typical in the field, we will not be able to answer all our questions).

Some first results for our general model are then presented in Sects. 3.1 and 3.2. The particular case of [3] is revisited in Sect. 4.

We turn then to the complete viro-therapy and immunity model with logistic growth in Sect. 5.

## 2 Warm-up: the three-dimensional viral model [1, 5]

The three-dimensional tumor-virus model proposed in [1, eq. (5)] and [2] is:

\[
\begin{align*}
\frac{dx}{dt} &= \lambda x \left( 1 - \frac{x + y}{K} \right) - \beta xy \\
\frac{dy}{dt} &= \beta xy - \gamma y \\
\frac{dv}{dt} &= b\gamma y - \beta xy - \delta v, \quad x + y \leq K, \quad v \leq \frac{b\gamma K}{\delta}.
\end{align*}
\]

**Brief history.** A similar three-dimensional \((x, y, v)\) model, with linear growth, and with the term \(\beta xy\) present in all the equations seems to have been first proposed by Anderson, May and Gupta [51], as a model for the interaction of parasites with...
host-cells, in particular red blood cells (RBC). Subsequently, this became known as the Novak-May model [9], and has been applied in many other directions, for example by Tuckwell & Wan [22], as a model for HIV-1 dynamics. See also [1, 2] for a version with delay, [52] for a stochastic version, and see [53] for a stochastic version with “saturated infection rate” in which $\beta$ is replaced by $\beta(x, y) = \frac{\beta}{x+y+\alpha}$.

Factorization yields easily the three equilibrium points for the model (2). The first two $E_0 = (0, 0, 0)$, $E_K = (K, 0, 0)$ are “infection-free”, and the third equilibrium

$$E_* = \left( \frac{\delta}{\beta(b-1)}, \lambda \frac{\delta}{\beta(b-1)} \frac{K\beta(b-1) - \delta}{K\beta\gamma(b-1) + \lambda \delta}, \lambda \frac{\gamma}{\beta} \frac{K\beta(b-1) - \delta}{K\beta\gamma(b-1) + \lambda \delta} \right)$$

is interior to the domain.

The explicit eigenvalues of the Jacobian at the first equilibrium point make it a saddle point. Similarly, examining the Jacobian shows that the second point is stable when

$$R_0 := \frac{K\beta}{\delta}(b-1)$$

is smaller than 1 and unstable when $R_0 > 1$, where $R_0$ is the famous “basic reproduction number” of mathematical epidemiology. This is computed using the next-generation matrix approach [54–56], which splits the problem into two computations: that of the boundary equilibrium, and that of the largest (Perron-Frobenius) eigenvalue of a matrix that involves only the “infection equations”. For the convenience of the reader, we include two Mathematica scripts which perform this computation, for any “model={dyn,X}” defined as a pair of dynamics and its variables, and any subset “inf(ectious)” where the values of the fixed point are known to be 0:

```mathematica
DFE[mod_,inf_] := Module[{dyn,X},
  dyn=mod[[1]];X=mod[[2]];
  Flatten[Solve[Thread[dyn==0]/.Thread[X[[inf]]->0],X]];
]

NGM[mod_,inf_] := Module[{dyn,X,dyni,infc,M,V,li,Fv,F,K},
  dyn=mod[[1]];X=mod[[2]];dyni=dyn[[inf]];(*cd=DFE[mod,inf];*)
  infc=Complement[Range[Length[X]],inf];
  M=Grad[dyn[[inf]],X[[inf]]];
  V=-M/.Thread[X[[infc]]->0];
  li= V . X[[inf]] ;
  Fv=(dyni )+li;
  F=Grad[Fv,X[[inf]]];K=(F . Inverse[V])/.Thread[X[[inf]]->0]
]
```

In our case, “inf={2,3}” and the call of the second function will yield the next-generation matrix with eigenvalues $\left\{ 0, \frac{1}{\delta} \frac{b-1}{\beta} \right\}$. It only remains to plug the $x$ value furnished by the first script. Note that here we get two “disease-free” equilibria, but one, $x = 0$, may be discarded as having no biological meaning, leaving us with $x = K$. 

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The critical $b$ which makes $R_0 = 1$ is

$$b_0 = 1 + \frac{\delta}{\beta K},$$

confirming [1, Lemma 3.4].

We may write the third point as

$$E^* = \left( \frac{\delta}{\beta (b - 1)}, \frac{\lambda \delta^2}{\beta (b - 1)^2}, \frac{\lambda \delta}{\beta (b - 1) + \lambda \delta}, \frac{(R_0 - 1)}{\beta (b - 1) + \lambda \delta} \right),$$

which shows that this point enters the positive domain “precisely when we need it”, when $R_0 = 1$.

It is convenient to rescale time by $\gamma$ and the variables by $K$, the net result being that these variables may be assumed to equal 1 [1, Sec. 3.1]. Hence, in the rest of this section, we will assume that $K = \gamma = 1$. The third point simplifies then to

$$E^* = \left( \frac{\delta}{\beta (b - 1)}, \frac{\lambda \delta}{\beta (b - 1) + \lambda \delta}, \frac{(R_0 - 1)}{\beta (b - 1) + \lambda \delta} \right),$$

and we see that this point enters the nonnegative domain precisely when $R_0 = 1$, at $E^* = E^*_0 = (1, 0, 0)$.

The equilibrium $E^*$ is interior to the invariant domain if and only if $R_0 > 1$. Its stability may be tackled via the Routh-Hurwitz conditions, which, at order three, amount to

$$\begin{align*}
\text{Tr}(J) &< 0, \\
\text{Tr}(J)M_2(J) &< \text{Det}(J) < 0,
\end{align*}$$

where $M_2$ is the sum of the second-order principal leading minors of the Jacobian matrix $J$ at $E^*$. Now, the first and last inequalities are always satisfied in our case [1, Thm. 3.7] since

\[
\begin{cases}
\text{Tr}(J) := -1 + \frac{\delta(b + \beta + \lambda)}{\beta(1 - b)} < 0, \\
\text{Det}(J) := (1 - R_0) \left( \frac{\delta^2 \lambda}{\beta (b - 1)} \right) < 0,
\end{cases}
\]

and thus the local stability of the point $E^*$ holds if and only if

$$H(b) := \text{Det}(J) - \text{Tr}(J)M_2(J) = -a_3 + a_1a_2 > 0,$$

where

$$\begin{align*}
a_1 &:= \frac{\beta(b + b \delta - 1) + \delta \lambda}{(b - 1) \beta}, \\
a_2 &:= \frac{\delta \lambda(\beta - 1 + \delta + b(1 - \beta + \delta)) + ((b - 1)^2 \beta + b \delta^2) \lambda)}{(b - 1)^2 \beta ((b - 1) \beta + \delta \lambda)}, \\
a_3 &:= \delta \lambda \left(1 + \frac{\delta}{\beta(1 - b)}\right).
\end{align*}$$

Remark 4 As a check, note that $H(b_0) = \lambda(1 + \delta + \beta)(1 + \delta + \lambda + \beta) > 0$, and so $E^*$ is stable at the critical point when $E_K$ loses its stability, as expected.
To analyze the sign of $H(b)$, we note first that its denominator $(b - 1)^3 \beta^2 ((b - 1) \beta + \delta \lambda)$ is always positive (see second cell in notebook [57]). Positivity reduces thus to the positivity of the numerator, which is a fourth-order polynomial

$$\Phi(b) = B_4 b^4 + B_3 b^3 + B_2 b^2 + B_1 b + B_0,$$

and may be investigated via Descartes’ rule.

