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Deterministic vs stochastic formulations and qualitative analysis of a recent tumour growth model

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Abstract: Mathematical modeling and control have recently played a pivotal role in the understanding of tumour growth and in treatment planning, with a special emphasis in the search for personalized therapies. In this note a recent tumour growth model is investigated. The model entails the proliferating and necrotic tumour cells dynamics, as well as the administered drug level. Inspired by a recent reaction-rate characterization of the model, the approach is further deepened with respect to cells and drug molecules copy numbers, hence resulting relevant under the double facet of the deterministic and stochastic frameworks. With regards to the deterministic model, the qualitative behavior analysis is carried out under the basic assumption of a baseline drug delivery: results are encouraging, since they show which parameter space regions allow effective control law results. Stochastic simulations are carried out by properly exploiting parameter values taken from the available experimental literature, and are consistent with the average value evolution inferred from the deterministic approach, paving the way to further stochastic investigation oriented to frameworks involving a reduced copy number.

Keywords: Tumour growth control; Chemical Master Equations; Qualitative behavior analysis

1. INTRODUCTION

Mathematical models of tumour growth and treatment offer a fundamental tool for studying the effects of different drugs on the tumour dynamics and for designing efficient personalized therapies. One success story in the field comes from Hahnfeldt et al. (1999), a minimally parameterized and low-dimensional mathematical model describing the vascular phase of tumour growth. Since then, different theoretical and application results have been achieved, dealing with closed- and open-loop administration of anti-angiogenic drugs (see, e.g. Cacace et al. (2018b,a); Drexler et al. (2017c); Ledzewicz and Schättler (2008); Sápi et al. (2016)), possibly in combination with chemotherapy (see, e.g. d'Onofrio et al. (2009); Ledzewicz et al. (2011)).

Beyond the Hahnfeldt model, recent modeling approaches accounted also for dead tumour volume dynamics and the drug pharmacodynamics. The former feature is still matter of investigation since necrotic regions may provide pro- or antitumour effects, Wang and Lin (2008); Proskuryakov and Gabai (2010), and mathematical models aiming to incorporate dead cells dynamics may suggest a novel biological insight to the medical community. The drug pharmacodynamics is another facet deserving investigation, since experiments have shown how a trivially linear effect of the administered drug has a reduced range of validity. Within this framework, recent results can be found in Drexler et al. (2019, 2017a,b). Although tumour growth models arise from a mechanism-based approach, a nice characterization of such a family of models bases on the formalism of Chemical Reaction Networks (CRN) that allows to derive the Ordinary Differential Equation (ODE) system from standard (i.e. mass action law) or non-standard (i.e. Michaelis-Menten saturating functions) reaction rate laws.

Inspired by the aforementioned approach, here we exploit the CRN associated to the tumour growth model in a stochastic framework, dealing with tumour cells and drug molecules copy number. To this end we consider the Chemical Master Equations (CME) broadly accepted as the most effective tool to capture copy number fluctuations as well as to explain how noise impacts and propagates through CRNs, especially in cases of low copy numbers. CMEs provide the copy number average value dynamics from a first-order approximation of the nonlinear propensities, van Kampen (2007). Finally, the usual mechanism-based model is derived by properly accounting for volumes and concentrations.

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The contribution of this note is twofold. On the one hand, we generalize the CRN-based approach suggested by Drexler et al. (2019) in a way that allows both deterministic and stochastic characterization of the model, depending on the final purpose of the mathematical investigation. Any chosen model can be solidly anchored to the formulation of Drexler et al. (2019) by scaling the model parameters, so that numerical simulations can be carried out in a meaningful way by exploiting the experimental values from the literature. Stochastic simulations are carried out according to the τ-leap approximation of the Gillespie algorithm, Gillespie (2001), and show the substantially trivial impact of noise in the tumour growth dynamics, at least for the chosen setting of model parameters.

On the other hand, a qualitative analysis of the deterministic model is carried out, providing a fruitful information concerning the effectiveness of a constant control law. Indeed, we prove that there exists a unique asymptotically stable equilibrium point, corresponding to a healthy complete eradication of the tumour, whose stability is tightly related to both model parameters and drug administration.

2. MODEL FORMULATION: DETERMINISTIC VS STOCHASTIC APPROACH

Following the chemical reaction formalism adopted in Drexler et al. (2019), we provide both a deterministic and a stochastic representation of a growing tumour cell population under chemotherapeutic treatment. In order to make the two models directly comparable, we use the same state variables for both formulations. In particular, we opt for countable state variables, i.e. number of tumour cells and drug molecules, which represent a more natural setting for the stochastic formulation.

