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Oscillation thresholds via the novel MBR method with application to oncolytic virotherapy*

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Abstract: Oncolytic virotherapy is a therapy for the treatment of malignant tumours. In some undesirable cases, the injection of viral particles can lead to stationary oscillations, thus preventing the full destruction of the tumour mass. We investigate the oscillation thresholds in a model for the dynamics of a tumour under treatment with an oncolytic virus. To this aim, we employ the minimum bifurcation roots (MBR) method, which is a novel approach to determine the existence and location of Hopf bifurcations. The application to oncolytic virotherapy confirms how this approach may be more manageable than classical methods based on the Routh–Hurwitz criterion. In particular, the MBR method allows to explicitly identify a range of values in which the oscillation thresholds fall.

Keywords: dynamical system, nonhyperbolic equilibrium, Hopf bifurcation, periodic solution, tumour.

1 Introduction

Malignant tumours (also termed *cancers*) are a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 [34]. One of the most promising therapy for tumour treatment is the *oncolytic virotherapy*, namely the use of replicating viruses that are genetically modified and destroy tumour cells. However, tumours may respond in different ways to viral particles. It has been experimentally observed that the interaction between tumour cells and viral particles can either lead to equilibria of partial/full tumour eradication or settle on periodic cycles [2, 31]. Oscillatory behaviours are well known in clinical settings. These fluctuations are always emerging after an initial tumour decline due to virus infection, but their persistence prevents the full destruction of the tumour mass (see, e.g., [11]).

Oncolytic virotherapy has been recently investigated from a mathematical point of view with the aid of different approaches. In particular, oscillatory behaviours as well as sufficient conditions for tumour eradication have been obtained by means of ordinary differential equations (ODEs) [2, 9, 10, 31], partial differential equations (PDEs) [21, 32], agent-based models [8, 28] and hybrid models. For example, Jenner et al. [8] employed an agent-based model to investigate the sensitivity of the treatment to the timing for the tumour infection. More recently, Pooladvand et al. [21] assessed the role of viral infectivity on the tumour evolution by using a system of PDEs for the spatiotemporal dynamics between tumour and virus.

We found particularly intriguing the works by Jenner et al. [9, 10], where the authors modeled the interaction between tumour cells and an oncolytic virus by using a minimal mathematical framework, given by a three-dimensional dynamical system. Due to its relative simplicity, their model is amenable to both analytical and numerical investigations from which some nontrivial and, in some cases, counterintuitive findings emerge. Also, the model includes all the major processes acting in virotherapy so that it turns out to be sufficient to replicate some experimental results. Specifically, in the paper [10] the model was tuned on the experimental data from Kim et al. [12]. After that, it was used to investigate the effects of the treatment on tumours of different virulence and magnitude. In the paper [9] the authors obtained numerically an extended area of the parameter space, where stable or unstable oscillations take place from Hopf bifurcations. The oscillation thresholds are obtained by using continuation and bifurcation software for ODEs.

Inspired by the papers above, one of the main goals of this paper is to analytically determine the oscillation thresholds for the model by Jenner et al. [9, 10]. We will use a novel approach for the existence and location of Hopf bifurcations in dynamical systems, called *minimum bifurcation roots* (MBR) method, recently introduced by Rionero [22, 24–27]. Therefore, the aim of this contribution is twofold. On the one hand, we revisit the MBR method in the case of one parameter-depending systems of ODEs. On the other hand, we provide an application of the MBR method to the model proposed by Jenner et al. [9, 10].

As a matter of fact, determining the existence and location of Hopf bifurcations in dynamical systems (and, as a consequence, of the emerging periodic solutions) could be arduous due to the cumbersome conditions deriving from classical methods, among which the most commonly used is the *Routh–Hurwitz criterion* [19]. This criterion requires the sign of the *Hurwitz determinants* (see Section 2.3). The search for alternative methods for determining Hopf bifurcations has attracted much attention in the last decades. A very well-known criterion was given by Liu in 1994 [17]. It states that in a n-dimensional dynamical system a simple Hopf bifurcation occurs at a given point if, and only if, the $(n-1)$th Hurwitz determinant passes through zero, all the other ones being positive. These classical criteria have been largely used in literature, including contributions in epidemiology (e.g., macrophages–tuberculosis interaction [33], waterborne diseases [1], etc.), crop production [20], and economics [5, 18, 27].

The MBR method is a quite general approach to Hopf bifurcations, where, instead of computing the Hurwitz determinants, the minimum roots of the coefficients of the characteristic polynomial are derived as functions of the bifurcation parameters. There- fore, compared to classical methods, the MBR method can greatly reduce the amount of computations needed. The MBR method was first used to determine

Hopf bifurcations in dynamical systems ruling the thermal convection in fluids [22, 24], and then extended to general parameters-depending dynamical systems [27]. Subsequent applications include mathematical models for the FitzHugh–Rinzel neurons [25] and for porous layers with stratified porosity [26]. To the best of our knowledge, applications in the field of medical sciences have not yet been given in the literature.

The rest of the paper is organized as follows. In Section 2, we present some preliminary settings and recall definitions and classical results from dynamical system theory and bifurcation theory. In Section 3, the MBR method is revisited in the general case of .-dimensional one parameter-depending dynamical systems. Also, we supply stronger conditions of practical use in the case of three-dimensional and four-dimensional dynamical systems. In Section 4, the MBR method is applied to the model by Jenner et al. [9,10] to determine the range in which the oscillation thresholds fall in terms of the parameters of the system. Concluding remarks are given in Section 5.

