Mathematical Modeling of Tumors Growth: Competition based on Gompertz model in Two Dimensions

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Abstract

This article studies the competition between cancer cells within the human body depending on Gompertz's growth. This model depends on two types of cancer cells, which grow to a certain extent, termed the carrying capacity. The carrying capacity is taken into account and defined as the number of cancer cells in which a certain density of cells eventually reaches stability. When this happens, the growth rate fluctuates, either it goes a little above or a little below the carrying capacity. This paper will cover the mathematical modeling aspects of Gompertz growth and a means to determine how competition creates growth and whether it leads to stability or instability. The paper includes growth equations that show two competing species which lead to extinction, coexistence or the emergence of one species superior to the other.

Keywords: Competition, Coexistence, Equilibrium points, Extinction, Gompertz model.

Introduction

Cancer is a condition that affects the body, invades surrounding cells and tissues, and creates malignant tumors[1]. These tumors expand uncontrollably and can infect any organ in the body[2]. Humans can get cancer at any age, and the chance of infection rises as people age[3]. The malignant tumor may turn out to be benign, and it may be removed with no chance of recurrence, as surgery eliminates it. However, it develops into a cancerous tumor if it is not removed. Malignant tumors expand throughout the body and multiply between cells; these cannot be fully gotten rid of. Human growth and healthy life require the cooperation of more than 10 million cells for the health of the organism[4]. This cooperation is maintained by signals and cell checkpoints that prevent cell division, death, and differentiation. The phenomenon of cancer can be defined at different levels. At the most basic level, cancer is the collapse of cooperation. This leads to an uncontrolled state of cells in the body, as it multiplies and eventually leads to the death of the organism[5]. Cancer is generally thought to be a DNA-related disease. In other words: the uncontrolled proliferation of cells is the result of changes or mutations in the genetic material[6]. This indicates that, in order for cancer to have developed, multiple mutations will have accumulated, destroying cells. This is a regulatory network that ensures cooperation[7].

A cancer cell is created and can undergo a process called clone expansion[8,9]. According to current statistics, in the USA, one in three women and one in five men will develop cancer at some time in their life.[10] Many areas of biology use the well-known and popular Gompertz model[11]. It has been employed numerous times to characterize bacterial population growth, plant and animal growth, as well as the

quantity of cancer cells[12]. Regarding usage frequency, the Gompertz model is possibly only second to the logistic model among sigmoid models fitted to growth data and other data. From the expansion of wildlife, including aquatic species, terrestrial species, and plants to the growth of tumors and bacteria, the Gompertz model has been utilized by scientists as a growth model for all types of growth, more so than its particularly popular counterpart, the logistic model [13]. The Gompertz equation generally offers a more suitable fit than the logistic equation [14] when the data encompass a broad spectrum of sizes. Given that the Gompertz curve is sigmoid, it seems reasonable that the equation would operate more accurately when the data are plotted. As such, it becomes evident that the Gompertz equation is far better than the various other models[15]. Self-limited growth expansion is simulated using the Gompertz equation and its related differential equation.

The rise of mathematical functions like the Gompertz and logistic models for analyzing population growth, alongside the investigation of countless clinical and scientific research, amply demonstrates the evolution of this discipline. These models have functioned well for many different growth curves. In population biology, the Gompertz function is a crucial concept[16,17]. It is especially useful for explaining how an organism or population grows rapidly. When the carrying capacity has been obtained, the function may be utilized for illustrating its ultimate horizontal asymptote. The Gompertz model has been modified by several scientists to take into consideration anything from bacterial to plant and animal growth[18]. This paper is laid out as follows: in the second section, the Gompertz growth pertaining to a single species of cells is presented and a linear stability analysis s performed. In the third section, this model is extended to explain the competition between two different cancer cell types. In the fourth section, the behavior of the two-species model is elucidated by implementing simulations and linear stability analysis. The fifth section contains the numerical solutions. Finally, the conclusions are presented.

