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GOMPERTZ MODEL WITH DELAYS AND TREATMENT: MATHEMATICAL ANALYSIS

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ABSTRACT. In this paper we study the delayed Gompertz model, as a typical model of tumor growth, with a term describing external interference that can reflect a treatment, e.g. chemotherapy. We mainly consider two types of delayed models, the one with the delay introduced in the per capita growth rate (we call it the single delayed model) and the other with the delay introduced in the net growth rate (the double delayed model). We focus on stability and possible stability switches with increasing delay for the positive steady state. Moreover, we study a Hopf bifurcation, including stability of arising periodic solutions for a constant treatment. The analytical results are extended by numerical simulations for a pharmacokinetic treatment function.

1. **Introduction.** For many processes observed in nature, like a single cellular population growth, often only the data for the population size are available. Hence, it is reasonable to model the dynamics using one equation in such a case. On the other hand, we observe oscillatory or even periodic dynamics quite frequently, compare [14]. Therefore, the approach of ordinary differential equations (ODEs) is not proper for the description of that type of phenomena, since solutions of any single ODE are always monotonic. From the theory of delay differential equations (DDEs), it is well known that a time delay introduced into ODE can lead to destabilization of the stable steady state. Moreover, typically when the delay crosses some threshold, a Hopf bifurcation occurs and periodic solutions arise. Hence, a single DDE can be successfully used in modeling of phenomena we discuss. In that context we can analyze an important problem of stability of arising periodic orbits, or equivalently, we can ask about a direction of the Hopf bifurcation.

On the other hand, an external interference into the considered system, such as a drug administration, is also usually periodic. Hence, the next important question arises. We can ask if there is some synergy between the inner periodic dynamics of the model reflected by periodic solutions of the equation and the periodic drug administration. Is it possible to choose the period of drug administration to eliminate oscillations or can these two oscillatory processes be in resonance causing a large increase of the oscillations amplitude?

Since the Gompertz model is frequently used in the tumor growth modeling [9, 5, 4, 13, 12, 6, 16, 18], we decided to investigate these problems for the delayed Gompertz model with an additional term reflecting a treatment. Similar analysis was done for the

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logistic equation, for which not only a pharmacokinetic treatment [15] but also an impulsive treatment was studied [7].

The paper is organized as follows. In the next subsection we introduce the Gompertz model and review some basic facts about it. In Section 2 we prove some properties of the delayed Gompetrz model with a treatment function. Next, in Section 3 we investigate the existence of a Hopf bifurcation and we prove that it is supercritical when occurs. Finally, in Section 4 we numerically investigate the behavior of solutions of the models for a pharamconkinetic treatment function.

1.1. **Gompertz model.** In the Gompertz model, [8], the per capita growth of a population is described by a logarithmic function. From the analytical point of view it is convenient to extend this equation for non-positive values. Hence, we consider

$$\dot{V}(s) = rV(s)f\left(\frac{V(s)}{H}\right), \tag{1.1}$$

where

$$f(x) = \begin{cases} -\ln x & x > 0, \\ 0 & x \leq 0, \end{cases} \tag{1.2}$$

with an initial condition $V(0) = V_0 > 0$. In the model (1.1), the variable $V(s)$ denotes the number of cells per volume unit at time s and H is the maximal possible tumor size (given by the maximal number of cells per volume unit) that can be achieved without an external supply of nutrients, while r denotes the maximal reproduction rate of the tumor. It is obvious that for any positive $V_0 < H$ solutions of Eq. (1.1) increase to the maximal size H.

Remark 1. Notice that the Gompertz model is usually used to describe the size of population and the variable V describes the number of cells or their total volume. However, to avoid the problems with units in the presented analysis we rescale variables through an appropriate reference volume obtaining mathematically the same but physically undimensional equation.

1.2. **Gompertz model with delays.** In this paper, we would like to compare the dynamics of solutions of the Gompertz model with delays and a treatment function introduced into the system. In general, the time delay can be introduced into the model in two different biologically motivated ways: in the classical population approach it is introduced in the per capita growth rate, while in the cellular approach in the net growth; we discussed this problem in [17] in more details. Moreover, generalizing these two ideas we proposed

$$\dot{V}(s) = rV(s-\tau_1)f\left(\frac{V(s-\tau_2)}{H}\right), \tag{1.3}$$

that is the Gompertz model with two delays. Existence and the type of a Hopf bifurcation for Eq. (1.3) were investigated analytically and numerically in [17]. Notice that for $\tau_1 = 0$ we have the single delayed Gompertz equation

$$\dot{V}(s) = rV(s)f\left(\frac{V(s-\tau)}{H}\right), \tag{1.4}$$

which is similar to the Hutchinson equation [11] (the single delayed logistic equation), while for $\tau_1 = \tau_2$ we have

$$\dot{V}(s) = rV(s-\tau)f\left(\frac{V(s-\tau)}{H}\right), \tag{1.5}$$

which is now the Gompertz model with the double delay (compare the double delayed logistic equation proposed in [19]).

Biological interpretation of the parameter τ can differ, however it strongly depends on the type of phenomena described by the model. For example in the context of the tumor growth Eq. (1.4) appears as one of the equations in the family of angiogenesis models considered in [5] or [16]. In that case, the time delay represents the time lag in the process of tumor growth/regression due to the time needed for the cells to recognize and adapt to changes.