The simpler deterministic formulation can be preferred in some applications to have an idea of the average behaviour of the system; indeed, in some cases, the deterministic model can be a good approximation of the 1-st order moments of the stochastic formulation. However, correlations between variables and their fluctuations are nullified by the deterministic approach, so that a stochastic formulation is required if we are interested in following such a behaviour of the system dynamics, see van Kampen (2007). In the following we will denote with X a species, with n its copy number and with $[X]$ its copy number concentration.

The fictional chemical species involved in the chemical reactions are X_1, the proliferating tumour cells, X_2, the dead tumour cells, and X_3, the drug molecules. As done in Drexler et al. (2019), we describe by means of the following chemical reactions some physiological aspects of the tumour, as well as its interaction with drugs used to inhibit its growth:

$$\begin{array}{lll} R_1: & X_1 \to 2X_1, & \text{(cell proliferation)} \\ R_2: & X_1 \to X_2, & \text{(cell necrosis)} \\ R_3: & X_2 \to \emptyset, & \text{(washout of dead cells)} \\ R_4: & X_3 \to \emptyset, & \text{(drug clearance)} \\ R_5: & X_1 + X_3 \to X_2, & \text{(drug action)} \\ R_6: & \emptyset \to X_3. & \text{(drug administration)} \end{array} \tag{1}$$

The deterministic formulation can be given introducing for each reaction R_i, $i = 1, \dots, 6$, a flux ν_i, providing the concentration of the produced metabolite through R_i per unit time. The quantity ν_i indicates how fast the related reaction is working and its expression strictly depends on the concentrations of the reactants of R_i, as well as on the kinetics assumed to represent the reaction mechanism. More in details, it is

$$\nu_i = k_i f_i([X_1], [X_2], [X_3]), \qquad i = 1, \dots, 6,$$

where k_i is the reaction rate constant and f_i is a proper function of the concentrations $[X_j]$, $j = 1, 2, 3$, related to the reactants X_j involved into the reaction R_i.

The simplest and most used kinetic mechanisms are given by (i) the mass-action law, where f_i is given by the product of the reactant concentrations to the power of their stoichiometric coefficients, and by (ii) the Michaelis-Menten law (MM), exploiting a sigmoidal function. Both kinetic laws are used in the model formulation and, in particular, according to Drexler et al. (2019) we choose mass-action laws for ν_i, $i = 1, 2, 3$, whilst MM laws for ν_i, $i = 4, 5$. The different choice made for ν_i, $i = 4, 5$, is motivated by the need for a more realistic pharmacodynamics/pharmacokinetics modelling, as it is explained in Drexler et al. (2017b). Conversely, ν_6 does not depend on chemical species: it is the administration rate that the user can manipulate, i.e. it is the input of the system. More in details, we have:

$$\begin{array}{l} \nu_1 = k_1[X_1],\ \nu_2 = k_2[X_1],\ \nu_3 = k_3[X_2],\ \nu_6 = k_6, \\ \nu_4 = k_4[X_3]/(K_4 + [X_3]),\ \nu_5 = k_5[X_1][X_3]/(K_5 + [X_3]). \end{array} \tag{2}$$

We note that the dimensions of the reaction rate constants k_i, $i = 1, \dots, 6$, are not uniform. They obviously depend on the chosen reaction kinetics since the dimension of ν_i is a concentration per time unit.

The deterministic formulation of the chemical reaction system (1) is given by the ODE

$$\frac{d[\mathbf{X}]}{dt} = S\mathbf{v}([\mathbf{X}]), \tag{3}$$

where S is the related stoichiometry matrix, $[\mathbf{X}]$ is the vector of the metabolite concentrations $([X_1], [X_2], [X_3])^T$, while $\mathbf{v}$ is the flux vector $(\nu_1, \dots, \nu_6)^T$. In order to make the deterministic model directly comparable with the stochastic one, we express the dynamical system (3) in terms of number of tumour cells/drug molecules. This is done with a little abuse of notation, since we provide a continuous description in terms of ODEs of copy numbers, which are intrinsically discrete state variables. Denoting by n_j the number of cells/molecules of the species X_j and by V the volume of the reaction system (it can be interpreted as the ideal reaction chamber around the tumour mass), the species concentrations can be expressed as $[X_j] = n_j/V$, $j = 1, 2, 3$. So, accounting for the flux expressions given in (2), the deterministic ODE system (3) can be rewritten in terms of the variables n_j as