2 Some preliminaries on bifurcations and oscillations

2.1 Hyperbolic and nonhyperbolic equilibria

Let us consider a system of ODEs depending on a parameter $\mu \in \mathbb{R}$:

$$\dot{x} = f(x, \mu), \tag{1}$$

where $x \in \mathbb{R}^n$, $f \in \mathcal{C}^1(\mathbb{R}^{n+1})$, and the upper dot denotes the time derivative.

Let x^0 be an equilibrium of system (1) for μ belonging to an interval $\mathcal{I} \subseteq \mathbb{R}$, namely $f(x^0, \mu) = 0$ for $\mu \in \mathcal{I}$. We denote the Jacobian matrix of system (1) evaluated at the equilibrium by

$$J(x^0, \mu) = D_x f(x^0, \mu),$$

with $\mu \in \mathcal{I}$. The eigenvalues of $J(x^0, \mu)$ are the roots of the characteristic polynomial

$$p(\lambda, \mu) = \lambda^n + a_1(\mu)\lambda^{n-1} + \cdots + a_{n-1}(\mu)\lambda + a_n(\mu), \tag{2}$$

having μ-dependent real coefficients $a_h \in \mathcal{C}^1(\mathcal{I}), h = 1, \dots, n.$

The well-known Lyapunov's indirect method [19] states that, if at a given μ all the eigenvalues of $J(x^0, \mu)$ (namely all the roots of $p(\lambda, \mu)$) have negative real part, then the equilibrium x^0 is locally asymptotically stable. Otherwise, if at least one eigenvalue has positive real part, then x^0 is unstable. But no conclusions can be drawn if one or more eigenvalues have zero real part, while the other ones have negative real part.

It is straightforward to verify that a necessary condition for all the roots of $p(\lambda,\mu)$) to have negative real part is that (see, e.g., [23, Property 1])

$$a_h(\mu) > 0 \quad \forall h \in \{1,\dots,n\}. \tag{3}$$

Nonetheless, since the parameter μ varies in $\mathcal{I}$, it may happen that the equilibrium passes from being locally asymptotically stable to unstable (or *vice versa*) and/or the asymptotic behaviour of the system solutions changes. Namely, the flow of system (1) may be not qualitatively the same by varying $\mu \in \mathcal{I}$.

Specifically, if at a given μ the equilibrium x^0 is hyperbolic (i.e., none of the eigenvalues of $J(x^0,\mu)$ have zero real part), then varying μ slightly does not change the nature of the stability of the equilibrium (see, e.g., [30, Chaps. 12 and 20]). However, when x^0 is nonhyperbolic, i.e., when $J(x^0,\mu)$ has some eigenvalues with zero real part, by slightly varying μ radically new dynamical behaviour can occur. For example, equilibria can be created or destroyed and time-dependent behaviour such as periodic, quasiperiodic, or even chaotic dynamics can arise.

2.2 Steady, Hopf and Hopf-steady bifurcations

An equilibrium x^0 of system (1) is said to undergo a *bifurcation* at $\mu = \mu_c$, with $\mu_c \in \mathcal{I}$, if the flow of system (1) for μ near μ_c is not qualitatively the same as the flow at$\mu = \mu_c$ (more formal definitions of bifurcation can be found in classical books [13, 16, 30]). A bifurcation occurs when the real part of at least one eigenvalue of $J(x^0,\mu)$ changes sign at $\mu = \mu_c$, implying that x^0 "loses its hyperbolicity" at $\mu = \mu_c$. Disregarding the case of a multiplicity change of eigenvalues, at $\mu = \mu_c$ either one of the following holds:

i. a real eigenvalue passes through zero, and in such a case the corresponding bifurcation is called steady bifurcation;
ii. the real part of a pair of complex conjugate eigenvalues passes through zero, and in such a case the corresponding bifurcation is called Hopf bifurcation;
iii. the combination of (i) and (ii), and in such a case the corresponding bifurcation is called Hopf–steady bifurcation (or zero–Hopf bifurcation [16]).

In each of the cases mentioned above, all the other eigenvalues of $J(x^0,\mu_c)$ have nonzero real part. Note that for a steady bifurcation to occur at $\mu = \mu_c$, it is necessary that the constant term of the characteristic polynomial $p(\lambda,\mu)$ vanishes, namely $a_n(\mu_c) = 0$.

We underline that the condition that x^0 is nonhyperbolic at $\mu = \mu_c$. is a necessary but not sufficient condition for a bifurcation to occur (see, e.g., [30, p. 361] for a counterexample).

2.3 The Routh–Hurwitz criterion

The most celebrated criterion for determining the occurrence of a Hopf bifurcation without the explicit computation of all the eigenvalues of $J(x^0, \mu)$ is the well-known Routh–Hurwitz criterion. The basic idea is to arrange the coefficients of the characteristic polynomial $p(\lambda, \mu)$ of $J(x^0, \mu)$ into a $n \times n$ square matrix, the socalled *Hurwitz matrix,* H, such that all the roots of $p(\lambda, \mu)$ have negative real part if, and only if,

$$\Delta_h > 0 \quad \forall h \in \{1, \dots, n\}, \tag{4}$$

where Δ_h are the Hurwitz determinants. Conversely, if one of the inequalities in (4) is reversed, then some of the roots of $p(\lambda, \mu)$ have positive real part, implying the instability of x^0. Formally, the Routh–Hurwitz criterion can be stated as follows (see [19, Thm. 4.6]).