In this paper, we would like to discuss the existence of the same phenomena but for the models including a general treatment function, $T(s) > 0$. Hence, we study the models with the term $T(s)V(s)$ introduced into the right-hand side. However, in our analysis we limit ourselves to the case of the single and double delayed Gompertz model, that is we study

$$\dot{V}(s) = rV(s-\tau_1)f\left(\frac{V(s-\tau_2)}{H}\right) - T(s)V(s), \tag{1.6}$$

where $\tau_1 = 0$ and $\tau_2 = \tau > 0$ or $\tau_1 = \tau_2 = \tau > 0$, respectively. Moreover, for simplicity we make the change of variables $t = \frac{s}{\tau}$ and $x(t) = \frac{V(s)}{H}$ obtaining

$$\dot{x}(t) = r\tau F(x(t), x(t-1)) - \tau S(t)x(t), \tag{1.7}$$

where $S(t) = T(s)$ and $F(x(t), x(t-1)) = x(t)f(x(t-1))$ for the single delayed equation, while $F(x(t), x(t-1)) = x(t-1)f(x(t-1))$ for the double delayed one.

Clearly, for the model (1.7), in the case of the single and double delayed equations, we define the initial condition $x(t) = \varphi(t)$ for $t \in [-1, 0]$ and $\varphi \in \mathbf{C}([-1, 0]; \mathbb{R}_{\geq 0})$.

Mathematical analysis of the model (1.3), or (1.7) for $S = 0$, equivalently, including the global existence and uniqueness of solutions, as well as the discussion on non-negativity/lack of non-negativity, was performed in [17]. For both the single and double delayed Gompertz equations the right-hand side is properly defined and continuous for all $V \in \mathbb{R}$ as a consequence of the fact that for the Gompertz type models, there exists the limit

$$\lim_{V \to 0^+} V \ln V = 0. \tag{1.8}$$

This also allows us to consider $\hat{V} = 0$ as a steady state of the model. Thus, both the single and double delayed logistic equations have two steady states: the trivial one $\hat{V} = 0$ and the positive one $\bar{V} = H$. In [17] it was shown that the trivial steady state is unstable independently of the magnitude of delays, while the stability of the positive steady state strongly depends on the bifurcation parameter, that is τ_2. Moreover, Piotrowska&Foryś investigated analytically and numerically the type of occurring Hopf bifurcations for all considered Gompertz type equations, see [17] for details.

2. Basic properties of the Gompertz model with delays and a treatment function.

In this paper, we study two versions of the model (1.7)

- the single delayed Gompetrz model with a treatment function that reads

$$\dot{x}(t) = r\tau x(t) f\left(x(t-1)\right) - \tau S(t)x(t); \tag{2.1}$$

- the double delayed Gompetrz model with a treatment function that reads

$$\dot{x}(t) = r\tau x(t-1) f\left(x(t-1)\right) - \tau S(t)x(t). \tag{2.2}$$

In the following section we study the basic properties of the models (1.7), (2.1) and (2.2). The existence and uniqueness results are valid for a general Eq. (1.6).

Proposition 1. *For any non-negative initial function φ solutions of Eq. (1.6) exist globally and are unique.*

Proof. Local existence and uniqueness follow from the standard theory of DDEs (compare e.g. [10]). The global existence can be easily seen by the step method. □

Let us consider non-negativity of solutions. Notice that although the non-negativity property needs not to be preserved by the solution, the definition 1.2 of the function f implies that if $x(t_1) < 0$ for some $t_1 > 0$, then $x(t) \equiv x(t_1 + 1)$ for any $t \geq t_1 + 1$. Moreover, although Eqs. (2.1) and (2.2) are both the delayed Gompertz equations, the non-negativity results are different for them.

Proposition 2.
- *Solutions of Eq.* (2.1) *are non-negative for non-negative initial data.*
- *If S is bounded below from 0, $S(t) \geq \varepsilon > 0$ for all $t \geq 0$, and $\frac{r}{\mathrm{e}\varepsilon} \leq 1$, then solutions of Eq.* (2.2) *are non-negative for any initial function $\varphi(t) \in [0, 1]$, $t \in [-1, 0]$. On the other hand, there exist non-negative initial data for which solutions of Eq.* (2.2) *take negative values.*

Proof. Non-negativity of solutions of Eq. (2.1) is obvious due to the form of the right-hand side. The possible negativity for Eq. (2.2) is an immediate consequence of theorems proved in [1].

For Eq. (2.2) with $S(t) \geq \varepsilon$ we have

$$\dot{x}(t) \leq r\tau x(t-1)f(x(t-1)) - \tau\varepsilon x(t).$$

Furthermore, due to the properties of the function $g(x) = -x \ln x$ which has its maximum $g_{\max} = \frac{1}{\mathrm{e}}$ at $t = \frac{1}{\mathrm{e}}$, we obtain

$$\dot{x}(t) \leq \frac{r\tau}{\mathrm{e}} - \tau\varepsilon x(t).$$

Considering the equation $\dot{z}(t) = \frac{r\tau}{\mathrm{e}} - \tau\varepsilon z(t)$ with $z(0) = \varphi(0)$ we see that $z(t) \to \frac{r}{\mathrm{e}\varepsilon} \leq 1$. The theory of differential inequalities yields $x(t) \leq z(t) \leq 1$ for all $t \geq 0$. Now it is easy to see that for $x(t) \in [0, 1]$ we have $\dot{x}(t) \geq -S(t)x(t)$ which implies non-negativity. □

It turns out that the dynamics of Eq. (2.1) is quite simple and in fact does not differ from the dynamic of the single delayed Gompertz model, at least in the case of the constant treatment function. Thus, we describe it briefly in the next subsection. On the other hand, the dynamics of the double delayed Gompertz model with a treatment function is more complicated. For the constant treatment a Hopf bifurcation can occur. We study the bifurcation type in the next Section.