The Basic Dynamics of the Gompertz Growth of One Species

The basic equation for the model of Gompertz growth is

$$\frac{dW}{dt} = rW \ln\left(\frac{D}{W}\right), \qquad 1$$

where r is the intrinsic growth rate and D is the carrying capacity. In order to solve the above nonlinear equation with the initial condition $W(0) = W_0$, through separation variables and partial fractions, it is deducted that

$$W(t) = D\left[e^{-\left(\ln\left(\frac{D}{W_0}\right)e^{-rt}\right)}\right]. \qquad 2$$

The fixed points of Eq.1 are given by $W = 0$ and $W = D$. Inspecting this stability of W (fixed root point), it has been observed that there is an upward slope at $W = 0$ and a negative slope at $W = D$. Consequently, the point $W = D$ is stable and the point $W = 0$ is unstable.

Dynamics of Competition in Two-Dimensions for Gompertz Growth

Based on the Gompertz model of single species Eq. 1, the deterministic two-dimensions competition model with Gompertz growth [19,20] can be written as,

$$\dot{X} = r_x X\left[\ln\left(\frac{D_1}{\alpha_{xx}X + \alpha_{yx}Y}\right)\right], \qquad 3$$

$$\dot{Y} = r_y Y\left[\ln\left(\frac{D_2}{\alpha_{xy}X + \alpha_{yy}Y}\right)\right]. \qquad 4$$

The variables in the above system and their descriptions are summarized in Table 1.

Table 1. Summary of the key quantities and model parameters of the Gompertz model Eqs 3-4

Quantity	Description	Dimensions	Effect
$X(t)$	The densities of species X	Number	When X(t) disappears, the model becomes a single model and Y grows as a Gompertz growth
$Y(t)$	The densities of species Y	Number	When Y(t) disappears, the model becomes a single model and X grows as a Gompertz growth
r_x	The growth rates relative to species X	1/time	Increase in r_x leads to the X(t) reaching to carrying capacity faster
r_y	The growth rates relative to species Y	1/time	Increase in r_y leads to the Y(t) reaching to carrying capacity faster
D_1	The carrying capacities of species X	Number	Increased D_1 leads to an increased number of cancer cells of species X
D_2	The carrying capacities of species Y	Number	Increased D_2 leads to an increased number of cancer cells of species Y
α_{yx}	The inhibitory effect of species Y on X	Dimensionless	Increase in α_{yx} leads to a negative impact on X and a positive impact on Y
α_{xy}	The inhibitory effect of species X on Y	Dimensionless	Increase in α_{xy} leads to negative impact on Y and positive impact on X
α_{xx}	The strength of intraspecific competitions inside species X	Dimensionless	Negative effect on X species only
α_{yy}	The strength of intraspecific competitions inside species Y	Dimensionless	Negative effect on Y species only

The longer-term behaviors of its solutions will be examined by conducting a linear stability analysis of its fixed points, when $\alpha_{xx} = \alpha_{yy} = 1$, which means the intraspecific competitions will be ignored in this study. Finally, the carrying capacities of different species will take the same value as a special case $D_1 = D_2 = D$, then the system of Eqs 3-4 becomes,

$$\dot{X} = r_x X \left[\ln \left(\frac{D}{X + \alpha_{yx} Y} \right) \right], \qquad 5$$

$$\dot{Y} = r_y Y \left[\ln \left(\frac{D}{\alpha_{xy} X + Y} \right) \right]. \qquad 6$$

Linear Stability Analysis of Competition for Gompertz Growth

The equilibrium points can be found by making the right-hand sides of Eqs 5 and 6 equal to zero as a first step, $\dot{X} = \dot{Y} = 0$.

$$r_x X \left[\ln \left(\frac{D}{X + \alpha_{yx} Y} \right) \right] = 0, \qquad 7$$

$$r_y Y \left[\ln \left(\frac{D}{\alpha_{xy} X + Y} \right) \right] = 0. \qquad 8$$

For Eq. 7, $r_x X = 0$, this leads to either $X = 0$ or $\left(\ln \left(\frac{D}{X + \alpha_{yx} Y} \right) \right) = 0$, so $D - X - \alpha_{yx} Y = 0$.