Routh–Hurwitz criterion. *Let us consider a polynomial*

$$p(\lambda) = \lambda^n + \sum_{h=1}^{n} a_h \lambda^{n-h},$$

with $a_h \in \mathbb{R}, h = 1, \dots, n,$ *and let* $H = (H_{ij})_{i,j=1}^n$ *be the corresponding Hurwitz matrix, namely*

$$H_{ij} = \begin{cases} 1 & \textit{if } 2j - i = 0, \\ a_{2j-i} & \textit{if } 2j - i \in \{1, \dots, n\}, \\ 0 & \textit{if } 2j - i \notin \{0, \dots, n\}. \end{cases}$$

Then all the roots of $p(\lambda)$ *have negative real part if, and only if, the determinants of the principal submatrices of* H *(Hurwitz determinants) are all positive.*

3 Oscillation thresholds via the MBR method

In spite of its undisputed strength, oftentimes the stability conditions deriving from the Routh–Hurwitz criterion can be cumbersome. In this section, we revisit an approach recently proposed by Rionero [27], which relies on the computations of the minimum roots of the coefficients of the characteristic polynomial $p(\lambda,\mu)$. In particular, in the general n-dimensional case the MBR method provides sufficient conditions for a hyperbolic and locally asymptotically stable equilibrium to lose its hyperbolicity at some point where a Hopf bifurcation is possible, while in the case $n=3$ and $n=4$ we further prove that the Hopf bifurcation occurs and the equilibrium destabilizes.

We anticipate that, for the MBR method to be applied, it is necessary that condition (3) on the coefficients of the characteristic polynomial of $J(x^0,\mu)$ does not hold for every $a_h(\mu)$. Otherwise, if all the coefficients remain positive by varying $\mu \in \mathcal{I}$, then classical methods are needed to verify the occurrence of Hopf bifurcations.

3.1 *The general formulation of the MBR method*

For mathematical convenience, in the following we assume that

$$\mathcal{I} = [\mu_0, +\infty),$$

with $\mu_0 \in \mathbb{R}$. It is straightforward to verify that analogous results hold in the case of different kinds of interval $\mathcal{I}$ [27] (see also Remark 1).

Let us start by considering the coefficients of the polynomial $p(\lambda,\mu)$, as given in (2), namely $a_h \in \mathcal{C}^1(\mathcal{I}),\ h=1,\ldots,n$, and introduce the definition of *minimum bifurcation root* of $a_h(\mu),\ h=1,\ldots,n$.

We denote by

$$R_h = \{\mu \geqslant \mu_0\colon\ a_h(\mu) = 0\} \tag{5}$$

the set of roots of $a_h(\mu)$ in the interval $\mathcal{I}$.

If $R_h \neq \emptyset$, namely if there exists $\mu \geqslant \mu_0$ such that $a_h(\mu)=0$, then we define the minimum bifurcation root of $a_h(\mu)$ as the lowest of its roots: $\mu_{m,h} = \min R_h$. Otherwise, if $R_h \neq \emptyset$, namely if $a_h(\mu) \neq 0$ of all $\mu \geqslant \mu_0$, then we define the minimum bifurcation root of $a_h(\mu)$ as $\mu_{m,h} = +\infty$

In sum, for each $h \in \{1,\ldots,n\}$, the minimum bifurcation root of $a_h(\mu)$ is

$$\mu_{m,h} = \begin{cases} \min R_h & \text{if } R_h \neq \emptyset, \\ +\infty & \text{if } R_h = \emptyset, \end{cases} \tag{6}$$

with R_h given in (5).

On the basis of the results given in the work [27], the following criterion is established. The basic idea is that, if at $\mu = \mu_0$ the equilibrium x^0 is hyperbolic and locally asymptotically stable and at least one between the first $n-1$ coefficients of $p(\lambda,\mu)$ vanishes in $\mathcal{I}$ before the nth coefficient does, then the equilibrium has lost its hyperbolicity at some point, and a Hopf bifurcation may have occurred.

Theorem 1. *Let* x^0 *be an equilibrium of system* (1) *for* $\mu \geqslant \mu_0$, *and let* $p(\lambda,\mu)$, *as given in* (2), *be the characteristic polynomial of* $J(x^0,\mu) = D_x f(x^0,\mu)$. *Let us assume that at* $\mu = \mu_0$ *the equilibrium* x^0 *is hyperbolic and locally asymptotically stable.*

If there exists $\bar{h} \in \{1,\dots,n-1\}$ *such that* $\mu_{m,\bar{h}}$, *the minimum bifurcation root of* $a_h(\mu)$ *as defined in* (6), *is*

$$\mu_{m,\bar{h}} \leqslant \mu_{m,h} \quad \forall h \neq n, \quad \textit{and} \quad \mu_{m,\bar{h}} < \mu_{m,n}, \tag{7}$$

then at $\mu = \mu_H$, *with* $\mu_0 < \mu_H \leqslant \mu_{m,\bar{h}}$, *the equilibrium* x^0 *is nonhyperbolic, and a Hopf bifurcation can occur.*

Proof. Let us denote by

$$\lambda_h(\mu) = \alpha_h(\mu) + \mathrm{i}\beta_h(\mu), \quad h = 1,\dots,n,$$

the eigenvalues of $J(x^0,\mu)$ that are the roots of $p(\lambda,\mu)$.