2.1. **The single delayed Gompertz model with treatment.** Here, we investigate properties of the Gompertz model with the single delay and the treatment function, that is Eq. (2.1). In fact, this equation can be easily transformed to the linear one introducing a new variable $y(t) = \ln x(t)$. Due to Proposition 1 solutions of Eq. (2.1) are positive (for $\varphi(0) > 0$) and this change of the variable is well defined. In the new variable Eq. (2.1) reads

$$\dot{y}(t) = -r\tau y(t-1) - \tau S(t). \tag{2.3}$$

As Eq. (2.3) is linear it is much simpler to analyze, even for non-constant function S. Having a solution $y(t)$ of Eq. (2.3) we can recover the solution of Eq. (2.1) writing $x(t) = \exp(y(t))$.

In the case of the constant treatment, namely when $S(t)$ is a constant, it turns out that the behavior of solutions of Eq. (2.3) (and so as solutions of Eq. (2.1)) is basically the same as for the Gompertz model with the single delay. If $S(t) \equiv S$ is constant, a simple shift of the variable $z = y + \frac{S}{r}$ leads to a linear equation

$$\dot{z}(t) = -r\tau z(t-1). \tag{2.4}$$

We summarize the knowledge about Eq. (2.4) and interpret it within the context of Eq. (2.1).

Proposition 3. *Let $x(t)$ be a solution of Eq. (2.1). Then*

(i) *if $r\tau < \pi/2$, then for any positive initial function*

$$\lim_{t\to+\infty} x(t) = \mathrm{e}^{-S/r};$$

(ii) *if $r\tau = \pi/2$, then for any positive initial function there exist positive real constants α, β such that*

$$\lim_{t\to+\infty}\left(x(t) - \mathrm{e}^{-S/r}\exp\left(\alpha\sin\left(\frac{\pi}{2}s\right) + \beta\cos\left(\frac{\pi}{2}s\right)\right)\right) = 0;$$

(iii) *if $r\tau > \pi/2$, then for any positive initial functions there exist positive real constants α, β, ω, η such that*

$$\lim_{t\to+\infty}\left((\ln x(t))\,\mathrm{e}^{-\omega t} - \alpha\sin\left(\eta t\right) - \beta\cos\left(\eta t\right)\right) = 0.$$

Moreover, $\lambda = \omega \pm i\eta$ is the solution of the characteristic equation $\lambda + r\tau\,\mathrm{e}^{-\lambda} = 0$ with the greatest real part.

Proof. The theorem is a simple consequence of the standard theory of DDEs and the properties of the characteristic equation $\lambda + r\tau\,\mathrm{e}^{-\lambda} = 0$, for details see e.g. [10]. □

3. **A Hopf bifurcation for the double delayed Gompertz model with a constant treatment.** Now, we study the possible stability switch with increasing τ for a positive steady state of Eq. (2.2).

Theorem 3.1. *The positive steady state of Eq. (2.2) has the form $\bar{x} = \mathrm{e}^{-S/r}$. The following statements are true:*

(i) *If $r < 2S$, then the positive steady state is locally asymptotically stable for all $\tau > 0$.*

(ii) *If $r > 2S$, then the positive steady state is stable for $0 < \tau < \tau_0$ and unstable for $\tau > \tau_0$, where $\tau_0 = \dfrac{\arccos\left(\frac{S}{S-r}\right)}{\sqrt{(r-S)^2 + S^2}}$. At the point τ_0 the supercritical Hopf bifurcation occurs.*

Proof. It is easy to check that $\bar{x} = \mathrm{e}^{-S/r}$ is the unique positive steady state of Eq. (2.2).

We change the variable $y = x - \bar{x}$ to move the positive steady state $\bar{x}$ to 0. Hence, Eq. (2.2) reads

$$\dot{y} = \tau\Big(r(y(t-1)+\bar{x})f\left(y(t-1)+\bar{x}\right) - S\left(y(t)+\bar{x}\right)\Big). \tag{3.1}$$

Clearly, the linear operator for Eq. (3.1) in the functional form reads

$$L(y_t) = -\tau(r-S)y_t(-1) - \tau S\,y_t(0), \tag{3.2}$$

while the non-linear part reads

$$G(y_t) = \tau\left(y_t(-1)+\bar{x}\right)\Big(rf(y_t(-1)+\bar{x})\Big) + \tau(r-S)y_t(-1), \tag{3.3}$$

where $y_t \in C = \mathbf{C}([-1,0],\mathbb{R})$. Next, calculating the characteristic function for Eq. (3.1) around the steady state $\bar{y} = 0$ we obtain

$$\Delta(\lambda,\tau) = \lambda + \tau S + a_1\tau\,\mathrm{e}^{-\lambda}, \tag{3.4}$$

where $a_1 = r - S$. From the classical theory of DDEs (compare e.g. [10]) it is know that if $|a_1| < S$, then the positive steady state is locally asymptotically stable. It can be easily seen that if $a_1 = r - S < 0$, then $|a_1| < S$. Thus, if $r < 2S$, then $|a_1| < S$ and the part (i) is proved.