$$\begin{aligned} \frac{dn_1}{dt} &= (k_1 - k_2)n_1 - k_5 n_1 \frac{n_3}{M_5 + n_3}, \\ \frac{dn_2}{dt} &= k_2 n_1 - k_3 n_2 + k_5 n_1 \frac{n_3}{M_5 + n_3}, \\ \frac{dn_3}{dt} &= -\rho \frac{n_3}{M_4 + n_3} - k_5 n_1 \frac{n_3}{M_5 + n_3} + r, \end{aligned} \tag{4}$$

where $\rho = Vk_4$, $r = Vk_6$ and $M_j = VK_j$, $j = 4, 5$. Note that the scaled flux r is the drug administration rate (given in number of molecules per time unit), i.e. the input of the

system, and, in principle, it can be a time varying function $r(t)$ dependent on the chosen administration regimen. We finally note that the measurement units of the model parameters of system (4) are: time^{-1} (in particular we use day^{-1}) for k_j, $j = 1, 2, 3, 5$; number of cells/molecules for M_j, $j = 4, 5$ (K_j, $j = 4, 5$, are concentrations); number of molecules per time unit for ρ (k_4 is a concentration per time unit).

To introduce the stochastic formulation consider the state variables $n_1(t)$, $n_2(t)$, $n_3(t)$ at a given time t as random variables. In particular, $n(t) = (n_1(t), n_2(t), n_3(t))^T$ is a continuous time Markov chain, assuming values in a discrete (countable) set. To completely define the stochastic process $n(t)$, we need to assign the reaction parameters c_i that identify the probabilities of reactions R_i, $i = 1, \dots, 6$, to occur in an infinitesimal time interval. More in details, the fundamental hypothesis underlying the stochastic formulation is that the probability at time t (to first order in dt) that a particular combination of the reactant molecules of R_i will react in $(t, t+dt)$ is given by $c_i dt$. Moreover, introducing the propensities a_i, $i = 1, \dots, 6$, the probability in t that a generic reaction step R_i will happen in $(t, t+dt)$ in the reaction volume V is given by

$$a_i dt = h_i c_i dt, \tag{5}$$

where h_i is a function of reactant cell/molecule copy numbers $n_j(t)$ available for one occurrence of R_i at time t. So, the probabilities $a_i dt$ completely identify the stochastic process $n(t) = (n_1(t), n_2(t), n_3(t))^T$ and its grand probability function $P(\eta_1, \eta_2, \eta_3; t)$, which gives the probability of being in the state $(n_1(t) = \eta_1,\ n_2(t) = \eta_2,\ n_3(t) = \eta_3)$ at time t in the reaction volume V.

The stochastic formulation of the reaction system (1) consists in the chemical master equation that rules the dynamical behaviour of $P(\eta_1, \eta_2, \eta_3; t)$. The choice of h_i, $i = 1, \dots, 6$, is a modelling problem similar to the choice of the functions f_i for the fluxes of the deterministic approach, and again different (kinetic) laws can be adopted to identify such functions. In particular, we choose for h_i the same function types adopted for f_i, but expressing now h_i in terms of cell/molecule copy numbers. Therefore, we assume the following expressions for the propensities a_i:

$$\begin{array}{l} a_1 = c_1 n_1,\ a_2 = c_2 n_1,\ a_3 = c_3 n_2,\ a_6 = c_6, \\ a_4 = c_4 n_3/(H_4 + n_3),\ a_5 = c_5 n_1 n_3/(H_5 + n_3). \end{array} \tag{6}$$

Denoting by δ_i the i-th column of S and by $\eta = (\eta_1, \eta_2, \eta_3)^T$ the current value of $n(t)$, the CME is given by

$$\frac{\partial P(\eta; t)}{\partial t} = -\sum_{i=1}^{6} \left(a_i(\eta) P(\eta; t) + a_i(\eta - \delta_i) P(\eta - \delta_i; t) \right). \tag{7}$$

The CME given in (7) cannot be solved either analytically or numerically, because of the combinatorial explosion of the possible state values. However, there exist exact (directly derived from the fundamental hypothesis (5)) or approximated methods for simulating the time behaviour of single realizations of the stochastic process $n(t)$. For instance, the exact algorithm proposed in Gillespie (1976) or the τ-leap approximation proposed by the same author in Gillespie (2001).