The coefficients are

$$
\begin{align*}
B_4 &:= -\beta^3, \\
B_3 &:= \beta^2(-\beta(\delta - 3) + \delta(\delta + 3) + \lambda + 1), \\
B_2 &:= \beta(\beta^2(2\delta - 3) - 3\beta(2\delta + \lambda + 1) + \delta\lambda(\delta(\delta + 3) + \lambda + 1)), \\
B_1 &:= -\beta^3(\delta - 1) + \beta^2(-\beta^2 + 3\delta + 3\lambda + 3) - \beta\delta\lambda(3\delta + 2\lambda + 2) + \delta^3\lambda^2, \\
B_0 &:= \beta(\lambda + 1)(\delta\lambda - \beta).
\end{align*}
$$

By using $B_4 < 0$ and $\Phi(b_0) = \frac{\delta^3(1+\lambda)(1+\beta+\delta)(1+\beta+\delta+\lambda)}{\beta} > 0$, [1, Lem. 3.8] concludes that the fourth-order polynomial $\Phi(b)$ must have at least one root larger than $b_0$, and one root smaller than $b_0$. Letting $b_H$ denote the smaller root larger than $b_0$, [1, Thm 3.9] concludes that local stability holds in $(b_0, b_H)$. Also, $b_H$ is a candidate for a Hopf bifurcation, by the following elementary Lemma.

**Lemma 1** [1, Lem. 3.10] A cubic polynomial $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$ with real coefficients has a pair of pure imaginary roots if and only if $a_2 > 0$ and $a_3 = a_1 a_2$. When it has pure imaginary roots, these are given by $\pm i \sqrt{a_2}$, the real root is given by $-a_1$, and $a_1 a_3 > 0$.

**Remark 5** Higher dimension extensions exist as well—see [58, 59].

In [1], Tian conjectured that $E_*$ may regain its stability at still larger values of $b$, after crossing yet larger roots, and the question of whether this may occur: “What conditions can guarantee that the function $H(b)$ has four, three, and two distinct real zeros?”

The precise classification of polynomials by their number of roots is a complicated problem [60], and we do not address it below. We may answer however the stability question, using the observation in the next remark.

**Remark 6** The real roots smaller than $b_0$ have no importance (for stability), so the real question is whether the fourth-order polynomial $\Phi(b)$ given by (6) may have more than one real root larger than $b_0$.

This can be tackled by shifting the polynomial to $\hat{\Phi}(\xi) := \Phi(b_0 + \xi)$, where $\xi = b - b_0$, and applying Descartes’ upper bound on the maximum number of positive roots via the number of sign changes in the sequence of coefficients of the shifted polynomial.

**Lemma 2** The polynomial $\Phi(b)$ defined in (6) has precisely one real root $b_H$ larger than $b_0$.}

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Fig. 2 Bifurcation diagram when \( b \) varies, when \( \lambda = 0.36, \beta = 0.11, \delta = 0.44, K = \gamma = 1 \rightarrow b_0 = 1 + \frac{\delta}{\beta} = 5, b_H = 27.7664 \). When \( b \) is bigger than the Hopf bifurcation point \( b_H \), there are no stable fix points.

Proof The coefficients of the shifted polynomial \( \tilde{\Phi}(\xi) \) are

\[
\begin{align*}
\tilde{B}_0 &:= \delta^3(\lambda+1)(\beta+\delta+1)(\beta+\delta+\lambda+1), \\
\tilde{B}_1 &:= \delta^2 \left( \beta(2\delta\lambda + 3\delta + 3\lambda + 3) + (\delta + 2)\lambda^2 + 2\delta(\delta + 3)\lambda + \delta(3\delta + 5) + 5\lambda + 3 \right), \\
\tilde{B}_2 &:= \beta\delta(-\beta^2 + \delta(\delta + 3)\lambda + 3\delta(\delta + 1) + \lambda^2 + 4\lambda + 3), \\
\tilde{B}_3 &:= \beta^2(-\beta(\delta + 1) + (\delta - 1)\delta + \lambda + 1), \\
\tilde{B}_4 &:= -\beta^3.
\end{align*}
\]

The first two are positive and the last negative. Hence, in order for \( \Phi \) to have three roots larger than \( b_0 \), the third coefficient of \( \tilde{\Phi} \) must be negative and the fourth positive. Now each of these inequalities admits solutions, but the commands

\[
\text{cofi} = \text{CoefficientsList}[\text{pol}, i] \\
\text{Reduce}[[\text{cofi}[[i]] > 0 & \& \text{cofi}[[3]] < 0]]
\]

yield False (see the end of the second cell in the Mathematica file [57]), which tells us that the system of the two inequalities has no solutions. \(^3\)

A bifurcation diagram of model (2) as \( b \) varies is illustrated in Fig. 2.

Figure 3a and b show an illustration of the cycle arising with the parameter set above, at a value \( b = 28 \) slightly larger than \( b_H \), see also [2, Figure 7].

\(^3\) The diligent reader is invited to provide an analytical proof, but warned that this seems hard.
3 The four-compartment viro-therapy and immunity model (1)

3.1 Boundedness

**Theorem 3** The epidemiological domain

\[ \Omega = \left\{ (x, y, v, z) \in \mathbb{R}^4_+; x(t) + y(t) \leq K, v(t) \leq \frac{b\gamma K}{\delta}, z(t) \leq \zeta \right\}, \]

where

\[ \zeta = \begin{cases} \frac{\rho \beta y K^2}{\delta \min\{\gamma, c\}}, & \text{if } \epsilon = 0; \\ \frac{\rho \beta v K}{c}, & \text{if } \epsilon = 1. \end{cases} \]

is a positively invariant set.