At $\mu = \mu_0$, since x^0 is hyperbolic and locally asymptotically stable, from the Lyapunov's indirect method one yields

$$\alpha_h(\mu_0) < 0 \quad \forall h \in \{1,\dots,n\},$$

implying that the coefficients of $p(\lambda,\mu_0)$ are all positive (see (3)):

$$\alpha_h(\mu_0) < 0 \quad \forall h \in \{1,\dots,n\},$$

From (7) and the definition of minimum bifurcation root (6) it follows that $\mu_{m,\bar{h}}$, with $\bar{h} \in \{1,\dots,n-1\}$, is the minimum value of $\mu > \mu_0$such that $a_{\bar{h}}(\mu) = 0$, and $a_h(\mu_{m,\bar{h}}) \geqslant 0$ for all $h \neq n$, $a_n(\mu_{m,\bar{h}}) > 0$. In turn, by using the Descartes' rule of signs, this implies that at $\mu = \mu_{m,\bar{h}}$ the polynomial $p(\lambda,\mu_{m,\bar{h}})$ admits at least a pair of complex conjugate roots with nonnegative real part. Namely, there are two indexes $h^{\pm} \in \{1,\dots,n\}$ such that

$$\alpha_{h^{\pm}}(\mu_{m,\bar{h}}) \geqslant 0, \qquad \beta_{h^-}(\mu_{m,\bar{h}}) = -\beta_{h^+}(\mu_{m,\bar{h}}) \neq 0.$$

Since $\alpha_{h^{\pm}}(\mu_{m,\bar{h}}) \geqslant 0 > \alpha_{h^{\pm}}(\mu_0)$, there exists μ_H, with $\mu_0 < \mu_H \leqslant \mu_{m,\bar{h}}$, such that$\alpha_{h^{\pm}}(\mu_H) = 0$ and $\beta_{h^-}(\mu_H) = -\beta_{h^+}(\mu_H)$. Furthermore, $\beta_{h^{\pm}}(\mu_H) \neq 0$ because the polynomial $p(\lambda,\mu)$ has a zero root if, and only if, $a_n(\mu) = 0$ and $\mu_H < \mu_{m,n}$ (see (7)).

In conclusion, we have proved that the equilibrium x^0 is nonhyperbolic at $\mu = \mu_H$. More precisely, $J(x^0, \mu_H)$ admits at least a pair of pure imaginary eigenvalues. The assert follows.

Note that in the work [27] the results are given in terms of the reciprocal of the minimum bifurcation roots, there called *instability coefficients power*.

As anticipated above, if condition (3) holds for every $\mu \in \mathcal{I}$, then the minimum bifurcation roots of $a_h(\mu)$ are $\mu_{m,h} = +\infty$ for all $h \in \{1,\ldots,n\}$, and Theorem 1 does not apply because the inequality $\mu_{m,\bar{h}} < \mu_{m,n}$ in (7) cannot be satisfied.

3.2 Further results in the specific case n = 3 and n = 4

In the case of three-dimensional and four-dimensional dynamical systems, we also prove that, if the assumptions of Theorem 1 are fulfilled, then the fact that one between the first $n-1$ coefficients of $p(\lambda,\mu)$ vanishes in $\mathcal{I}$ before all the other ones do, not only indicates the lost of hyperbolicity of the equilibrium x^0, but also ensures that it has been destabilized via a Hopf bifurcation. Note that this result can be also obtained by applying the criterion by Liu [17], which provides conditions for a simple Hopf bifurcation in terms of the Hurwitz determinants of $p(\lambda,\mu)$. At the increasing of μ from $\mu = \mu_0$, the coefficient first becoming zero provides for the upper bound to the possible locations of the bifurcation.

Theorem 2. *Let us consider the assumptions of Theorem 1. If* $n = 3$ *or* $n = 4$ *and*

$$\mu_{m,\bar{h}} < \mu_{m,h} \quad \forall h \neq \bar{h}, \tag{8}$$

then at $\mu = \mu_H$ *, with*

$$\mu_0 < \mu_H < \mu_{m,\bar{h}}, \tag{9}$$

the equilibrium x^0 *destabilizes via a Hopf bifurcation.*

Proof. Let us resume the proof of Theorem 1 and make use of the Routh–Hurwitz criterion (see Section 2.3). We distinguish between the cases:

- $n = 3$ Then the Hurwitz determinants are

$$\Delta_1(\mu) = a_1(\mu), \qquad \Delta_2(\mu) = a_1(\mu)a_2(\mu) - a_3(\mu), \qquad \Delta_3(\mu) = a_3(\mu)\Delta_2(\mu). \tag{10}$$

At $\mu = \mu_0$, all the roots of $p(\lambda, \mu_0)$ have negative real part, hence $\Delta_h(\mu_0) > 0$ for all $h \in \{1, 2, 3\}$

One can easily verify that for $p(\lambda, \mu)$ to admit a pair of pure imaginary roots, it is necessary that $\Delta_2(\mu) = 0$. Indeed, let us consider the quantities $\alpha(\mu), \beta(\mu) \in \mathbb{R}$, then

$$p(\lambda, \mu) = \big(\lambda - \alpha(\mu)\big)\big(\lambda^2 + \beta^2(\mu)\big) \\ \iff \quad p(\lambda, \mu) = \lambda^3 - \alpha(\mu)\lambda^2 + \beta^2(\mu)\lambda - \alpha(\mu)\beta^2(\mu),$$

implying that $\Delta_2(\mu) = a_1(\mu)a_2(\mu) - a_3(\mu) = 0.$

From (8) and the definition of minimum bifurcation root (6) it follows that at $\mu = \mu_{m,\bar{h}}$ with $\bar{h} \in \{1, 2\}$

$$\Delta_2(\mu_{m,\bar{h}}) = -a_3(\mu_{m,\bar{h}}) < 0,$$

and $p(\lambda, \mu_{m,\bar{h}})$ admits a real negative root and a pair of complex conjugate roots with positive real part. This implies that there exists μ_H, with $\mu_0 < \mu_H < \mu_{m,\bar{h}}$, such that at $\mu = \mu_H$ the real part of a pair of complex conjugate roots passes through zero, the third root being real and negative.