On the other hand, if $r > 2S$, then at $\tau_0 = \dfrac{\arccos\left(\frac{S}{S-r}\right)}{\sqrt{(r-S)^2+S^2}}$ the characteristic equation (3.4) has purely imaginary roots $\pm i\omega_0$, where

$$\omega_0 = \arccos\left(\frac{S}{S-r}\right), \tag{3.5}$$

and a Hopf bifurcation occurs. To investigate the stability of periodic solutions we follow the Diekmann et al. approach, [3]. To check if new born periodic solutions are stable or not we need to find the sign of

$$\mu_2 = \frac{\operatorname{Re} c}{\operatorname{Re}\left(\mathbf{q}D_2\Delta(i\omega_0,\tau_0)\mathbf{p}\right)}, \tag{3.6}$$

where $\mathbf{p}$, $\mathbf{q}$ are, respectively, right and left eigenvectors of $\Delta(i\omega_0,\tau_0)$ chosen such that $\mathbf{q}D_1\Delta(i\omega_0,\tau_0)\mathbf{p} = 1$, where D_1 and D_2 denote the derivative with respect to the first (λ) and second (τ) variable, respectively, and

$$\begin{aligned} c &= c_I + c_{II} + c_{III},\\ c_I &= \frac{1}{2}\mathbf{q}D_1^3G(0,\tau_0)(\Phi,\Phi,\overline{\Phi}),\\ c_{II} &= \mathbf{q}D_1^2G(0,\tau_0)\left(\Psi_{II},\Phi\right),\\ c_{III} &= \frac{1}{2}\mathbf{q}D_1^2G(0,\tau_0)\left(\Psi_{III},\overline{\Phi}\right), \end{aligned} \tag{3.7}$$

where D_1^j, $j = 2, 3$, denotes the derivative of the jth order with respect to the first variable, G is the non-linear part defined in Eq. (3.3), $\Phi(\theta) = \mathbf{p}\exp(i\omega_0\theta)$, and

$$\begin{aligned} \Psi_{II}(\theta) &= (\Delta(0,\tau_0))^{-1}D_1^2G(0,\tau_0)(\Phi,\overline{\Phi}),\\ \Psi_{III}(\theta) &= \mathrm{e}^{2i\omega_0\theta}(\Delta(2i\omega_0,\tau_0))^{-1}D_1^2G(0,\tau_0)(\Phi,\Phi). \end{aligned}$$

The coefficient μ_2 is the third term in a Taylor expansion of the periodic solution. Hence, if $\mu_2 > 0$ and the stationary solution $\bar{y} = 0$ loses stability at $\tau = \tau_0$, then the periodic solutions appearing due to the Hopf bifurcation are stable, while for $\mu_2 < 0$ they are unstable.

Equality $\Delta(i\omega_0,\tau_0) = 0$ yields

$$\mathrm{e}^{-i\omega_0} = -\frac{1}{a_1\tau_0}(S\tau_0 + i\omega_0). \tag{3.8}$$

In the following, identity (3.8) is frequently used.

Now, we choose a suitable eigenvectors of $\Delta(i\omega_0,\tau_0)$. For simplicity we take $\mathbf{p} = 1$. Then,

$$D_1\Delta(i\omega_0,\tau_0) = 1 - a_1\tau_0\,\mathrm{e}^{-i\omega_0} = 1 + S\tau_0 + i\,\omega_0 \implies \mathbf{q} = \frac{1+S\tau_0 - i\,\omega_0}{(1+S\tau_0)^2+\omega_0^2},$$

due to (3.8). Now, we proceed to calculate the denominator of μ_2. Using (3.8) we obtain

$$D_2\Delta(i\omega_0,\tau_0) = S + a_1\,\mathrm{e}^{-i\omega_0} = -i\frac{\omega_0}{\tau_0}.$$

Hence,

$$\operatorname{Re}\left(\mathbf{q}D_2\Delta(i\omega_0,\tau_0)\mathbf{p}\right) = \operatorname{Re}\left(-\frac{i\omega_0}{\tau_0}\frac{1+S\tau_0-i\omega_0}{(1+S\tau_0)^2+\omega_0^2}\right) = -\frac{\omega_0^2}{\tau_0\left((1+S\tau_0)^2+\omega_0^2\right)} < 0. \tag{3.9}$$

It remains to determine the sign of the numerator of μ_2. We calculate the numerator of μ_2 part by part using (3.7). First, we need to calculate derivatives of the non-linear part G (3.3). Let u, v, w be any test functions from $\mathbf{C}([-1,0];\mathbb{C})$. Then

$$D_1G(\phi,\tau_0)(u) = \tau_0\Big(-r\Big(\ln(\phi(-1)+\bar{x})+1\Big)+a_1\Big)u(-1)\,,$$
$$D_1^2G(\phi,\tau_0)(u,v) = -\Big(\frac{r\tau_0}{\phi(-1)+\bar{x}}\Big)u(-1)v(-1)\,,$$
$$D_1^3G(\phi,\tau_0)(u,v,w) = \frac{r\tau_0}{(\phi(-1)+\bar{x})^2}u(-1)v(-1)w(-1)\,.$$

We start from calculating c_I. Using (3.8) we arrive at

$$D_1^3G(0,\tau_0)(\Phi,\Phi,\overline{\Phi}) = \frac{r\,\tau_0}{\bar{x}^2}\,\mathrm{e}^{-i\omega_0} = -\frac{r}{\bar{x}^2a_1}\Big(S\,\tau_0+i\omega_0\Big)\,,$$

and therefore

$$c_I \;= -\frac{1}{2}\mathbf{q}\frac{r}{\bar{x}^2a_1}\Big(S\,\tau_0+i\omega_0\Big)\,. \tag{3.10}$$