For Eq. 8, $r_y Y = 0$ and this leads to either Y=0 or $\left(\ln \left(\frac{D}{\alpha_{xy} X + Y} \right) \right) = 0$, so, $D - Y - \alpha_{xy} X = 0$.

Three fixed points are found, $S_x = (D, 0), S_y = (0, D)$ and $S_{xy} = \left(\frac{D(1 - \alpha_{yx})}{1 - \alpha_{xy}\alpha_{xy}}, \frac{D(1 - \alpha_{xy})}{1 - \alpha_{xy}\alpha_{yx}} \right)$

Now, to find the Jacobin matrix for the nonlinear system (5) and (6), $f(X, Y) = r_x X \left[\ln \left(\frac{D}{X + \alpha_{yx} Y} \right) \right]$ and $g(X, Y) = r_y Y \left[\ln \left(\frac{D}{\alpha_{xy} X + Y} \right) \right]$ is used. For the first function $f(X, Y)$, $\frac{\partial f}{\partial X} = r_x \left[\ln \left(\frac{D}{X + \alpha_{yx} Y} \right) \right] - \frac{r_x X}{X + \alpha_{yx} Y}$ and $\frac{\partial f}{\partial Y} = -r_x X \left(\frac{\alpha_{yx}}{X + \alpha_{yx} Y} \right)$.

For the second function $g(x, y)$, $\frac{\partial g}{\partial X} = -r_y Y \left(\frac{\alpha_{xy}}{Y + \alpha_{xy} X} \right)$ and $\frac{\partial g}{\partial Y} = r_y \left[\ln \left(\frac{D}{\alpha_{xy} X + Y} \right) \right] - \frac{r_y Y}{\alpha_{xy} X + Y}$.

According to the definition of the Jacobin matrix[21,22]

$$J(X,Y) = \begin{bmatrix} \frac{\partial f}{\partial X} & \frac{\partial f}{\partial Y} \\ \frac{\partial g}{\partial X} & \frac{\partial g}{\partial Y} \end{bmatrix},$$

$$\therefore J(X,Y) =$$

$$\begin{bmatrix} r_x\left[\ln\left(\frac{D}{X+\alpha_{yx}Y}\right)\right]-\frac{r_x X}{X+\alpha_{yx}Y} & -r_x X\left(\frac{\alpha_{yx}}{X+\alpha_{yx}Y}\right) \\ -r_y Y\left(\frac{\alpha_{xy}}{Y+\alpha_{xy}X}\right) & r_y\left[\ln\left(\frac{D}{\alpha_{xy}X+Y}\right)\right]-\frac{r_y Y}{\alpha_{xy}X+Y} \end{bmatrix}$$

For the first equilibrium point $S_x = (D, 0)$,

$$J(D,0) = \begin{pmatrix} -r_x & r_x \alpha_{yx} \\ 0 & r_y \ln\left(\frac{1}{\alpha_{xy}}\right) \end{pmatrix}.$$

The first eigenvalue is $-r_x < 0$ and to ensure another negative eigenvalue, $r_y \ln\left(\frac{1}{\alpha_{xy}}\right)$ should be < 0 and this occurs when $\alpha_{xy} > 1$, as shown in Figs 1(a) and (c).

For the second equilibrium point $S_y = (0, D)$,

$$J(0,D) = \begin{pmatrix} r_x \ln\left(\frac{1}{\alpha_{yx}}\right) & 0 \\ -r_y \alpha_{xy} & -r_y \end{pmatrix}$$

The second eigenvalue is $-r_y < 0$, and to ensure the first negative eigenvalue, the condition $r_x \ln\left(\frac{1}{\alpha_{yx}}\right)$ should be less than 0; this happens when $\alpha_{yx} > 1$, as shown in Figs 1(a) and (d).