**Remark 7** The first conditions on \( x, y, v \) appear already in [3, Lem. 1].

**Proof** By adding the first two equations in (1), one obtains

\[ \dot{x} + \dot{y} = \lambda x \left(1 - \frac{x + y}{K}\right) - \beta x v + \beta x u - \beta_y y z - \gamma y \leq \lambda x \left(1 - \frac{x + y}{K}\right). \]

By a comparison argument, we obtain that \( \lim_{t \to \infty} x(t) + y(t) \leq K \). This implies that for all \( \epsilon > 0 \), there is \( t_1 > 0 \) such that if \( t > t_1 \) then \( x(t) \leq K + \epsilon \) and \( y(t) \leq K + \epsilon \).
Then, for $t > t_1$ we have

$$
\dot{v} = b\gamma y - \beta xv - \delta v - \beta v^2 \leq b\gamma (K + \varepsilon) - \delta v,
$$

from which we deduce that $\limsup_{t \to \infty} v(t) \leq \frac{b\gamma K}{\delta}$. 

Lastly, for the boundedness of $z$, we will divide the proof in two cases. Let $\varepsilon_2 > 0$ and take $t_2 > 0$ such that

$$
x(t) + y(t) \leq K + \varepsilon_2 \quad \text{and} \quad v(t) \leq \frac{b\gamma K}{\delta} + \varepsilon_2 \quad \text{for} \quad t > t_2.
$$

Consider first the case $\varepsilon = 0$. Let $w(t) = y(t) + \frac{1}{\rho} z(t)$. Then, for $t > t_2$, we have

$$
\dot{w} = \dot{y} + \frac{1}{\rho} \dot{z} = \beta xv - \gamma y - \frac{c}{\rho} z 
\leq \beta (K + \varepsilon_2) \left( \frac{b\gamma K}{\delta} + \varepsilon_2 \right) - \sigma \left( y + \frac{1}{\rho} z \right),
$$

where $\sigma := \min\{\gamma, c\}$. It follows that

$$
\limsup_{t \to \infty} \frac{1}{\rho} z(t) \leq \limsup_{t \to \infty} w(t) \leq \frac{\beta b\gamma K^2}{\delta \sigma},
$$

and finally

$$
\limsup_{t \to \infty} z(t) \leq \frac{\rho\beta b\gamma K^2}{\delta \min\{\gamma, c\}}.
$$

Lastly, in the case when $\varepsilon = 1$, we obtain

$$
\dot{z} = \rho\beta yz - cz^2
\leq \rho\beta (K + \varepsilon_2) z - cz^2
= \rho\beta (K + \varepsilon_2) z \left( 1 - \frac{c}{\rho \beta y (K + \varepsilon_2) z} \right)
$$

for $t > t_2$. From this, we deduce that $\limsup_{t \to \infty} z(t) \leq \frac{\rho\beta y K}{c}$. 

\[\square\]

### 3.2 Boundary equilibria and their stability

Factoring the last and first equilibrium equations yields four points having either $z = 0$ or $x = 0$:

**Theorem 4** The fixed points with $z = 0$ or $x = 0$ are, respectively:
\[ E_0 = (0, 0, 0, 0) \]
\[ E_K = (K, 0, 0, 0) \]

\[
E_\ast = \left( x_\ast = \frac{\delta}{\beta(b-1)}, \quad y_\ast = \frac{K}{R_0} \frac{\lambda(R_0 - 1)}{\lambda + \gamma R_0}, \quad v_\ast = \frac{\gamma}{\beta} \frac{\lambda(R_0 - 1)}{\lambda + \gamma R_0}, \quad 0 \right)
\]

\[ E_N = \left( 0, \quad y_e = \frac{\xi}{s}, \quad -y_e \frac{b\gamma \mu_y}{\gamma \mu_y - \delta \mu_y}, \quad -\frac{\gamma}{\mu_y} \right) \text{ when } \epsilon = 0 \text{ and } \left( 0, -y_e \frac{\nu}{\beta}, \quad y_e \frac{\gamma^2 b}{\beta \nu - \delta \mu}, \quad -\frac{\gamma}{\beta} \right) \text{ when } \epsilon = 1. \]

This is always outside the domain and will be ignored from now on.

**Remark 8** The first three fixed points appear already as solutions of the three-dimensional system \([1, (5)]\) obtained when the immune system is inexistent.

Indeed, with \(K = 1, \gamma = 1\) (after rescaling), as in section \([1, \text{ Sec. 3.1}]\), the second and third points become \((1, 0, 0)\) and \(\left( \frac{\delta}{(b-1)^\beta}, \frac{\delta \lambda((b-1)^{-\beta} - \delta)}{(b-1)^\beta((b-1)^{-\beta} + \delta \lambda)}, \frac{\lambda((b-1)^{-\beta} - \delta)}{(b-1)^\beta + \delta \lambda}, \right)\), respectively—see \([1, \text{ Sec. 3.2}]\).

The fourth fixed point also appeared already in the linear growth problem of \([4]\).

The Jacobian matrix of the system when \(K = 1, \gamma = 1\) is given by

\[
J(x, y, v, z) = \begin{pmatrix}
\lambda - \frac{\lambda(2x+y)}{K} & -\beta v & -\frac{\lambda x}{K} & 0 \\
\frac{\beta v}{x} & -\gamma - z \mu_y & -\beta x & -\gamma \mu_y \\
-\beta v & -\frac{\beta y}{y} & -z \mu_y + \beta \lambda (x) & -v \mu_v \\
0 & s \gamma & 0 & s \gamma - c(\epsilon + 1) \epsilon^x
\end{pmatrix}
\]

At the boundary fixed points, the Jacobian has a block-diagonal form, which simplifies the stability analysis.

**Theorem 5** \(E_0\) is always a saddle point.

**Proof** Since

\[
J(E_0) = \begin{pmatrix}
\lambda & 0 & 0 & 0 \\
0 & -\gamma & 0 & 0 \\
0 & b \gamma & -\delta & 0 \\
0 & 0 & 0 & c_e
\end{pmatrix},
\]

where \(c_e = c(-0^\epsilon)(\epsilon + 1) = \begin{cases} -c & \epsilon = 0 \\ 0 & \epsilon = 1 \end{cases}\), it has always one positive eigenvalue \(\lambda > 0\), and at least two negative eigenvalues \(-\gamma, -\delta\). \(\square\)

### 3.2.1 Stability of the boundary fixed point \(E_K\)

Here, we will prove the existence of a stability transition of \(E_K\) when \(R_0 = 1\), in the spirit of the “\(R_0\) alternative”. The proof is standard when \(\epsilon = 0\),\(^4\) but the result is more delicate when \(\epsilon = 1\), since the Jacobian is singular at \(E_K\):

\(^4\) and global stability holds as well under the assumptions \(R_0 < 1\) and \(y_e > 1\) \([3, \text{ Prop. 4}]\).
Theorem 6 When $\epsilon = 1$, $E_K = (K, 0, 0, 0)$ is

1. unstable if $R_0 > 1 \iff b > b_0$;
2. if $R_0 < 1$, then the equilibrium $E_K$ is locally stable, and local asymptotic stability holds with respect to $(x, y, v)$, i.e., every solution that starts close enough to $E_K$ satisfies $\lim_{t \to \infty} (x, y, v)(t) = (K, 0, 0)$.