Now, we proceed to calculate c_{II}. Since $(\Delta(0,\tau_0))^{-1} = \frac{1}{\tau_0(S+a_1)}$ and $\mathbf{p}=1$, one calculates

$$\Psi_{II}(\theta) = \frac{1}{\tau_0(S\,+a_1)}D_1^2G(0,\tau_0)(\Phi,\overline{\Phi}) = -\frac{r}{\bar{x}(S\,+a_1)},$$

and we arrive at

$$c_{II} = -\mathbf{q}\frac{r^2}{\bar{x}^2a_1(S\,+a_1)}(S\,\tau_0+i\omega_0)\,. \tag{3.11}$$

The expression for c_{III} is the most complicated one. We calculate it step by step. First, we find

$$(\Delta(2i\omega_0,\tau_0))^{-1} = \frac{1}{2i\omega_0+S\,\tau_0+a_1\tau_0\,\mathrm{e}^{-2i\omega_0}}.$$

The equality $D_1^2G(0,\tau_0)(\Phi,\Phi) = -\frac{r\,\tau_0}{\bar{x}}\,\mathrm{e}^{-2i\omega_0}$ implies

$$\Psi_{III}(2i\omega_0\,\theta) = -\frac{r\,\tau_0}{\bar{x}}\,\frac{\mathrm{e}^{2i\omega_0\theta}}{2i\omega_0+S\,\tau_0+a_1\tau_0\,\mathrm{e}^{-2i\omega_0}}\,\mathrm{e}^{-2i\omega_0},$$

and thus

$$c_{III} = \frac{1}{2}\mathbf{q}\frac{r^2\,\tau_0^2}{\bar{x}^2}\,\frac{\mathrm{e}^{-3i\omega_0}}{2i\omega_0+S\,\tau_0+a_1\tau_0\,\mathrm{e}^{-2i\omega_0}}\,.$$

Using (3.8) we obtain

$$c_{III} = -\frac{1}{2}\mathbf{q}\frac{r^2}{\bar{x}^2\,a_1^2}\,\frac{(S\,\tau_0+i\omega_0)^3}{a_1\tau_0(2i\omega_0+S\,\tau_0)+(S\,\tau_0+i\omega_0)^2}\,. \tag{3.12}$$

To determine the sign of $\mathrm{Re}\,c$ we write c as some positive constant multiplied by a function of the ratio S/a_1. Let us denote $\zeta = \frac{S}{a_1}$. The assumption $0 \le S\, < a_1$ yields $0 \le \zeta < 1$. Using that notation we rewrite

$$\omega_0 = \arccos(-\zeta)\,,\quad \tau_0 = \frac{\arccos(-\zeta)}{a_1\sqrt{1-\zeta^2}}\,,\quad S\,\tau_0 = \frac{\zeta\arccos(-\zeta)}{\sqrt{1-\zeta^2}}\,. \tag{3.13}$$

The expression for $\mathbf{q}$ given by (3.13) reads

$$\mathbf{q}(\zeta) = \frac{\sqrt{1-\zeta^2}\Big(\sqrt{1-\zeta^2}+\zeta\arccos(-\zeta)-i\sqrt{1-\zeta^2}\arccos(-\zeta)\Big)}{\Big(\sqrt{1-\zeta^2}+\zeta\arccos(-\zeta)\Big)^2+(1-\zeta^2)\arccos^2(-\zeta)}\,. \tag{3.14}$$

After applying (3.13), the expressions for c_I, c_{II} and c_{III} take the forms

$$c_I = -\frac{1}{2}\frac{r\arccos(-\zeta)}{\bar{x}^2\, a_1\sqrt{1-\zeta^2}}\mathbf{q}\Big(\zeta + i\sqrt{1-\zeta^2}\Big),$$
$$c_{II} = -\frac{r^2\arccos(-\zeta)}{\bar{x}^2\, a_1^2\sqrt{1-\zeta^2}}\mathbf{q}\frac{1}{1+\zeta}\Big(\zeta + i\sqrt{1-\zeta^2}\Big),$$
$$c_{III} = -\frac{1}{2}\frac{r^2\arccos(-\zeta)}{\bar{x}^2\, a_1^2\sqrt{1-\zeta^2}}\mathbf{q}\frac{\Big(\zeta + i\sqrt{1-\zeta^2}\Big)^3}{\zeta + 2i\sqrt{1-\zeta^2} + \Big(\zeta + i\sqrt{1-\zeta^2}\Big)^2}.$$

Thus, we may write

$$c = -\frac{1}{2}c_r(\zeta; a_1)\hat{q}(\zeta)c_2(\zeta)\Big(\frac{a_1}{r}(1+\zeta)(5-4\zeta) + c_1(\zeta)\Big),$$

where

$$c_r = \frac{r^2\ \arccos(-\zeta)}{\bar{x}^2\, a_1^2\Big(\Big(\sqrt{1-\zeta^2} + \zeta\arccos(-\zeta)\Big)^2 + (1-\zeta^2)\arccos^2(-\zeta)\Big)(1+\zeta)(5-4\zeta)},$$
$$\hat{q}(\zeta) = \sqrt{1-\zeta^2} + \zeta\arccos(-\zeta) - i\sqrt{1-\zeta^2}\arccos(-\zeta),$$
$$c_2(\zeta) = \zeta + i\sqrt{1-\zeta^2},$$
$$c_1(\zeta) = \Big(11 - 2\zeta(3+\zeta)\Big) + 2i\Big(1-\zeta\Big)\sqrt{1-\zeta^2}.$$

Notice that

$$\hat{q}(\zeta)c_2(\zeta) = \zeta\sqrt{1-\zeta^2} + \arccos(-\zeta) + i\Big(1-\zeta^2\Big).$$