Because of the aforementioned *curse of dimensionality*, typical of CMEs, one usually resorts to inferring information on the stochastic process by computing first- and second-order moments, exploiting a moment closure technique in order to write the moment equations in closed form, see Singh and Hespanha (2011). Within this framework, it can be shown, see van Kampen (2007), that by applying the first-order approximation to the nonlinear propensities, the first-order moment obeys to

$$\frac{d\mathrm{E}\{n(t)\}}{dt} = S a \left(\mathrm{E}\{n(t)\} \right), \tag{8}$$

so that, in our case, we obtain

$$\begin{array}{l} \dfrac{d\mathrm{E}\{n_1\}}{dt} = (c_1 - c_2)\mathrm{E}\{n_1\} - c_5 \mathrm{E}\{n_1\} \dfrac{\mathrm{E}\{n_3\}}{H_5 + \mathrm{E}\{n_3\}}, \\ \dfrac{d\mathrm{E}\{n_2\}}{dt} = c_2 \mathrm{E}\{n_1\} - c_3 \mathrm{E}\{n_2\} + c_5 \mathrm{E}\{n_1\} \dfrac{\mathrm{E}\{n_3\}}{H_5 + \mathrm{E}\{n_3\}}, \\ \dfrac{d\mathrm{E}\{n_3\}}{dt} = -c_4 \dfrac{\mathrm{E}\{n_3\}}{H_4 + \mathrm{E}\{n_3\}} - c_5 \mathrm{E}\{n_1\} \dfrac{\mathrm{E}\{n_3\}}{H_5 + \mathrm{E}\{n_3\}} + c_6. \end{array} \tag{9}$$

It is worth to notice that only two propensities are nonlinear and that system (4) has the same structure of system (9), meaning that the deterministic model is actually an approximation of the 1-st order moment of the stochastic formulation provided that the same set of the model parameters is chosen, namely:

$$c_i = k_i,\ i = 1,2,3,5,\ c_4 = \rho,\ c_6 = r,\ H_i = M_i,\ i = 4,5. \tag{10}$$

The parameter setting of both formulations can be related to the parameter estimates given in Drexler et al. (2019). Indeed, the deterministic model (4) can be rewritten in terms of the physically measurable quantities considered in that paper, i.e. tumour volumes or the drug level, simply scaling the model parameters by means of suitable factors. The state variables considered in Drexler et al. (2019) are x_1, the proliferating tumour volume (mm^3), x_2, the dead tumour volume (mm^3), x_3, the drug level (mg of drug per kg of body weight). Such variables can be expressed in terms of cells/molecules copy numbers, i.e.

$$x_1 = n_1 V_c,\ x_2 = n_2 V_c,\ x_3 = n_3 \alpha, \tag{11}$$

where V_c is the average cell volume of the considered tumour cell line and $\alpha = m/M$, where m is the molecular mass of the drug and M is the body mass of the patient. Substituting the relations (11) into the deterministic dynamical system (4), we can easily obtain the model equations given in Drexler et al. (2019), below reported with the same notation for the ease of the reader:

$$\begin{array}{rcl} \dot{x}_1 &=& (a - n)x_1 - b x_1 \dfrac{x_3}{ED_{50} + x_3}, \\ \dot{x}_2 &=& n x_1 - w x_2 + b x_1 \dfrac{x_3}{ED_{50} + x_3}, \\ \dot{x}_3 &=& -c \dfrac{x_3}{K_B + x_3} - b_k x_1 \dfrac{x_3}{ED_{50} + x_3} + u, \end{array} \tag{12}$$

where the following relations exist between the model parameters of the two formulations:

$$\begin{array}{l} a = k_1,\ n = k_2,\ \omega = k_3,\ c = \alpha\rho,\ b = k_5, \\ b_k = (\alpha/V_c) k_5,\ K_B = \alpha M_4,\ ED_{50} = \alpha M_5,\ u = \alpha r. \end{array} \tag{13}$$

The stochastic model (7) behavior has been compared to the deterministic ODE system (4). The model parameters in Eqs. (4) are set according to relations (10), (13) and to the nominal values of the parameters given in Drexler et al. (2019) (related to breast cancer cells in mice, treated with Pegylated Liposomal Doxorubicin drug). The cell volume V_c is fixed to $1.76 \cdot 10^{-6}$ mm^3 according to Wagner et al. (2011). The coefficient α is computed according to the relation $\alpha = V_c b_k / b$. So we set $\alpha = 6.5 \cdot 10^{-12}$ mg/kg. The

administration rates c_6 and r are set to the same constant value that has been chosen in the interval $(\beta\rho, \rho)$, where β is given by Eq. (23). Note that the chosen values of the model parameters and of the constant administration rate guarantee the existence of a unique asymptotically stable equilibrium (see Figure 1 of Section 3).