Proof The Jacobian at $E_K$ is

$$J(E_K) = \begin{bmatrix} -\lambda & -\lambda & -K\beta & 0 \\ 0 & -\gamma & \beta K & 0 \\ 0 & b & -K\beta - \delta & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

The block diagonal structure puts in evidence an upper $1 \times 1$ block with negative eigenvalue $-\lambda$, and a lower $1 \times 1$ block with eigenvalue equal to 0. The remaining middle $2 \times 2$ diagonal block has determinant $\gamma\delta(1 - R_0)$, implying eigenvalues of different sign when $R_0 > 1$, yielding the first part of the result.

When $R_0 < 1$, our system is in the delicate situation covered by the Lyapunov–Malkin Theorem (since the fixed point is not hyperbolic and the Hartman–Grobman Theorem does not apply). However the Lyapunov–Malkin Theorem [61, Ch. IV, Sect. 34], [62] yields simple local stability, but the asymptotic behavior of $z$ cannot be inferred anymore. This proves the second part of the theorem. $\square$

3.2.2 Stability of the boundary fixed point $E_*$

At $E_*$, the Jacobian has a block-tridiagonal form:

**Theorem 7** If $R_0 = \frac{\beta K}{\delta}(b - 1) > 1$ (same value as in the three-dimensional model), $E_*$ is non-negative, and an unstable equilibrium point.

Proof The Jacobian is given by

$$J(E_*) = \begin{bmatrix} a_1 & a_2 & a_3 & 0 \\ a_4 & a_5 & a_6 & a_7 \\ -a_4 & b y & a_8 & a_9 \\ 0 & 0 & 0 & c_\epsilon + \rho \beta y_* \end{bmatrix}, \quad (8)$$

where $c_\epsilon = \begin{cases} -c & \epsilon = 0 \\ 0 & \epsilon = 1 \end{cases}$, where $y_* = \frac{K}{R_0} \frac{\lambda(R_0 - 1)}{\lambda + \gamma R_0}$ is the $y$ coordinate of the fixed point $E_*$ (7), and where $a_1, a_2, a_3, a_4, a_5, a_6, a_7, a_8$ and $a_9$ have complicated expressions, given in the first cell in [63].
When $\epsilon = 1$, using $b > 1$ and $1 < R_0 < b$ implies that $J(E_*)$ has at least one positive eigenvalue and therefore is unstable.

When $\epsilon = 0$, we still get a sufficient condition for instability

$$y_* > y_e = \frac{c}{\rho \beta y},$$

but this condition is not necessary, since a second instability interval (due to the other three eigenvalues) may appear—see Fig. 4. The full analysis is reported to Sect. 4.2.

The interior equilibria of system (1) will be studied in the following sections for two special cases of the model. From now on, we will use mainly the rescaled equations with $K = \gamma = 1$.

### 4 The four-dimensional viro-therapy model with $\epsilon = 0$ [3]

The dynamical system when $K = \gamma = 1$ and $\epsilon = 0$, is:

$$\begin{align*}
\frac{dx}{dt} &= \lambda x (1 - x - y) - \beta x v \\
\frac{dy}{dt} &= \beta x v - \beta y y z - y \\
\frac{dv}{dt} &= by - \beta x v - \beta y v z - \delta v \\
\frac{dz}{dt} &= z(\beta z y - c),
\end{align*}$$

with

$$y \leq 1 - x, \quad v \leq \min \left[ \frac{\lambda}{\beta} (1 - y_e), \frac{y_e}{\delta} (b - 1) \right], \quad y_e = \frac{c}{\beta z}.$$

Besides the three equilibrium points $E_0$, $E_K$, $E_*$ of the three-dimensional viral system (extended by the values $z = 0$), we may have up to two new equilibria with $z > 0$, both having $y = y_e$, provided that $y_e \leq 1$—see below.

#### 4.1 Interior equilibria

When $z \neq 0$, from the last equation in (10) we have $y = y_e = \frac{c}{\beta z}$, and by substitution into the first equation of (10), we get

$$x = 1 - y_e - \frac{v \beta}{\lambda} =: h(v).$$

If $y_e > 1$, there are no equilibrium points with $z > 0$. When $y_e \leq 1$, then $x$ positive requires $v \leq \frac{\lambda}{\beta} (1 - y_e)$.
Moreover, substituting this into the sum of the second and third equations in (10) yields

\[ z = \frac{y_e(b - 1) - v \delta}{y_e \beta y + v \beta v} =: \frac{f(v)}{g(v)}, \]

which is positive if and only if \( v \leq \frac{c(b - 1)}{\beta \delta}, \) and the second equilibrium equation in (10) implies

\[
P(v) = v \beta h(v) - y_e \left(1 + \beta y \frac{f(v)}{g(v)}\right) = v^3 + a_2 v^2 + a_1 v + a_0 = 0,
\]

\[
\begin{align*}
  a_2 &:= y_e(1 + \frac{\lambda}{\beta y}) - \frac{\lambda}{\beta y} = b_0 y_e - b_0 + 1, \\
  a_1 &:= \frac{\lambda}{\beta^2 y_e} \left[1 + \frac{\beta \mu y}{\beta y} (y_e - b_0)\right], \\
  a_0 &:= \frac{bc^2 \lambda \mu y}{\beta^2 \beta^2 y_e}.
\end{align*}
\]

This third-order equation determining \( v \) may have at most two sign changes, attained when \( y_e \leq \max\{(b_0 - 1)/b_0, \quad b_0 - \beta \delta/\beta y\} \), and thus we may have either 0, 1 or 2 positive endemic equilibria, denoted by \( E_{im}, E_+ \); there may also exist a solution \( E_- \) with negative \( v \), which is of no concern to us. All situations may occur—see the bifurcation diagram in Fig. 4—depending on the sign of the discriminant of \( P(b) \), which will be denoted by \( Dis \).