- $n = 4$. Then the Hurwitz determinants are

$$\Delta_1(\mu) = a_1(\mu), \qquad \Delta_2(\mu) = a_1(\mu)a_2(\mu) - a_3(\mu), \\ \Delta_3(\mu) = a_3(\mu)\Delta_2(\mu) - a_1^2(\mu)a_4(\mu), \qquad \Delta_4(\mu) = a_4(\mu)\Delta_3(\mu).$$

At $\mu = \mu_0$, all the roots of $p(\lambda, \mu_0)$ have negative real part, hence $\Delta_3(\mu) = 0$ for all $h \in \{1, \dots, 4\}$

One can easily verify that for $p(\lambda, \mu)$ to admit a pair of pure imaginary roots, it is necessary that $\Delta_3(\mu) = 0$. Indeed, if the other two roots are real, then one yields

$$p(\lambda, \mu) = \big(\lambda - \alpha(\mu)\big)\big(\lambda - \beta(\mu)\big)\big(\lambda^2 + \gamma^2(\mu)\big) \\ \iff \quad p(\lambda, \mu) = \lambda^4 - \big(\alpha(\mu) + \beta(\mu)\big)\lambda^3 + \big(\alpha(\mu)\beta(\mu) + \gamma^2(\mu)\big)\lambda^2 \\ - \big(\alpha(\mu) + \beta(\mu)\big)\gamma^2(\mu)\lambda + \alpha(\mu)\beta(\mu)\gamma^2(\mu),$$

with $\alpha(\mu), \beta(\mu), \gamma(\mu) \in \mathbb{R}$. Otherwise, if the other two roots are complex and conjugate, then one yields

$$p(\lambda, \mu) = \big((\lambda - \alpha(\mu))^2 + \beta^2(\mu)\big)\big(\lambda^2 + \gamma^2(\mu)\big) \\ \iff \quad p(\lambda, \mu) = \lambda^4 - 2\alpha(\mu)\lambda^3 + \big(\alpha^2(\mu) + \beta^2(\mu) + \gamma^2(\mu)\big)\lambda^2 \\ - 2\alpha(\mu)\gamma^2(\mu)\lambda + \big(\alpha^2(\mu) + \beta^2(\mu)\big)\gamma^2(\mu), \tag{11}$$

with $\alpha(\mu), \beta(\mu), \gamma(\mu) \in \mathbb{R}$. In both cases,

$$\Delta_3(\mu) = a_1(\mu)a_2(\mu)a_3(\mu) - a_3^2(\mu) - a_1^2(\mu)a_4(\mu) = 0.$$

From (8) and the definition of minimum bifurcation root (6) it follows that at $\mu = \mu_{m,\bar{h}}$, with $\bar{h} \in \{1,2,3\}$,

$$\Delta_3(\mu_{m,\bar{h}}) < 0,$$

and $p(\lambda, \mu_{m,\bar{h}})$ admits at least a pair of complex conjugate roots with positive real part. This implies that there exists μ_H, with $\mu_0 < \mu_H < \mu_{m,\bar{h}}$, such that at $\mu = \mu_H$ the real part of a pair of complex conjugate roots passes through zero, all the other ones having negative real part. Indeed, if at $\mu = \mu_H$ the real part of two pairs of complex conjugate roots passed through zero, then it should be $\alpha(\mu_H) = 0$ in (11), namely $a_1(\mu_H) = a_3(\mu_H) = 0$, which contradicts the inequality $\mu_H < \mu_{m,\bar{h}}$.

The assert follows

Remark 1. If we considered the interval $\mathcal{I} = (-\infty, \mu_0]$, with $\mu_0 \in \mathbb{R}$, and x^0 hyperbolic and locally asymptotically stable at $\mu = \mu_0$, then we would introduce the definition of *maximum bifurcation root* of $a_h(\mu), h = 1, \ldots, n$, as

$$\mu_{M,h} = \begin{cases} \max R_h & \text{if } R_h \neq \emptyset, \\ -\infty & \text{if } R_h = \emptyset, \end{cases}$$

with R_h given by $R_h = \{\mu \leqslant \mu_0 \colon a_h(\mu) = 0\}$. In such a case, the analogues of Theorems 1 and 2 are simply obtained by substituting $\mu_{m,h}$ with $\mu_{M,h}$ and reversing the sign of all the inequalities in the statements.

4 Oscillations in oncolytic virotherapy

4.1 The model and its equilibria

Let us consider the three-dimensional dynamical system proposed by Jenner et al. [9, 10] that captures the *in vivo* dynamics of a tumour under treatment with an oncolytic virus. As stressed in Section 1, this model is particularly relevant because it was calibrated on experimental results and unveiled some drawbacks in the existing strategies adopted in the oncolytic virotherapy [10].