Regards to the stochastic simulation, the random paths are obtained exploiting the τ-leap simulation algorithm (see Gillespie (2001)). Results (not reported here) reveal that the first-order approximation very well resemble the first-order moment dynamics, and that the impact of noise fluctuations seems negligible according to the chosen parameter values and to the tumour dimension.

3. QUALITATIVE ANALYSIS OF THE MODEL

In this section we analyze the equilibrium points of the time-invariant deterministic model, i.e. of system (4) with $r(t) = \bar{r}$, and their stability properties. Note that all the reported results are obviously valid for the dynamical system (9), related to the 1-st order moment approximation of the stochastic formulation, but also for the physically relevant formulation given in Drexler et al. (2019), after a proper parameter scaling.

We first prove that the solution of the ODE (4) is always non-negative for non-negative initial conditions $n(0) \geq 0$ and non-negative input $r \geq 0$. To this end, consider the n_3 dynamics: it could become negative if, and only if, there exists a time instant $\bar{t}$ such that $n_3(\bar{t}) = 0$ with $\dot{n}_3(\bar{t}) < 0$. But this is not possible since, if $n_3(\bar{t}) = 0$, then

$$\dot{n}_3(\bar{t}) = -\rho\frac{n_3(\bar{t})}{M_4+n_3(\bar{t})} - k_5 n_1(\bar{t})\frac{n_3(\bar{t})}{M_5+n_3(\bar{t})} + r = r \geq 0. \quad (14)$$

Analogously, n_1 would become negative if, and only if, there exists a time instant $\bar{t}$ such that $n_1(\bar{t}) = 0$ with $\dot{n}_1(\bar{t}) < 0$. But this is not possible since, if $n_1(\bar{t}) = 0$, then

$$\dot{n}_1(\bar{t}) = (k_1 - k_2)n_1(\bar{t}) - k_5 n_1(\bar{t})\frac{n_3(\bar{t})}{M_5 + n_3(\bar{t})} = 0 \quad (15)$$

and, finally, n_2 would become negative if, and only if, there exists a time instant $\bar{t}$ such that $n_2(\bar{t}) = 0$ with $\dot{n}_2(\bar{t}) < 0$. But this is not possible since, if $n_2(\bar{t}) = 0$, then

$$\dot{n}_2(\bar{t}) = k_2 n_1(\bar{t}) + k_5 n_1(\bar{t})\frac{n_3(\bar{t})}{M_5 + n_3(\bar{t})} \geq 0, \quad (16)$$

because we have previously shown that $n_1, n_3 \geq 0$.

Let us now find the equilibria of the time-invariant system. Denoting by $E = (n_1^*, n_2^*, n_3^*)$ a generic equilibrium point of system (4) with $r(t) = \bar{r}$, we have that E must satisfy the following algebraic equations coming from $\dot{n} = 0$:

$$\begin{aligned} &\left(k_1 - k_2 - k_5\frac{n_3^*}{M_5 + n_3^*}\right) n_1^* = 0, \\ &k_2 n_1^* - k_3 n_2^* + k_5 n_1^*\frac{n_3^*}{M_5 + n_3^*} = 0, \\ &-\rho\frac{n_3^*}{M_4 + n_3^*} - k_5 n_1^*\frac{n_3^*}{M_5 + n_3^*} + \bar{r} = 0. \end{aligned} \quad (17)$$

From the first equation of the algebraic system (17) we get

$$i)\ n_1^* = 0, \quad \text{or} \quad ii)\ k_5\frac{n_3^*}{M_5 + n_3^*} = k_1 - k_2. \quad (18)$$

By substituting $i)$ in the remaining algebraic equations of system (17), we get the first equilibrium point

$$E_1 = \left(0,\, 0,\, M_4\frac{\bar{r}}{\rho - \bar{r}}\right), \quad (19)$$

that is non-negative, and then physically relevant, only under the condition on the administration rate

$$\bar{r} < \rho. \quad (20)$$

Conversely, from $ii)$ we obtain

$$n_3^* = \frac{M_5(k_1 - k_2)}{k_5 - k_1 + k_2}, \quad (21)$$

which is strictly positive only when $k_1 - k_2 > 0$ and $k_5 > k_1 - k_2$ or identically zero when $k_1 = k_2$. So, under the parameter conditions $k_1 > k_2$, $k_5 > k_1 - k_2$, substituting the expression of n_3^* given by (21) in the last two equations of (17), we obtain the second equilibrium point