Note that

\[
Dis(b) = 0 \iff b = (b_{1+}, b_{2+})
\]

\[
= \frac{1}{27 \beta^2 c^2 \lambda \beta^2 \beta^2 y_e^2} \times \left[2 \left(\beta^2 \beta^2 \beta^2 y_e^2 + \lambda \beta^2 (\lambda(c - \beta z)^2 - 3c \beta z) + c \lambda \beta_v \beta_y (\beta z + 3\delta) - \beta c\right)^3 \right.
\]

\[
- \beta \beta \beta \beta y (\lambda(c - \beta z) \beta v + \beta c \beta y)
\]

\[
\times \left(2 \beta^2 \beta^2 \beta^2 y_e^2 + \lambda \beta^2 (2\lambda(c - \beta z)^2 - 9c \beta z) + c \lambda \beta_v \beta_y (-5\beta c + 5\beta \beta z + 9\delta \beta z)\right)\].
\]

**Remark 9** Biologically, the equilibrium \( E_0 \) is a boundary case in which the model is inappropriate. The equilibrium \( E_K \) occurs when viro-therapy fails, and the tumor cell density reaches its carrying capacity in the long run. Lastly, \( E_+ \) represents a partial success of viro-therapy where healthy and infected tumor cells coexist, and which may be achieved by viruses only, without help from the immune system.

Finally, \( E_{im} \) represents another possible coexistence, which requires help from the immune system, and \( E_\pm \) represent equilibria which are exterior to the domain or unstable.
4.2 The stability of $E_*$ when $\epsilon = 0$

As already hinted by (9), the stability of $E_*$ is affected by the value of $y_\epsilon$.

**Lemma 8** [3, Prop. 6, 7] $E^*$ is locally stable if and only if $b \in (b_0, b_H) \cap (b_1, b_2)^c$, where $(b_1, b_2)$ is the interval on which $y_\epsilon(b) > y_\epsilon$.

We provide now a proof reducing the problem to three dimensions, which is considerably shorter than the original.

**Proof** This result follows from the block diagonal structure of the Jacobian at $E^*$, see (8), which yields one eigenvalue proportional to $y_\epsilon - y_\epsilon$, and must of course be negative for local stability. Under this condition, stability is thus equivalent to that of the remaining three-dimensional block, which is identical to that in [1] (unfortunately, that is not immediately obvious, due to different notations).

The new condition $p(b) = y_\epsilon(b)/y_\epsilon = \delta^2 \lambda_\beta_\beta (1-R_0) / (b-1)^2 (b+\delta \lambda) < 1$ may be explicitized with respect to $b$ into $b \notin (b_1, b_2)$,

$$b_{1,2} = \frac{2\beta c - c\delta \lambda \pm \sqrt{\lambda \lambda (c-\beta z)^2 - 4 c \beta z + \delta \lambda \beta z^2}}{2 \beta c} \quad (12)$$

In conclusion, the stability domain is the intersection of that in [1] with $b \notin (b_1, b_2)$. $\square$

4.3 Stability of the interior equilibria and bifurcation diagrams

We illustrate now the results of [3, Prop. 6–8] via bifurcation diagrams of $v$ and $x$ with respect to $b$ in a particular numeric case.

Since the variable of interest is $x$, we provide also a bifurcation diagram of $x$ with respect to $b$.

**Remark 10** Note that:

1. For a “weak virus” with $b < b_0$, $E_K$ is the only stable equilibrium, as expected from the fact that $E_K$ behaves essentially as the disease-free equilibrium from mathematical epidemiology.
2. At the first critical point $b = b_0$ which corresponds to $R_0$, the “stability relay” is passed from $E_K$ to the “virus only” equilibrium $E_*$, precisely when this enters the domain.
3. As the virus becomes more efficient, $E_*$ becomes unstable, precisely at the point $b = b_1$ when the fixed point $E_{im}$ which involves the immunity system enters the domain. This point carries the “stability relay” until $b_2$.
4. As the efficiency of the virus increases to $b = b_2$, $E_*$ becomes stable again and we have bistability, until $b_{2*}$. In this range, reaching a better outcome $E_*$ or a worse one $E_{im}$ depends on the boundary conditions, until $b_{2*}$.
5. After $b_{2*}$, $E_{im}$ becomes unfeasible, and $E_*$ remains the only stable equilibrium, until $b_H$.

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Fig. 4 Bifurcation diagram of system (10) when $K = \gamma = 1$, $\epsilon = 0$, and $\beta_v = 0.16$, $\beta_y = 0.48$, $\lambda = 0.36$, $\beta = 0.11$, $\delta = 0.2$, $\beta_z = 0.6$, $c = 0.036$, which yields $y_e = 0.06$, $b_0 = 2.81818$, $b_H = 19.01210747136$, and $Dis = 0 \Leftrightarrow b_{1s} = -0.00697038$, and $b_{2s} = 10.2462$. The values of $b_1$, $b_2$ are 3.58676, 8.66779.

Note that at these two values, $E_+$ equals $E_{im}$ and $E_+$, respectively, and that these points are at the yellow boundary of the domain of admissible values for $v$.

Fig. 5 Bifurcation diagram of system (10), representing the $x$ of the equilibrium points, as functions of $b$. The last curve corresponds to the constraint $v \geq 0$. The parameters are $K = \gamma = 1$, $\epsilon = 0$, and $\beta_v = 0.16$, $\beta_y = 0.48$, $\lambda = 0.36$, $\beta = 0.11$, $\delta = 0.2$, $\beta_z = 0.6$, $c = 0.036$

6. After $b_H$, $E_+$ loses again its stability, in favor of a limit cycle.

Let us discuss now the stability of the interior equilibrium points, via the so-called Routh-Hurwitz-Lienard-Chipart-Schur-Cohn-Jury (RH) criteria [64–66], which are formulated in terms of the coefficients of the characteristic polynomial $Det(\lambda I_n - L) = \lambda^n + a_1 \lambda^{n-1} + \ldots + a_n$, and of certain Hurwitz determinants $H_i$ [65, (15.22)].

In the fourth order case, the characteristic polynomial is $Det(J - z I_4) = z^4 + a_3 z^3 + a_2 z^2 + a_1 z + a_0 = z^4 - Tr(J) z^3 + z^2 M_2(J) - z M_3(J) + Det(J)$, where $M_2$ and $M_3$ are the sums of the second and third order principal leading minors of the
The partition of the $(b, \beta)$ plane into six regions, when $\beta_v = 0.16, \beta_y = 0.48, K = \gamma = 1, \Lambda = 0.36, \delta = 0.2, \cdot = 0.6, c = 0.036$. The region containing at least one attractor cycle is bounded below by the Hopf bifurcation curve $H_v(b, \beta) = 0$. Next follows a region where $E_\ast$ is stable, bounded below by the curve $\Delta(b, \beta) = 0$, and then the bistability region $b \in (b_2, b_2^*)$, bounded below by the upper branch of $y_e = 1$. In between the two branches of $y_e = 1$ we have a region where $E_{im}$ is stable and $E_\ast$ is unstable. Only $E_\ast$ is stable in the next region, bounded below by the transcritical bifurcation curve $R_0(b, \beta) = 1$. In the last region, $E_K$ is the only stable point. The phase plots at the points $b_7$ and $b_8$ are illustrated in Figs. 7 and 8.