For the third coexistence equilibrium point, $S_{xy} = \left(\frac{D(1-\alpha_{yx})}{1-\alpha_{xy}\alpha_{yx}}, \frac{D(1-\alpha_{xy})}{1-\alpha_{xy}\alpha_{yx}}\right)$, the Jacobin matrix is

$$J\left(\frac{D(1-\alpha_{yx})}{1-\alpha_{xy}\alpha_{yx}}, \frac{D(1-\alpha_{xy})}{1-\alpha_{xy}\alpha_{yx}}\right) =$$

$$\begin{bmatrix} \frac{-r_x(1-\alpha_{yx})}{1-\alpha_{yx}\alpha_{xy}} & \frac{r_x \alpha_{yx}(1-\alpha_{yx})}{1-\alpha_{yx}\alpha_{xy}} \\ \frac{r_y \alpha_{xy}(1-\alpha_{xy})}{1-\alpha_{yx}\alpha_{xy}} & \frac{-r_y(1-\alpha_{xy})}{1-\alpha_{yx}\alpha_{xy}} \end{bmatrix}.$$

The characteristic equation for the matrix A= $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ is $f(\lambda)=\lambda^2 - (a+d)\lambda + (ad - bc)$.

Assume that $f(\lambda)=\lambda^2-B\lambda+C$, where $B = -\left[\frac{r_x(1-\alpha_{yx})+r_y(1-\alpha_{xy})}{1-\alpha_{yx}\alpha_{xy}}\right]$, $C = \frac{r_y(1-\alpha_{yx})r_x(1-\alpha_{xy})}{1-\alpha_{yx}\alpha_{xy}}$

If $\alpha_{yx} < 1$ and $\alpha_{xy} < 1$. This leads to B > 0 and C > 0; this ensures negative eigenvalues and coexistence for the species, as shown in Fig 1(b).

Finally, the explanation of these equilibrium points is as follows:

• The first and second fixed point is where the extinction of one of the species occurs.

• The third fixed point is where both species can coexist.