$$E_2 = \left(\frac{\bar{r} - \beta\rho}{k_1 - k_2},\, \frac{k_1}{k_3}\frac{\bar{r} - \beta\rho}{k_1 - k_2},\, \frac{M_5(k_1 - k_2)}{k_5 - k_1 + k_2}\right), \quad (22)$$

$$\text{where} \quad \beta = \frac{M_5(k_1 - k_2)}{M_4(k_5 - k_1 + k_2) + M_5(k_1 - k_2)}, \quad (23)$$

that is non-negative under the further condition on the administration rate

$$\bar{r} \geq \beta\rho. \quad (24)$$

We note that the conditions on the model parameters required for the existence of E_2 imply $\beta < 1$, see Eq. (23). We also notice that, when $\bar{r} = \beta\rho$, it is $E_1 = E_2$ (this equivalence can be easily verified by substituting $\bar{r} = \beta\rho$ in both equilibria (19) and (22)).

Finally, under the singular parameter condition $k_1 = k_2$ we have $n_3^* = 0$ from Eq. (21), and then, from the last two equations of system (17), we get the following family of equilibria

$$f = \left\{\left(z,\, \frac{k_1}{k_3}z,\, 0\right) : z \geq 0\right\}, \quad \text{with} \quad \bar{r} = 0. \quad (25)$$

Table 1 summarizes these results. Note that, in case $k_1 > k_2$ and $k_5 > k_1 - k_2$, the interval $(\beta\rho, \rho)$ is well defined since it is $\beta < 1$.

Region of the param space		Administration rate	Equilibria
$k_1 < k_2$		$0 \leq \bar{r} < \rho$	E_1
		$\bar{r} \geq \rho$	$\nexists$
$k_1 = k_2$		$\bar{r} = 0$	$f(\supset \{E_1\})$
		$0 < \bar{r} < \rho$	E_1
		$\bar{r} \geq \rho$	$\nexists$
$k_1 > k_2$	$k_5 \leq k_1 - k_2$	$0 \leq \bar{r} < \rho$	E_1
		$\bar{r} \geq \rho$	$\nexists$
	$k_5 > k_1 - k_2$	$0 \leq \bar{r} < \beta\rho$	E_1
		$\bar{r} = \beta\rho$	$E_1 \equiv E_2$
		$\beta\rho < \bar{r} < \rho$	E_1, E_2
		$\bar{r} \geq \rho$	E_2

Table 1. Existence of the equilibria of (4).

3.1 Local stability of E_1

The stability properties of E_1 are summarized by Theorem 1. We remind that the existence of E_1 does not depend on the values of the model parameters but depends on the size of the administration rate, i.e. $\bar{r} \in [0, \rho)$.

Theorem 1. Regards to E_1 stability, it is:

(1) if $k_1 < k_2$, then E_1 is locally asymptotically stable $\forall \bar{r} \in [0, \rho)$;
(2) if $k_1 = k_2$, then E_1 is locally asymptotically stable $\forall \bar{r} \in (0, \rho)$;
(3) if $k_1 > k_2$, then
   (a) if $k_5 \leq k_1 - k_2$, then E_1 is unstable $\forall \bar{r} \in [0, \rho)$;
   (b) if $k_5 > k_1 - k_2$, then E_1 is unstable for $\bar{r} \in [0, \beta\rho)$ while is locally asymptotically stable for $\bar{r} \in (\beta\rho, \rho)$.

Proof 1. The proof of Theorem 1 is given by computing the Jacobian of the time-invariant system for the equilibrium point E_1 and then studying the sign of the related eigenvalues. So, from system (4) with $r(t) = \bar{r}$, after computations, we obtain the following eigenvalues

$$\begin{aligned} \lambda_1 &= k_1 - k_2 - k_5 \frac{M_4 \bar{r}}{M_5(\rho - \bar{r}) + M_4 \bar{r}}, \\ \lambda_2 &= -k_3, \qquad \lambda_3 = -\frac{(\rho - \bar{r})^2}{\rho M_4}. \end{aligned} \tag{26}$$

Eigenvalues λ_2, λ_3 are strictly negative, since it is required $\bar{r} \in [0, \rho)$ for the existence of E_1. So, the local stability of E_1 only depends on the sign of λ_1. Points (1) and (2) of the theorem can be easily proved noting that: if $k_1 < k_2$ then it is $\lambda_1 < 0$ for any administration rate in $[0, \rho)$; otherwise, if $k_1 = k_2$ then it is $\lambda_1 < 0$ for $\bar{r} \in (0, \rho)$.