Defining

$$\begin{aligned}\gamma_{2,1}(\zeta) &= 11 - 6\zeta - 2\zeta^2,\\ \gamma_{2,2}(\zeta) &= \zeta\gamma_{2,1}(\zeta) - 2(1-\zeta^2)(1-\zeta),\end{aligned} \tag{3.15}$$

we may write

$$\operatorname{Re} c = -\frac{1}{2}c_r\Big(\frac{a_1}{r}(1+\zeta)(5-4\zeta)\Big(\zeta\sqrt{1-\zeta^2} + \arccos(-\zeta)\Big) + \\ + \gamma_{2,2}(\zeta)\sqrt{1-\zeta^2} + \gamma_{2,1}(\zeta)\arccos(-\zeta)\Big).$$

Simple calculations lead to the following identities:

$$\gamma_{2,2}(\zeta) = -4\zeta^3 - 4\zeta^2 + 13\zeta - 2,$$
$$\gamma'_{2,2}(\zeta) = 13 - 8\zeta - 12\zeta^2.$$

It is easy to see that $\gamma'_{2,2}$ has one zero for $\zeta \in (0,1)$ giving the maximum of $\gamma_{2,2}$. On the other hand, we have $\min\limits_{\zeta\in[0,1]}\gamma_{2,2}(\zeta) = \gamma_{2,2}(0) = -2$. As $\gamma_{2,1}(\zeta)$ is a decreasing function of $\zeta \geq 0$, $\min\limits_{\zeta\in[0,1]}\gamma_{2,1}(\zeta) = g_2(1) = 3$. Moreover, the minimum of $\arccos(-\zeta)$ on $[0,1]$ is $\frac{\pi}{2}$ yielding $\min\limits_{\zeta\in[0,1]}\gamma_{2,1}(\zeta)\arccos(-\zeta) \geq 3\pi/2 > 2$. Since $a_1 \geq 0$, $r > 0$ and c_r is a real positive number for any $\zeta \in [0,1)$, we have $\operatorname{Re} c < 0$. This completes the proof. □

4. **Pharmacokinetic treatment function.** In this section, we consider a treatment function of the form very often used in applications, that is pharmacokinetic one. We follow the approach proposed in [15], where the same function was considered in the context of logistic equation. We assume that the treatment is applied at times $\{t_i\}_{i=0}^{\infty}$, while the drug doses are equal to $a(t_i) = a_i$. Moreover, we assume the drug is cleared with a constant clearance rate $\tilde{\lambda} > 0$. Thus, the treatment function has the following form

$$S(t) = \sum_{t_i \le t} a_i \, \mathrm{e}^{-\lambda(t-t_i)}, \quad t \ge c, \qquad \text{and} \qquad S(t) = 0, \quad t < c,$$

where $c \ge 0$ indicates the beginning of the treatment.

Since both the single (2.1) and double (2.2) delayed Gompertz equations are autonomous, without loss of generality we may assume that the treatment begins at $t = 0$, thus we take $c = 0$. The common standard treatment protocols assume constant time intervals between successive drug administrations and the same dosage at each time. Hence, we consider only the case when time intervals $t_{i+1} - t_i$ are constant. This means the treatment is applied periodically, and $a_i = a/\kappa > 0$, where a and κ are the total daily drug dose and the number of applications every day, respectively. Thus, we consider the following treatment function

$$S(t) = \frac{a}{\kappa} \sum_{n \le \kappa t} \mathrm{e}^{-\lambda(t-n/\kappa)} = \frac{a}{\kappa} \frac{\mathrm{e}^{\lambda([\kappa t]+1-\kappa t)/\kappa} - \mathrm{e}^{-\lambda t}}{\mathrm{e}^{\lambda/\kappa} - 1}. \tag{4.1}$$

Note that if $\kappa < 1$, then the drug is given rarely than once every day, for example $\kappa = 1/2$ means the drug application once every two days. For numerical simulations we took the parameters values estimated in [2] for the Ehrlich Ascites mouse tumors. We choose the parameter series no. 0:

$$r = 0.1958, \quad H = 94.5913, \quad \tau = 3.5236, \quad V(0) = 5.3122, \tag{4.2}$$

for the Gompertz equation with the single delay and

$$r = 0.4699, \quad H = 118.6437, \quad \tau = 2.8261, \quad V(0) = 0.7036, \tag{4.3}$$

for the Gompertz model with the double delay, since it produces the smallest error among all parameters considered in [2].

First, we look for the influence of the treatment on solutions of Eqs. (2.1) and (2.2). For parameters (4.2) and (4.3), and without the treatment function, solutions of both the single and double delayed model tend to the steady state. In the case of Eq. (2.1), the value of time delay is much below the critical value $\tau_c \approx 8.02$, so oscillations are fast damped which is not very surprising. Clearly, solutions oscillate because of the periodic drug administration. Moreover, an increase of the daily dose or a decrease of the drug clearance rate leads to a decrease of the mean value of the solution. The only somehow surprising effect is that the initial time of the treatment had hardly any influence on the asymptotic behavior of the solution (compare Fig. 1).

The behavior of solutions of Eq. (2.2) is very similar. As before, the initial time for the treatment has hardly any influence. However, in this case, the time delay value is much closer to the critical value $\tau_c \approx 3.34$, and therefore without the treatment oscillations damp slower than for the single delay model. As before, an increase of the daily dosage or a decrease of the drug clearance rate leads to a decrease of the mean value of the solution (compare Fig. 2).