The nondimensional version of the model in the papers [9, 10] is given by

$$\dot{U} = m \ln\left(\frac{K}{U}\right)U - \frac{UV}{U+I}, \qquad \dot{I} = \frac{UV}{U+I} - \xi I, \qquad \dot{V} = -\gamma V + \xi I,$$

where all the parameters are positive constants, U is the density of uninfected tumour cells, I is the density of virus-infected tumour cells, V

represents the density of virus particles at the tumour site, and the term $U+I$ corresponds to the total tumour cell population. The model is the result of a nondimensionalisation process so that the parameters m, ξ, γ are all scaled by the infectivity rate, and they represent the tumour growth rate, the tumour cell death rate and the viral decay rate, respectively. The parameter K represents the carrying capacity of the tumour.

In (12), the uninfected tumour cells U grow according to a Gompertz function law to model the rapid growth at smaller time scales. This initial growth is what makes the Gompertz function a good approximation for tumours, which are known to grow rapidly early on.

The solutions of the system are imposed to be nonnegative in order to ensure the mathematical and biological well-posedness of the model. For more details about the modelling assumptions, see [9].

One can easily verify that model (12) admits three equilibria:

i. $E_0 = (0,0,0)$, that corresponds to the complete eradication of the tumour;
ii. $E_K = (K,0,0)$, where uninfected tumour cells equal the carrying capacity, indicating the ineffectiveness of the treatment;
iii. the internal equilibrium

$$\tilde{E} = \left(\tilde{U}, \frac{1-\gamma}{\gamma}\tilde{U}, \frac{\xi(1-\gamma)}{\gamma^2}\tilde{U}\right), \quad \text{with } \tilde{U} = K \exp\frac{\xi(\gamma-1)}{m\gamma},$$

that exists if $0 < \gamma \leqslant 1$, and represents the case of incomplete eradication, characterized by a quiescent tumour despite the nonnull viral load.

We apply Theorem 2 in order to prove that an equilibrium of model (12) can switch from being locally asymptotically stable to unstable (or *vice versa*) via a Hopf bifurcation. Of course, the equilibrium of interest for our purposes is that internal to the positive orthant, namely $\tilde{E}$. In the paper [9] the authors found through the use of continuation and bifurcation software an extended area of the parameter space where $\tilde{E}$ can change stability via (supercritical or subcritical) Hopf bifurcations. However, they did not analytically characterize the oscillation thresholds.

Remark 2.

i. The stability analysis of the equilibria E_0 and E_K can be found in the paper [9].
ii. Note that $\tilde{E} \to E_0$ if $\gamma \to 0$, and $\tilde{E} = E_K$ if $\gamma = 1$. Hence, it is not restrictive to limit our analysis to the case $0 < \gamma \leqslant 1$.
iii. The Jacobian of system (12) evaluated at the equilibrium E_0 of complete eradication is singular due to the presence of logarithmic and rational terms. In such a case, an analytical treatment of the Jacobian is not possible; Jenner et al. [9] used instead a different approach based on numerical integration and computation of eigenvalues under specific assumptions on U, I and V.

4.2 Application of the MBR method

We choose ξ, the death rate of the tumour cells, as bifurcation parameter and assume that the other parameters are fixed. Hence, ξ plays here the role of the parameter μ in the previous sections.

From simple algebra one obtains the Jacobian matrix of system (12) evaluated at the equilibrium $\tilde{E}$:

$$J(\tilde{E},\xi) = \begin{pmatrix} \frac{\xi(1-\gamma)}{\gamma} - m - \frac{\xi(1-\gamma)^2}{\gamma} & \xi(1-\gamma) & -\gamma \\ \frac{\xi(1-\gamma)^2}{\gamma} & \xi(\gamma-2) & \gamma \\ 0 & \xi & -\gamma \end{pmatrix}$$

whose characteristic equation is

$$p(\lambda,\xi) = \lambda^3 + a_1(\xi)\lambda^2 + a_2(\xi)\lambda + a_3(\xi), \tag{13}$$

with

$$\begin{aligned} a_1(\xi) &= -\operatorname{tr}\big(J(\tilde{E},\xi)\big) = \xi + m + \gamma > 0, \\ a_2(\xi) &= \frac{1}{2}\big[\operatorname{tr}^2\big(J(\tilde{E},\xi)\big) - \operatorname{tr}\big(J(\tilde{E},\xi)^2\big)\big] = -\frac{1-\gamma}{\gamma}\xi^2 + m(2-\gamma)\xi + m\gamma, \\ a_3(\xi) &= -\det\big(J(\tilde{E},\xi)\big) = m\gamma(1-\gamma)\xi > 0. \end{aligned}$$

Let us start to take ξ_0 such that $\tilde{E}$ is hyperbolic and locally asymptotically stable at $\xi = \xi_0$.

We assume that ξ_0 is close to zero: $0 < \xi_0 \ll 1$. Then one yields $a_1(\xi_0) > 0$, $a_3(\xi_0) > 0$ and

$$\Delta_2(\xi_0) = a_1(\xi_0)a_2(\xi_0) - a_3(\xi_0) \simeq m\big[(m(2-\gamma)+2\gamma)\xi_0 + (m+\gamma)\gamma\big] > 0,$$

where we neglected the effects of the remaining higher-order terms. From the Routh– Hurwitz criterion in the case $n = 3$ it follows that all the Hurwitz determinants are positive (see (10)), namely all the roots of $p(\lambda,\xi_0)$ (that are the eigenvalues of $J(\tilde{E},\xi_0)$) have negative real part. Hence, $\tilde{E}$ is hyperbolic and locally asymptotically stable at $\xi = \xi_0$.