Jacobian $J$, respectively. The Routh-Hurwitz criterion becomes [65, p. 137]

$$
\begin{align*}
&\left\{ \begin{array}{l}
Tr(J) < 0, \quad M_2 > 0, \quad M_3 < 0, \quad Det(J) > 0, \\
0 < Tr(J) (M_2M_3 - Tr(J)Det(J)) - M_3^2.
\end{array} \right.
\end{align*}
$$

Pinpointing the domains of attraction associated with the two equilibrium points $E_\ast, E_{im}$ symbolically is quite challenging, but feasible in particular cuts, see Figs. 6 and 7. Note that in this case our analysis may help with controlling the evolution of treatment, by privileging the desired final tumor size.

Figure 6 depicts a bifurcation diagram with respect to $b$ and $\beta$.

4.4 Time and phase plots illustrating bi-stability and a limit cycle, with $\epsilon = 0$

We provide now time and parametric plots illustrating these more “exotic” behaviours.

4.5 Bi-stability in the interval $(b_2, b_2^*)$

The parameters are fixed as in [3]: $\beta_v = 0.16, \beta_y = 0.48, K = 1, \gamma = 1, \lambda = 0.36, \beta = 0.11, \delta = 0.2, \beta_z = 0.6, c = 0.036, y_e = 0.06$. 

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Fig. 7  Plots of the evolution of the dynamics in time, and illustration of the convergence towards $E_*$ and $E_{im}$ when $b = 9.5$

(a) Time plots of $x$ with different initial values; $x(0) = (0.3, 0.9)$. They indicate the absence of stable attractor.

(b) Time plot of the four components indicates the convergence towards the attractor $E_{im}$ with $x_0 = z_0 = 0.5, y = 0.01$ and $v_0 = 1.2$.

(c) $(x, y)$-parametric plots illustrating the convergence towards the fixed point $E_{im}$ (in red) and towards $E_*$ (in blue) with $t_f = 1900$ and $t_f = 200$, respectively, when $b = 10$ and $(x_{0*}, y_{0*}) = (0.9, 0.01)$ and $(x_{0i}, y_{0i}) = (0.5, 0.01)$.

Fig. 8  $x$-time plots and display of the parametric plots when $b = 23$

When $b = 9.5 \in (b_2, b_{2*})$, we obtain that $E_* = (0.213904, 0.0562055, 2.38873, 0)$ and $E_{im} = (0.453156, 0.06, 1.59331, 0.67437)$, with the eigenvalues $(-1.25014, -0.0251954 \pm 0.211281i, -0.0022767)$ and $(-1.69595, -0.0714416 \pm 0.218669i, -0.00574855)$, respectively, are the unique stable attractors, as illustrated in Fig. 7.

4.5.1 Limit cycle in the interval $(b_H, b_\infty)$

When $b = 23 > b_H$, there is no stable attractor—see Fig. 8.
5 The four-dimensional viro-therapy model of [4], with $\epsilon = 1$ and logistic growth

In this section, we turn to the special case of (1) when $\epsilon = 1$, that is,  
\[
\begin{align*}
\frac{dx}{dt} &= \lambda x \left( 1 - \frac{x + y}{K} \right) - \beta xv \\
\frac{dy}{dt} &= \beta xv - \beta y yz - \gamma y \\
\frac{dv}{dt} &= b \gamma y - \beta xv - \beta vz - \delta v \\
\frac{dz}{dt} &= z(y - cz). 
\end{align*}
\]  
(13)

5.1 Interior equilibria

**Theorem 9** (A) There are at most three equilibrium points belonging to the interior of $\mathbb{R}^4_+$.  
(B) Their $y$ component is a zero of the third degree polynomial $Q(y)$ defined in (16), and lies within  
\[
\left( 0, \ y_b := \frac{c \gamma (b - 1)}{\mu \beta z} \right).
\]

**Proof** (A) is immediate.  
(B) From the last equation in (1), $z = y \beta z$. Adding the second and third equation in (1) yields  
\[
\gamma y(b - 1) - \beta y yz = v(\beta vz + \delta),
\]
we find that $v = y \frac{f(y)}{g(y)}$, where we put  
\[
\begin{cases}
  f(y) = c \gamma (b - 1) - y \beta s \\
  g(y) = \beta vz + \delta c.
\end{cases}
\]  
(14)

From the second equation in (1) $x = \frac{h(y) g(y)}{\beta f(y)}$, where $h(y) = y \frac{\beta vz}{c} + \gamma$, and  
\[
xv = \frac{h(y) g(y)}{\beta f(y)} \cdot \frac{f(y)}{g(y)} = y \frac{h(y)}{\beta}.
\]
From (1), $y$ must be a zero of the rational function  
\[
\lambda \left( 1 - \frac{y}{K} \right) - \frac{\lambda h(y) g(y)}{K \beta f(y)} - y \frac{\beta f(y)}{g(y)} := P(y) := \frac{Q(y)}{f(y) g(y)},
\]
(15)
and hence of its numerator, which is the third degree polynomial

\[ Q(y) = \lambda f(y)g(y)\left(1 - \frac{y}{K}\right) - \frac{\lambda h(y)g(y)^2}{\beta K} - \beta y f(y)^2. \tag{16} \]

For \( x, v \) and \( z \) to be positive, \( y \) must lie in \((0, y_b)\). \( \square \)

The formulas for the coefficients of \( Q(y) = a_3y^3 + a_2y^2 + a_1y + a_0 \) are:

- \( a_3 = \left(\frac{\beta v \beta s}{\beta K c}\right) (\beta \beta v c \lambda - \beta v^2 s \lambda - \beta v \beta y c) \)
- \( a_2 = \left(\frac{\beta v}{\beta K}\right) (\beta \beta v c r \delta + 2 \beta K \beta v \beta y \gamma (b - 1) - \beta K \beta v \beta y s \lambda \beta - \beta v \beta y c \gamma (b - 1) \lambda - 2 \beta v \beta y s \lambda \delta - \beta v \beta y c \gamma r) \)
- \( a_1 = \left(\frac{c}{\beta K}\right) (\beta K \beta v \gamma (b - 1) \lambda - \beta K \beta y \gamma \lambda \delta - \beta K \beta y s \lambda \delta - \beta K \beta y s \lambda \delta^2 - 2 \beta v \beta y s \gamma \lambda \delta - \beta v \beta y c \gamma^2 (b - 1)^2) \)
- \( a_0 = \frac{\lambda c^2 \gamma \delta}{\beta K} (\beta K (b - 1) - \delta) \).