In order to prove point (3), rewrite the first eigenvalue as

$$\lambda_1 = \frac{M_5(\rho - \bar{r})(k_1 - k_2) - (k_5 - k_1 + k_2) M_4 \bar{r}}{M_5(\rho - \bar{r}) + M_4 \bar{r}}. \tag{27}$$

The denominator is straightforwardly positive. Moreover, when $k_1 > k_2$, the first term of the numerator is also positive. This means that, in case $k_5 \leq k_1 - k_2$, it is $\lambda_1 > 0$ for any administration rate in $[0, \rho)$, so proving point (3a). Conversely, in case $k_5 > k_1 - k_2$, we get

$$\lambda_1 > 0 \iff \bar{r} \in [0, \beta\rho), \qquad \lambda_1 < 0 \iff \bar{r} \in (\beta\rho, \rho). \tag{28}$$

Relations (28) complete the proof of point (3b).

3.2 Local stability of E_2

The stability properties of E_2 are summarized by Theorem 2. We recall that E_2 can exist only in the region of the parameter space identified by $k_1 > k_2$, $k_5 > k_1 - k_2$, depending on the value of the administration rate, i.e. when $\bar{r} \geq \beta\rho$, where β is given by Eq. (23). So, the following result is valid only in the region given above and shows how the stability of E_2 depends on $\bar{r}$.

Theorem 2. The local stability of E_2 only depends on the value of the constant administration rate $\bar{r}$. In particular:

$$E_2 \ \text{ is } \ \text{unstable } \ \forall \bar{r} > \beta\rho. \tag{29}$$

Proof 2. The proof of Theorem 2 is given by computing the Jacobian at the equilibrium point E_2. After computations, the characteristic polynomial of $J|_{E_2}$ is given by:

$$\begin{aligned} p_{J|_{E_2}}(\lambda) = \Bigg(\lambda^2 &- \frac{(k_5 - k_1 + k_2)^2}{k_5 M_5 (k_1 - k_2)} (\gamma\rho - \bar{r}) \lambda \\ &- \frac{(k_5 - k_1 + k_2)^2}{k_5 M_5} (\bar{r} - \beta\rho) \Bigg) (\lambda + k_3). \end{aligned} \tag{30}$$

$$\text{where} \quad \gamma = \frac{M_5(M_5 - M_4)(k_1 - k_2)^2}{(M_4(k_5 - k_1 + k_2) + M_5(k_1 - k_2))^2}. \tag{31}$$

The eigenvalues $\lambda_1, \lambda_2, \lambda_3$ of $J|_{E_2}$ are the roots of $p_{J|_{E_2}}(\lambda)$, i.e. they satisfy the equation

$$p_{J|_{E_2}}(\lambda) = (\lambda - \lambda_1)(\lambda - \lambda_2)(\lambda - \lambda_3) = 0. \tag{32}$$

So, comparing Eqs. (30) and (32) we easily get

$$\begin{aligned} \lambda_1 + \lambda_2 &= \frac{(k_5 - k_1 + k_2)^2}{k_5 M_5 (k_1 - k_2)} (\gamma\rho - \bar{r}), \\ \lambda_1 \lambda_2 &= -\frac{(k_5 - k_1 + k_2)^2}{k_5 M_5} (\bar{r} - \beta\rho), \quad \lambda_3 = -k_3. \end{aligned} \tag{33}$$

At this point, it is important to note that the conditions $k_1 > k_2$ and $k_5 > k_1 - k_2$, required for the existence of E_2, imply the following inequalities:

$$\gamma < \beta^2 < \beta < 1. \tag{34}$$

Since E_2 is defined only when $\bar{r} \geq \beta\rho$, (34) guarantees also that $\gamma\rho - \bar{r} < 0$. In summary, sum and product of the first two eigenvalues given by Eq. (33) are characterized by

$$\lambda_1 + \lambda_2 < 0, \quad \lambda_1 \lambda_2 \leq 0. \tag{35}$$

The second inequality given above implies that one eigenvalue is always negative while the other one is non-negative. So, assuming it is $\lambda_2 < 0$, from the expression of $\lambda_1 \lambda_2$ given by Eq. (33), we have that:

$$\lambda_1 > 0 \ \text{ for any } \ \bar{r} > \beta\rho, \tag{36}$$

which completes the proof of the theorem.