Let us now compute the minimum bifurcation roots $\xi_{m,h}$ of the coefficients $a_h(\xi)$, $h = 1,2,3$, in the interval $\mathcal{I} = [\xi_0,+\infty)$ (see the definition (6)). One immediately gets $\xi_{m,1} = \xi_{m,3} = +\infty$, while $\xi_{m,2}$ is the unique positive root of $a_2(\xi)$, namely

$$\xi_{m,2} = \frac{m\gamma(2-\gamma) + \gamma\sqrt{m^2(2-\gamma)^2 + 4m(1-\gamma)}}{2(1-\gamma)}.$$

Since $\xi_{m,2} < \xi_{m,h}$ for all $h \neq 2$, Theorem 2 asserts that at $\xi = \xi_H$, with $\xi_0 < \xi_H < \xi_{m,2}$, the equilibrium $\tilde{E}$ destabilizes via a Hopf bifurcation.

Hence, the application of Theorem 2 has allowed us to complement the numerical investigations performed by Jenner et al. [9], by analytically determining the existence and location of Hopf bifurcations for the equilibrium $\tilde{E}$.

Remark 3. A classical method for determining the occurrence of Hopf bifurcations starting from the characteristic equation (13) consists in searching between the roots of the Hurwitz determinant$\Delta_2(\xi) = a_1(\xi)a_2(\xi) - a_3(\xi)$. Specifically, a Hopf bifurcation value ξ_H is a positive real root of

$$\Delta_2(\xi) = \frac{d_0\xi^3 + d_1\xi^2 + d_2\xi + d_3}{\gamma}, \qquad [14)]$$

where

$$\begin{aligned} d_0 &= -(1-\gamma) < 0, \\ d_1 &= m\gamma(2-\gamma) - (m+\gamma)(1-\gamma), \\ d_2 &= m\gamma\bigl(m(2-\gamma) + 2\gamma\bigr) > 0, \\ d_3 &= m(m+\gamma)\gamma^2 > 0, \end{aligned}$$

such that the test for nonzero speed is fulfilled [7]:

$$\left.\frac{\mathrm{d}\Delta_2(\xi)}{\mathrm{d}\xi}\right|_{\xi=\xi_H} \neq 0. \qquad (15)$$

In such a case, from the Descartes' rule of signs it follows that the cubic function $\Delta_2(\xi)$ in (14) has a unique positive real root. Also, condition (15) is satisfied since $\Delta_2(0) > 0$ and $\Delta_2(\xi) \to -\infty$ when $\xi \to +\infty$. Then at $\xi = \xi_H$ a pair of complex conjugate eigenvalues of $J(\tilde{E}, \xi)$ crosses the imaginary axis (the third one being real and negative), so that $\tilde{E}$ passes from being locally asymptotically stable to unstable via a Hopf bifurcation.

The procedure presented in Remark 3 involves the investigation of a cubic function, and the bifurcation value ξ_H must be obtained as a solution of a cubic equation (for the algebraic expression use, e.g., the solution formula for cubic equations given in the book [15]). In such a way, the oscillation thresholds are fully characterized and can be also written in terms of the other parameters of the system. Conversely, the MBR method requires the solution of a quadratic equation (that is, the roots of the coefficient $a_2(\xi)$) and provides a range of values $(\xi_0, \xi_{m,2})$ in which ξ_H falls.

4.3 The impact on the oscillation thresholds of the features of tumour and virus

In Fig. 1A, we display a contour plot of the value of Hopf bifurcations ξ_H in the plane $(m, \gamma) \in (0, 0.5]^2$. It turns out that the oscillation threshold increases as the tumour growth rate and/or the viral decay rate increases. In Fig. 1B, we set the tumour growth rate to $m = 0.1$ and display the values of both ξ_H (solid line) and the minimum bifurcation root $\xi_{m,2}$ (dashed line) as functions of the viral decay rate, γ. The white (resp. grey) colour denotes the region where $\tilde{E}$ is locally asymptotically stable (resp. unstable). We restrict the parameter space to the interval (0, 0.5] just to make the variations of the bifurcation values and of the distance between ξ_H and $\xi_{m,2}$ more appreciable.

For example, by assuming that $m = 0.1$ and $\gamma = 0.1$, Jenner et al. [9] numerically found that the value of the Hopf bifurcation is approximately equal to $\xi_H = 0.043$. One can easily verify that in such a case we have $\xi_{m,2} \simeq 0.046$, and inequality (9) of Theorem 2, which reads $\xi_H < \xi_{m,2}$, is satisfied (see Fig. 1B, vertical and horizontal lines). From Fig. 1B one can also notice that $\xi_{m,2}$ is in any case very close to ξ_H: the maximum distance $\xi_{m,2} - \xi_H$ is 0.018 when $\gamma = 0.5$.

A representative scenario in which $\tilde{E}$ is unstable and system (12) converges towards a periodic solution is shown in Fig. 2: it is obtained from Fig. 1B by setting $\gamma = 0.1$ and $\xi = 0.06 > \xi_H$. One observes that, asymptotically, the uninfected cells, U, are the first to reach the peak with a subsequent peak in the infected cells, I, and then in the viral load, V (Fig. 2A, black, blue and red lines, respectively).

Note that in the paper [9] several numerical simulations show that the Hopf bifurcations can be either supercritical (onset of stable oscillations) or subcritical (onset of unstable oscillations) depending on the model parameters. In particular, the bifurcations are likely to be supercritical (resp. subcritical) for small (resp. high) values of both the tumour growth rate, m, and the viral decay rate, γ.