**Theorem 10** Suppose \( R_0 > 1 \). Then, there is at least one interior equilibrium point.

1. If furthermore \( a_3 > 0 \) (large \( \beta \)), then there is exactly only one interior equilibrium point.
2. If \( a_3 < 0 \) there can be 1, 2 or 3 interior equilibrium points, depending whether the discriminant is negative, zero, or positive. These interior points (when they exist) will be denoted by \( E_+ \), \( E_- \), \( E_{im} \), corresponding to the highest, lowest and intermediate values of \( y \), respectively.

**Proof** Observe that \( P(0) = \lambda \left(1 - \frac{\delta}{\beta K (b-1)}\right) \) and \( P(0) > 0 \) if and only if \( \delta < \beta K (b - 1) \), which holds from the assumption. Also,

\[ \lim_{y \to y_b} P(y) = -\infty. \]

Thus, by continuity, \( P(y) \) has at least one root \( y_0 \) in \((0, y_b)\).

Alternatively, note that \( Q(y_b) = -\frac{\lambda h(y_b)g(y_b)^2}{\beta K} < 0 \) (since \( g(y) > 0 \) and \( h(y) > 0 \) for all \( y > 0 \)), and that \( Q(0) = \frac{\lambda c^2 \gamma \delta}{\beta K} (\beta K (b - 1) - \delta) < 0 \) when \( R_0 > 1 \).

1. Recall that \( a_0 > 0 \). Descartes’ rule of signs states that if there are \( k \) sign changes in the coefficients of a polynomial, ordered with decreasing order of exponents, then the number of positive real roots (counting multiplicities) equals \( k \) or is less than this number by a positive even integer.

If \( a_0 > 0 \) and \( a_3 > 0 \), then there can only be 0 or 2 sign changes. Theorem 4 guarantees that there cannot be 0 changes, so there are 2 sign changes.

Now \( \lim_{y \to \infty} Q(y) = +\infty \) and \( Q(y_b) = -\frac{r y_b}{K \beta} g(y_b)^2 < 0 \) imply that there is at least one root of \( Q(y) \) in \((y_b, +\infty)\). Thus there is only one root of \( P(y) \) in \((0, y_b)\), otherwise there would be at least 3 changes of signs and this cannot be possible.
2. If $R_0 > 1$ and $a_3 < 0$, there can only be 1 or 3 changes of signs. If there are 3 sign changes, then there can be 1, 2 or 3 roots on the interval $(0, y_b)$. This case can only happen when $a_1 < 0$, $a_2 > 0$, $a_3 < 0$. Notice that $a_1 \to -\infty$, $a_2 \to +\infty$, $a_3 \to -\infty$ as $\beta \to +\infty$, so the previous inequalities are indeed possible.

\[ \square \]

\textbf{Remark 11} 1. If $R_0 < 1$, there are no interior equilibrium points.
2. For the model of [4] with $K = \infty$, $Q(y)$ factors as the product of $y - y_b$ and a second order polynomial.

### 5.2 Stability of interior equilibria and bifurcation diagrams

The Jacobian matrix evaluated at an interior equilibrium point $E = (x, y, v, z)$ is given by

$$
J(E) = \begin{pmatrix}
\lambda - \frac{\lambda(2x+y)}{K} & -\frac{\lambda x}{K} & -\beta x & 0 \\
\beta v & -\beta y - \gamma & \beta x & -\beta y \\
-\beta v & \beta y & -\beta x - \beta v z - \delta & -\beta v y \\
0 & \beta z & 0 & \beta z - 2cz
\end{pmatrix}.
$$

The trace is given by

$$
\lambda \left( \frac{2(\beta_x y v + \gamma)(c\delta + sy\beta_v)}{\beta((b-1)c\gamma - sy\beta_v)} + y \right) + \frac{\beta y (c(y - b\gamma) + sy\beta_y)}{c\delta + sy\beta_v} - \frac{(\beta_z y v + \gamma)(c\delta + sy\beta_v)}{(b-1)c\gamma - sy\beta_y} - \frac{\beta_y y v}{c} - \frac{\beta z y v}{c} - \gamma - \delta + \lambda - sy,
$$

and is negative for $b \geq 1$.

The characteristic polynomial has a complicated form, and the expression of the determinant is also long, see the end of the first cell in [67].

Establishing the positivity of the determinant and checking the Hurwitz criteria exceeded our machine power—see [67, Subsection Ep1-2]—forcing us to work numerically, with MatCont. This way we discovered the existence of cycles, which bifurcate from the point $E_{im}$, and the fact that the Hurwitz determinant at $E_{im}$ has a unique root $b_H = 29.9035$ in our numeric example.

We show now in Fig. 9 a bifurcation diagram of the $y$ component with respect to $b$, for a particular choice of parameters—see [67, Subsection Ep1-3)] for the code.

For comparison, we offer also the bifurcation diagram with respect to $b$ and $x$ (see Fig. 10).

\[ \text{given by } H_{im}(b) = a_1 \times a_2 \times a_3 - a_1^2 a_0 - a_1^2 > 0, \text{ where } b^4 + a_3 b^3 + a_2 b^2 + a_1 b + a_0 \text{ is the characteristic polynomial of the Jacobian—see [67, fourth cell].} \]

\[ \text{Birkhäuser} \]
Fig. 9 Bifurcation diagrams of the fixed points corresponding to the dynamics in (1), with respect to $b$ and the coordinate $y$, with $\epsilon = 1$ and $K = 1$. Recall $y_+ = \frac{\lambda^2}{\beta((b-1)(b-1)\beta+K+1)}$, and that $y_+ = y_+ = 0$ when $b = b_0 = 1.02299$. Here, $\beta = \frac{87}{2}$, $\lambda = 1$, $\gamma = \frac{1}{128}$, $\delta = 1/2$, $\mu = 1$, $\beta_y = 1$, $\beta_v = 1$, $c = 1$, which yields the discriminant roots $b_{1*} = 29.361$, $b_{2*} = 45.9232$. The potential Hopf bifurcation point defined by $H_{1m}(b)$ is $b_H = 29.90350014$. The point of intersection of $y_b$ and $y_+$ is $b_{b*} = 14.0011$

Fig. 10 Bifurcation diagrams of the fixed points corresponding to the dynamics in (1), with respect to $b$ and the coordinate $x$ when $\epsilon = 1$ and $K = 1$. Here, $\beta = \frac{87}{2}$, $\lambda = 1$, $\gamma = \frac{1}{128}$, $\delta = 1/2$, $\mu = 1$, $\beta_y = 1$, $\beta_v = 1$, $c = 1$. When $b > b_0$, $x_+$ is very small, for example $x_+(15) = 0.0000821018$. After $b_{2*}$, $x_+$ is very small, for example $x_-(47) = 0.0017057$