To study the influence of the frequency of treatment as well as the average daily dosage on solutions to the single and double delayed models, we took the following parameters:

$$r = \frac{\pi}{2}, \quad H = 1, \quad \tau = 1, \quad V(0) = 0.8. \tag{4.4}$$

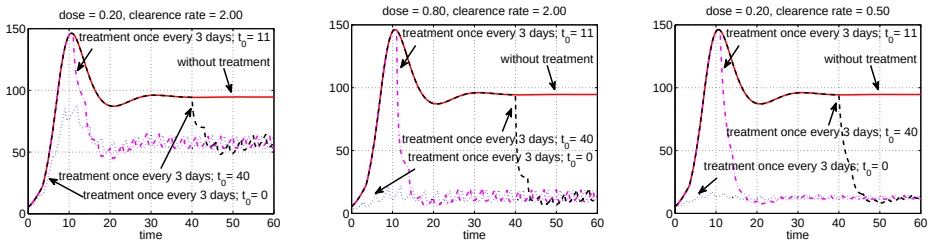

FIGURE 1. Solutions of Eq. (2.1) for the parameters (4.2) estimated in [2] (data series 0).

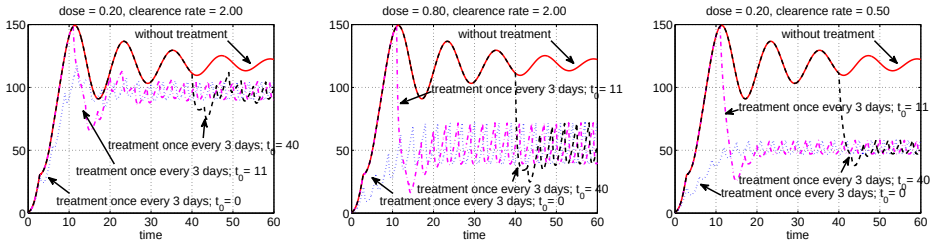

FIGURE 2. Solutions of Eq. (2.2) for the parameters (4.3) estimated in [2] (data series 0).

We choose the parameters in such a way that without the treatment we are at the critical point, at which the Hopf bifurcation occurs. The choice of this particular set of parameters (4.4) does not limit the generality of the results, since we can always rescale the models to get $H = 1$ and $\tau = 1$.

In Fig. 3 the plot of the dependence of the average value of the solution, its minimal and maximal value (thus the amplitude of the oscillations) after a long time (we calculated these values on the interval $[200, 250]$) on the frequency of the treatment is presented. For the double delayed model, we observe a non-trivial influence of the treatment function period on solutions. If this period is close to a multiplication of 4 (that is the multiplication of the oscillation period without the treatment) we observe a decrease of the mean value of the solution but an increase of the amplitude of oscillations (see Fig. 3 right). On the other hand, for the single delay, when the period of the treatment function is equal to a multiplication of 4, the amplitude of oscillations seems to be increasing to infinity (see Fig. 3 left).

The dependence of the solution on the daily dose is not surprising for the double delayed model, defined by Eq. (2.2). With an increase of this dose, the mean value of the solution of Eq. (2.2) decreases. If the single dose is sufficiently large, this may cause that solutions approach zero in a finite time (see Fig. 4 right).

The dependence of the solution on the daily dose is quite surprising for the singe delayed model, defined by Eq. (2.1). For frequent drug administration, the behavior of the solution of Eq. (2.1) is as it could be expected; an increase of the average daily dose causes that the mean value decreases. The amplitude of oscillations seems to decrease at the beginning and increase for larger doses (compare Fig. 5 left). However, if the administration is sufficiently rare then, surprisingly, the mean value of the solution of Eq. (2.1) begins to increase with an increase of the daily dose. The amplitude of oscillations seems to grow fast and this short period of very large values of the solutions seems to cause an increase of its mean

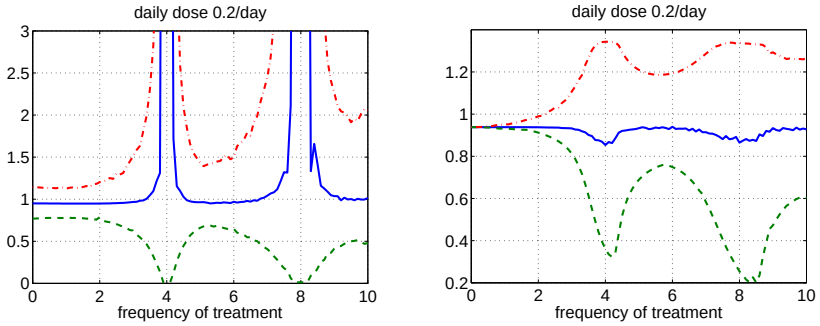

FIGURE 3. Dependence of the mean, maximal and minimal values of the solution after a long time on the treatment frequency for Eq. (2.4) (left) and Eq. (2.2) (right) for parameters given by (4.4) and $a = 0.2$, $\lambda = 2$.

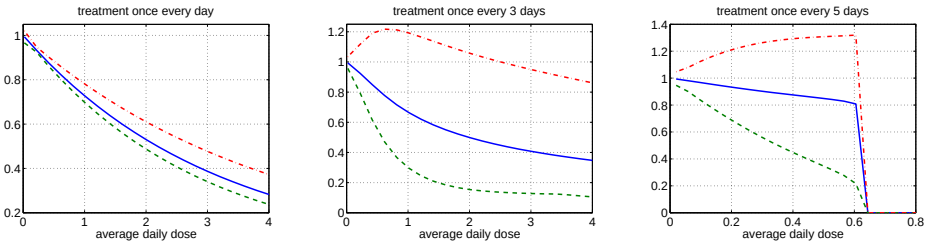

FIGURE 4. Dependence of the mean, maximal and minimal values of the solution of Eq. (2.2) after a long time on the daily dose for various drug administration protocols for $\lambda = 2$ and other parameters given by (4.4).