4. DISCUSSION

The qualitative behavior derived for the deterministic model (4) can be directly applied to system (9), which approximates the dynamics of the 1-st order moment of the stochastic formulation, and to the deterministic system given in Drexler et al. (2019), by suitably scaling the model parameters using respectively (10) and (13).

Remark 1. With regard to the model in Drexler et al. (2019), we need to warn the reader of some little differences due to the presence of two different rate constants, i.e. b and b_k, emerging from the drug action rates of $\dot{x}_i$, $i = 1, 2, 3$. In more detail, the constants b_k (in $\dot{x}_3$) and b (in $\dot{x}_1$, $\dot{x}_2$) have different dimensions and values and they appear when we transform system (3) into the equivalent formulation in terms of the more physically relevant variables x_j, $j = 1, 2, 3$ (see Section 2). So, in case of the model given in Drexler et al. (2019), the parameter k_5, distinguishing between the different cases in the equilibrium framework of Table 1 and between the different stability properties of E_1 in Theorem 1, must be substituted by the parameter b (and not by b_k). Moreover, the expressions of n_1^* and n_2^* of E_2 must be suitably multiplied by the scaling factor b/b_k.

Figure 1 is given in order to collect and summarize the existence and stability properties. As a preliminary comment, we stress that E_2 is of no interest, since there is no model parameter combination (including the constant control law) providing asymptotic stability. On the other hand, with regards to the E_1, it consists of a healthy condition where the tumour is completely eradicated under a baseline infusion, and the qualitative behavior analysis has shown that it can be stabilized by means of a constant control. We can formally divide the parameter space in three regions (see the upper panel in Figure 1). Region S_1 provides asymptotic stability for any value of the control

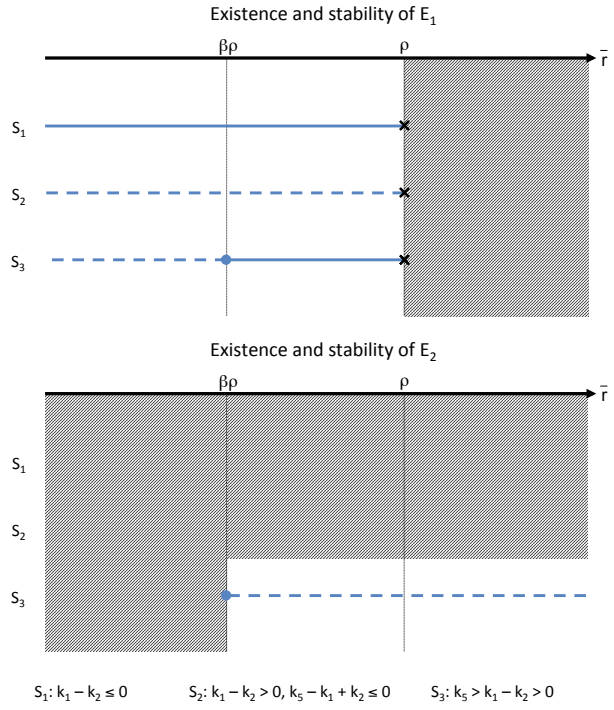

Fig. 1. Existence and stability of E_1, upper panel, and E_2, lower panel, as functions of $\bar{r}$. Shaded regions and black crosses evidence where the equilibria do not exist. Solid blue line: stability; dashed blue line: instability; blue points: nothing can be said according to the linearization.

infusion $\overline{r} < \rho$. This is an optimistic case where physiological cell necrosis is able to defeat tumour proliferation even without a control action. Reasonably this case may be associated to the initial spreading of the tumour, where an exogenous chemotherapy could be of some help just in enhancing the tumour eradication. For higher values of $\overline{r} > \rho$ the existence of the equilibrium point is lost because there would be an unbounded accumulation of the drug (with a corresponding eradication of tumour), eventually leading to a loss of meaningfulness of the model.

Region S_2, instead, refers to a case where there is no set of the control parameter ensuring stability. The strength of the positive net balance between tumour proliferation and necrosis is too high with respect to the strength of the exogenous chemotherapy, and the drug is not able to stabilize the growth, no matter what is the drug administration rate. In this case, of course, chemotherapy would provide only side effects, and would not be recommended.

Finally, region S_3 investigation tells us that, for a sufficiently high rate of drug administration, the equilibrium point E_1 can be stabilized: in this case a tradeoff between drug-induced tumour eradication and chemotherapy side effects could be found getting closer to lower bound of the stability range, i.e. $\overline{r} \to \beta\rho$.

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