5.3 Time and phase plots illustrating some possible behaviors

In this subsection, we use the fixed parameters $K = 1$, $\beta = 87/2$, $\lambda = 1$, $\gamma = 1/128$, $\delta = 1/2$, $\beta_y = 1$, $\beta_v = 1$, $\beta_z = 1$, $c = 1$ to illustrate via time plots and parametric plots some possible dynamic behaviors of the model (13), as $b$ is varied.
Fig. 11  Bifurcation diagram for the dynamics of system (13) with respect to $b$ and the $(x, y)$ coordinates, showing the size of limit cycles when $b \in (b_H, 30.85471275)$

5.3.1 $b \in (b_H, b_2^\ast)$: some MatCont diagrams

In this case, there exist three interior equilibria. For example, for $b = 42$, $E_+ = (0.494, 0.308, 0.004, 0.308)$ is stable with eigenvalues $(-22.81, -0.1575 \pm 0.2758Im, -0.3016)$, and $E_{im} = (0.145, 0.284, 0.0131, 0.284)$, $E_- = (0.002, 0.042, 0.021, 0.042)$ are unstable, with eigenvalues $(-7.860, -0.116 \pm 0.254Im, 0.264)$ and $(-0.842, 0.068 \pm 0.167Im, -0.0333)$, respectively.

We provide first a bifurcation diagram obtained with MatCont (Fig. 11), with respect to $b$ and the $(x, y)$ coordinates, showing the size of limit cycles as $b$ varies—see [28] for the code. This confirms that a Hopf bifurcation occurs at the root $b_H = 29.90350014$ of $Him(b) = 0$. The first Lyapunov coefficient, as computed by Matcont, is positive, which implies that the limit cycle bifurcating from the equilibrium $E_{im}$ at $b_H$ is unstable. Moreover, numerical simulations reveal that this limit cycle exists for $b \in (b_H, 30.85471275)$, where at the upper limit one of the Floquet multipliers grows very large (around $1 \times 10^{20}$) and Matcont cannot continue the limit cycles for $b$ larger than this value.

However, cycles reappear later, as illustrated in Fig. 12. At $b = 37.80702943$, Matcont detects two limit cycles bifurcating from each other via a fold bifurcation, and at least one cycle exists for $b \in (37.80702943, 44)$.

The existence of Hopf bifurcation points for the other interior equilibria remains as an open problem.

5.3.2 $b = 42 \in (37.807029, 44)$: a stable equilibrium $E_+$ and a stable cycle

As a check of MatCont, we provide now time plots for a stable cycle, when $b = 42$.

Figure 13 provides a two-dimensional parametric projection when $b = 42$, which includes also three special trajectories: blue, brown and red. The first two start respectively at $(x_-, y_-, v_-, z_-)$ and at $(x_{im}, x_{im}, x_{im}, x_{im})$, and seem to move
Fig. 12 Bifurcation diagram for the dynamics of system (13) with respect to \( b \) and the \((x, y)\) coordinates, showing the size of limit cycles when \( b \in (37.807029, 44) \). At \( b = 37.80702943 \), Matcont detects two cycles bifurcating from each other. At \( b = 37.80704543 \) and \( b = 38.70752198 \), period doubling bifurcations (denoted by red lines) are detected.

Fig. 13 A two-dimensional projection of the phase space, at the value \( b = 42 \). The blue trajectory starts near the limit cycle, and almost overlaps it, the brown trajectory rejoins the cycle after an initial quick stretch, and the red trajectory converges to the interior equilibrium \( E_+ \).

quickly to the cycle depicted in Fig. 14. The third path starting at \((x_0, y_0, v_0, z_0) = (0.05, 0.05, 0.0043, 0.1954)\) converges to \( E_+ \).

The next two three-dimensional figures (Figs. 15 and 16) show that when we draw a couple of paths, and look to three-dimensional projections, they seem to converge, see [68, last cells]. Understanding this is crucial, since asymptotically stable cycles are very important from the biological point of view. The Floquet multipliers of the limit cycle at \( b = 42 \), as computed by Matcont, are \((-5.6378 \times 10^{-18}, 2.9160 \times 10^{-5}, 0.39126, 0.94214)\). Since all Floquet multipliers lie inside the unit circle, the limit cycle is asymptotically stable [69, p. 90].
Fig. 14  Time plots of $x$, $y$, $v$, $z$ for the path depicted in the brown curve in Fig. 13

Fig. 15  3D $(x, y, v)$-parametric plot corresponding to Fig. 13
5.3.3 Uniqueness of the attractor $E_+ \text{ when } b \in (b_0, b_H)$

1. When $b = 29 \in (b_0, b_{1*})$, there is one stable interior point $E_{+} = (0.72, 0.213, 0.0015, 0.21)$ with eigenvalues $(-32.34, -0.65, -0.10 \pm 0.18 \ I m)$, and the point $E_{+} = (0.0004, 0.049, 0.021, 0)$ is unstable with eigenvalues $(-0.567, 0.0204 \pm 0.0804 \ I m, 0.0499)$.

2. When $b = 29.5 \in (b_{1*}, b_H)$ (see Fig. 18), the unique stable attractor is $E_{+} = (0.713, 0.217, 0.001, 0.217)$, with eigenvalues $(-32.06, -0.6453, -0.1098 \pm 0.1890 I m)$, despite the existence of two other interior equilibria: $E_{im} = (0.018, 0.121, 0.019, 0.121)$ and $E_{-} = (0.011, 0.099, 0.020, 0.099)$, with eigenvalues $(-1.918, 0.189, 0.022 \pm 0.0654 I m)$ and $(-1.54, 0.116 \pm 0.1115 I m, -0.0238)$, respectively.

6 Conclusions

In this study, we revisited the three-dimensional oncolytic virotherapy model of [1] and the four-dimensional model of [3], and we provided some new results. Furthermore, we proposed a novel model with virotherapy and immunity that generalizes some of the previous works and established several results on the equilibrium points of
Fig. 17  Plots of the evolution of the dynamics in time, and a parametric plot illustrating convergence to the attractor $E_+ = (0.720, 0.213, 0.00151, 0.213)$.

Fig. 18  Plots of the evolution of the dynamics in time, and a parametric plot corresponding to the attractor $E_+$ when $b = 29.5$

...this model. The use of electronic notebooks and software such as Mathematica and Matcont allowed us to illustrate the stability dynamics of the model and show the existence of stable limit cycles for certain sets of parameter values. Our paper has a theoretical focus, i.e., we studied our model for general values of the parameters, and delved less into specific biological interpretations, which may depend on parameter values corresponding to specific viruses. However, one standard interpretation is that the existence of a stable limit cycle shows that the healing process does not take place, but the disease does not worsen either, the evolution being periodic between certain limits. Further research in this direction is necessary.

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Declarations

Conflict of interest  The authors have no competing interests to declare that are relevant to the content of this article.
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