The numerical simulations are performed for the system of Eqs 5 and 6 to clarify the analytic behavior in order to provide a picture of the phase-plane[23,24]. As a result, the model can be predicted as to how it will behave given a variety of initial conditions but for a predetermined set of parameter values. Following the curve (a trajectory) from the initial values in the direction of the arrows is shown in Fig 1. The direction field generated by the differential equation for each value of X and Y is where the arrows originate by using MATHEMATICA[25,26]. The green points represent the stable points and the red points refer to unstable points[27].
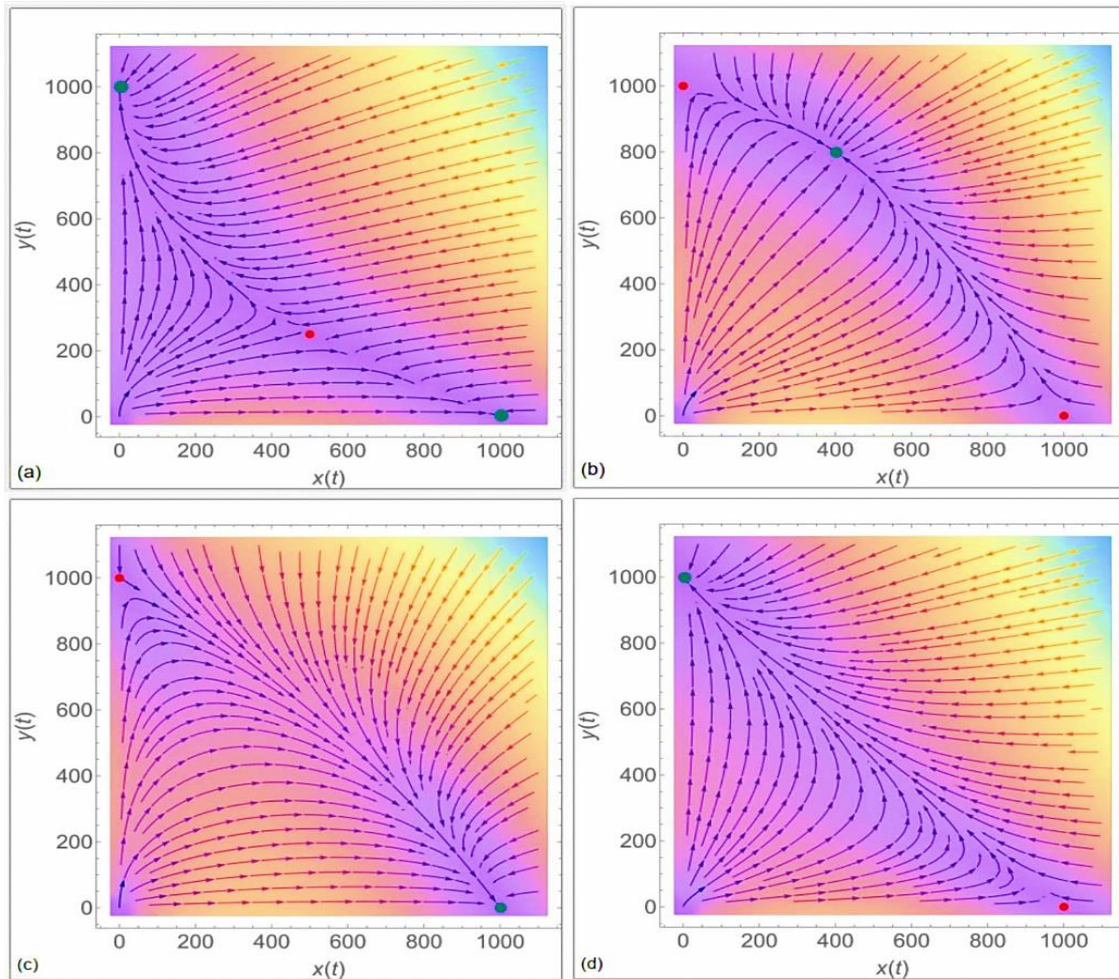
**Figure 1. MATHEMATICA-generated phase-plane diagram (Gompertz model) for**

a) If $\alpha_{xy} > 1$ and $\alpha_{yx} > 1$ Coexistence of two stable exclusion equilibria.
b) If $\alpha_{xy} < 1$ and $\alpha_{yx} < 1$ Stable coexistence of an internal equilibrium.
c) If $\alpha_{xy} > 1$ and $\alpha_{yx} < 1$ Species extinction, type one survival, type two extinction.
d) If $\alpha_{xy} < 1$ and $\alpha_{yx} > 1$ Species extinction, type two survival, type one extinction.