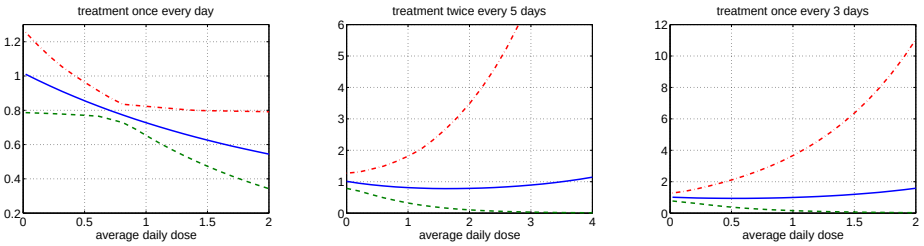

FIGURE 5. Dependence of the mean, maximal and minimal values of the solution of Eq. (2.4) after a long time on the daily dose for various drug administration protocols for $\lambda = 2$ and other parameters given by (4.4).

value. We have estimated that this phenomenon is observed for the treatment that is rarer than about once every 2.1 days (see Fig. 5 middle and right). For the treatment twice every 5 days, for the average daily dose 2, the maximal value of the solutions reaches 3, and 14 for the dose 4 (see Fig. 5 middle), while for the treatment once every three days, the maximal value reaches almost 12 for the average dose 2 and it exceeds 120 for the dose 4. (see Fig. 5 right, data showed only for doses less or equal to 2).

We also investigated the behavior of solutions of Eq. (2.3), believing that it would be easier to observe the dynamics for the linear equation. In fact, simulations suggest, that the

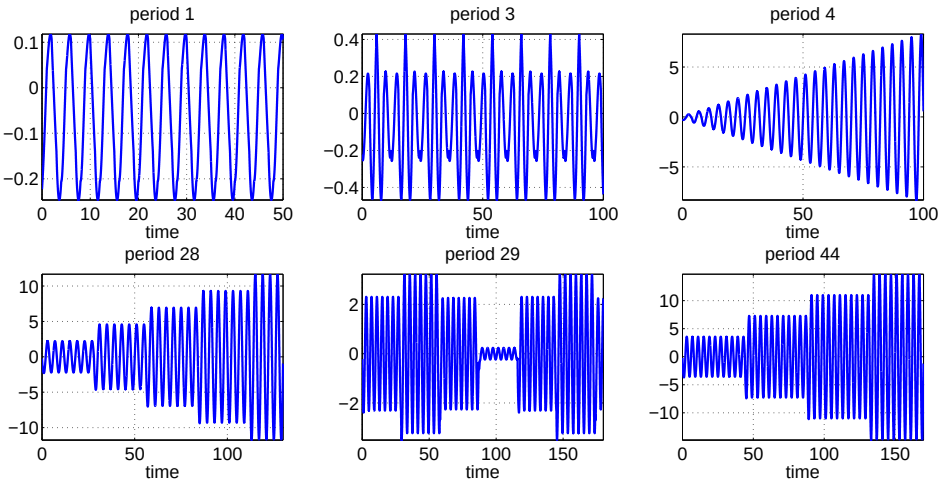

FIGURE 6. The behavior of solutions of Eq. (2.3) for $r = \pi/2$, $\tau = 1$, $H = 1$ and different periods (that is $1/\kappa$) of the treatment function. Here we took $a = 0.2$, $\lambda = 2$.

period $4k$, $k \in \mathbb{N}$, of the treatment function causes some kind of resonance with the oscillation of the solutions to the model without this external influence (see Fig. 6). Surprisingly, the phase of the treatment (starting time) has hardly any influence on the dynamics.

5. **Conclusion.** In the paper we have studied the influence of constant and pharmacokinetic treatment on the dynamics of two types of delayed Gompertz model, that is the single delayed model, in which the delay is introduced in the per capita growth rate, and therefore appears in only one term in the right-hand side of the equation, and the double delayed one, in which the delay is introduced in the net growth rate, and therefore appears in both terms of the right-hand side of the Gompertz equation. Although the dynamics of the single and double delayed Gompertz equation without a treatment does not differ significantly, that is it depends on the model parameters and is either eventually monotonic, damped oscillatory or oscillatory when a Hopf bifurcation occurs, cf. [16], we have found that there are many significant differences in the case studied in this paper. For the constant treatment, the single delayed Gompertz model does not change when we add the treatment; adding the treatment changes only the model parameters. This is the result of simple equivalence between the Gompertz model and the linear model obtained due to a logarithmic change of variables which is still valid in this case. On the other hand, for the double delayed model, adding a treatment we have obtained another model, in which the right-hand side depends not only on the past, but also on the present time. It should be noticed, that the double delayed models seem to be more appropriate in the description of cellular dynamics, as considered here tumor growth. Therefore, the results obtained by us for the double delayed model should better describe the case of real treatment. Notice that also in [7] there is a difference between the influence of impulsive treatment on the delayed logistic equation depending on the type of delayed model. Again, the double delayed model demonstrates the dynamics which agrees with our expectations, while for the single delayed model the dynamics is slightly strange. For the case of single delayed Gompertz model which is equivalent to the linear one, we hope to explain this behavior studying it in more details in the future.

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