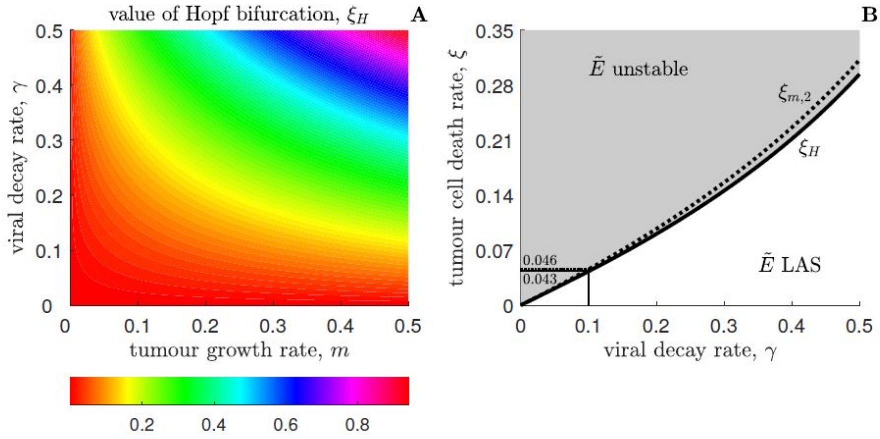

Figure 1

Bifurcation analysis of the equilibrium E˜ of model (12). Panel A: Contour plot of the value of Hopf bifurcation, ξH , versus the tumour growth rate, m, and the viral decay rate, γ. Panel B: Hopf bifurcation value, ξH (solid line), and minimum bifurcation root of a2(ξ), ξm,2 (dashed line), as functions of the viral decay rate, γ, by assuming m = 0.1. The intersection between vertical and horizontal lines indicates the values corresponding to γ = 0.1. Region colour is white (resp. grey) where E˜ is locally asymptotically stable (LAS) (resp. unstable)

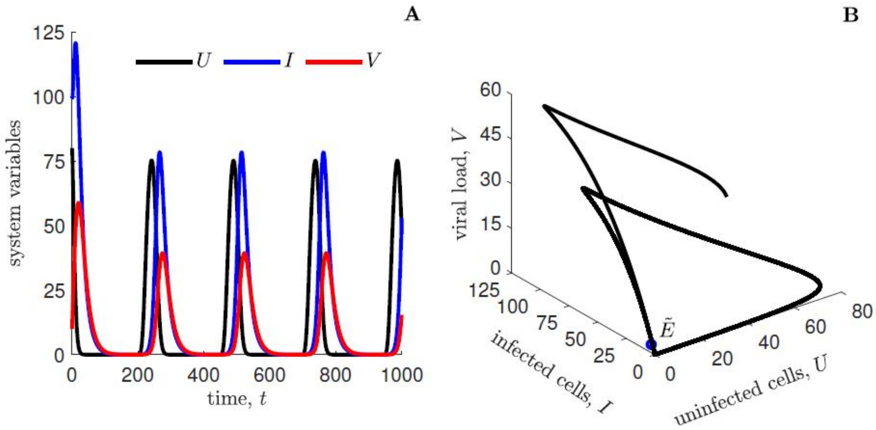

Figure 2

Numerical solutions of model (12) in case of stable stationary oscillations. Panel A: Temporal dynamics of uninfected tumour cells, U (black line), infected tumour cells, I (blue line), and viral load, V (red line). Panel B: Phase portrait in the space (U, I, V). Parameter values: K = 100, m = 0.1, ξ = 0.06, γ = 0.1. Initial conditions: U (0) = 80, I(0) = 100, V (0) = 10.

5 Concluding remarks

Our findings can be summarized in the following key points.

- In the general case of one parameter-depending dynamical systems, we provided in Theorem 1 sufficient conditions for a hyperbolic and locally asymptotically stable equilibrium to lose its hyperbolicity at some point where a Hopf bifurcation is possible.

- In the particular case of three-dimensional and four-dimensional dynamical systems, we further proved in Theorem 2 that the Hopf bifurcation indeed occurs and the equilibrium destabilizes.
- The assumptions of Theorems 1 and 2 may be more manageable and easier to verify in comparison with classical stability conditions, such as those provided by the Routh–Hurwitz criterion.
- For the oncolytic virotherapy model by Jenner et al. [9,10], the MBR method allows to find a range in which the critical value for the occurrence of the Hopf bifurcation falls. Such a range was determined in terms of the parameters of the dynamical system. Locating the oscillation thresholds can be relevant to further investigate the possibility that oncolitic viruses prevent the full destruction of the tumour mass.

We acknowledge that a limitation of the MBR method is the lack of general applicability. Indeed, for the MBR method to be applied, it is necessary that the coefficients of the characteristic polynomial of the Jacobian matrix of the system evaluated at the equilibrium are not always positive when the bifurcation parameter changes. Of course, there are many dynamical systems for which such coefficients are all positive for every value of the bifurcation parameter, but Hopf bifurcations occur. See, for instance, the three-dimensional epidemic models proposed by d'Onofrio et al. [3, 4].

This limitation stimulates further efforts to find more general sufficient conditions for a Hopf bifurcation to occur. Another future perspective of our research is to enlarge the range of applications of the MBR method, by focusing on those systems where internally driven oscillations play a key role (e.g., the predator–prey population cycles in ecology [6, 14], or the temporal series of some infectious diseases in epidemiology [29]).

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Notes

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