Results and Discussion

Numerical Results and Discussion

In this section, competition between two types of cells is also studied. Using the MATLAB[28] code to solve the model in Eqs 3 and 4, MATLAB 2015b is used to see the shape of the solution, where the blue curve refers to the first type of cell and the red curve to the second type of cell. Programming the Gompertz model is utilized for the use of Eqs 3 and 4. Drawing phase portraits can graphically portray each of these situations. It is seen from the numerical results in Fig 2 that the species are stable, and there is the coexistence of two stable exclusion equilibria. This is consistent with the analytical side of the problem, which is the linear stability analysis[29] in Fig 1(a). It is seen that in (b) of Fig 2, the species are stable, thus able to coexist, and that corresponds to Fig 1(b) of the stability analysis, where there is a stable coexistence of an internal equilibrium. The analysis in Fig 2(c) is supported by our observation that species extinction occurs in Fig 1(c), where only species 1 survives. In a similar vein, Fig 3(d) depicts the extinction of a species, but this time, species 2 survives.
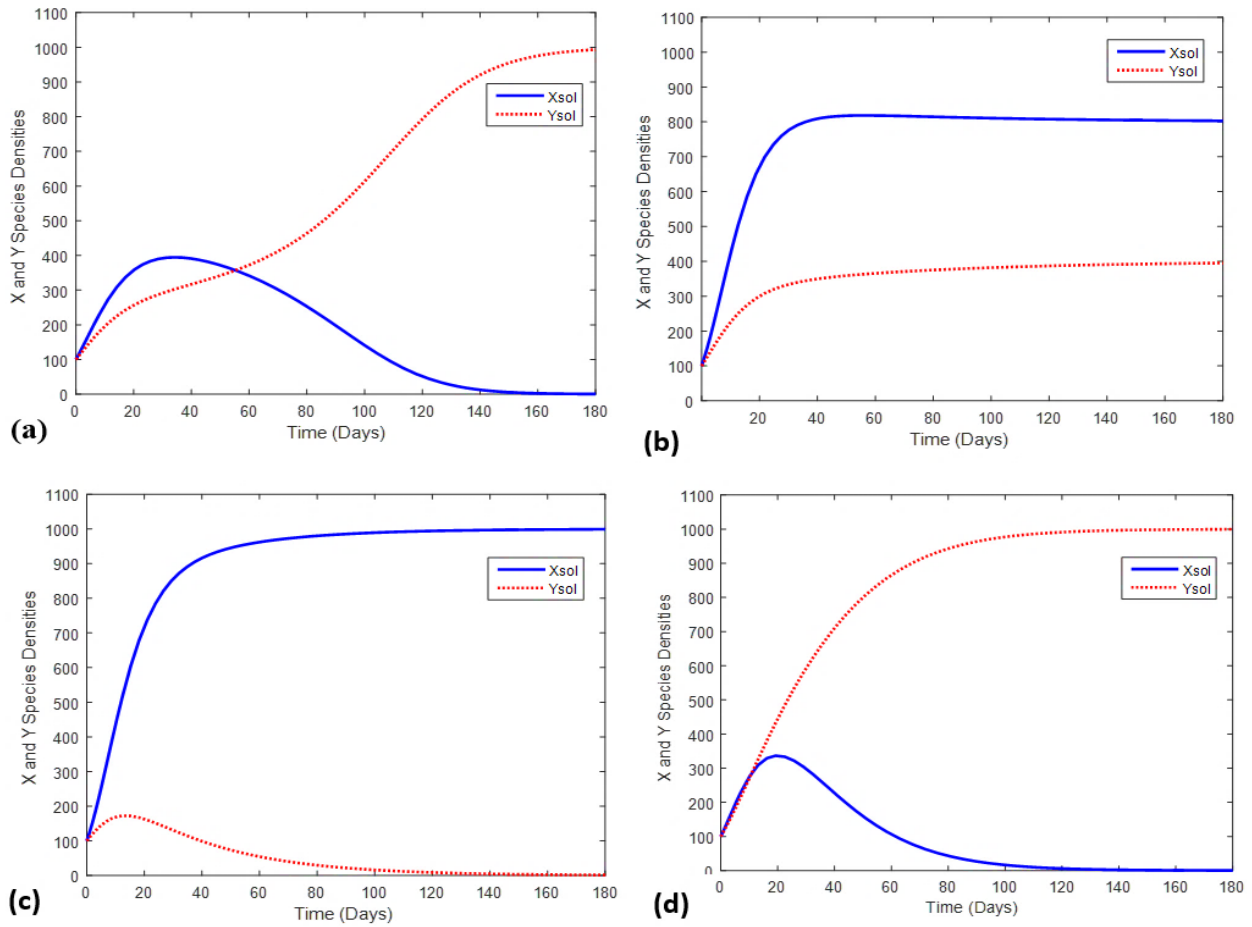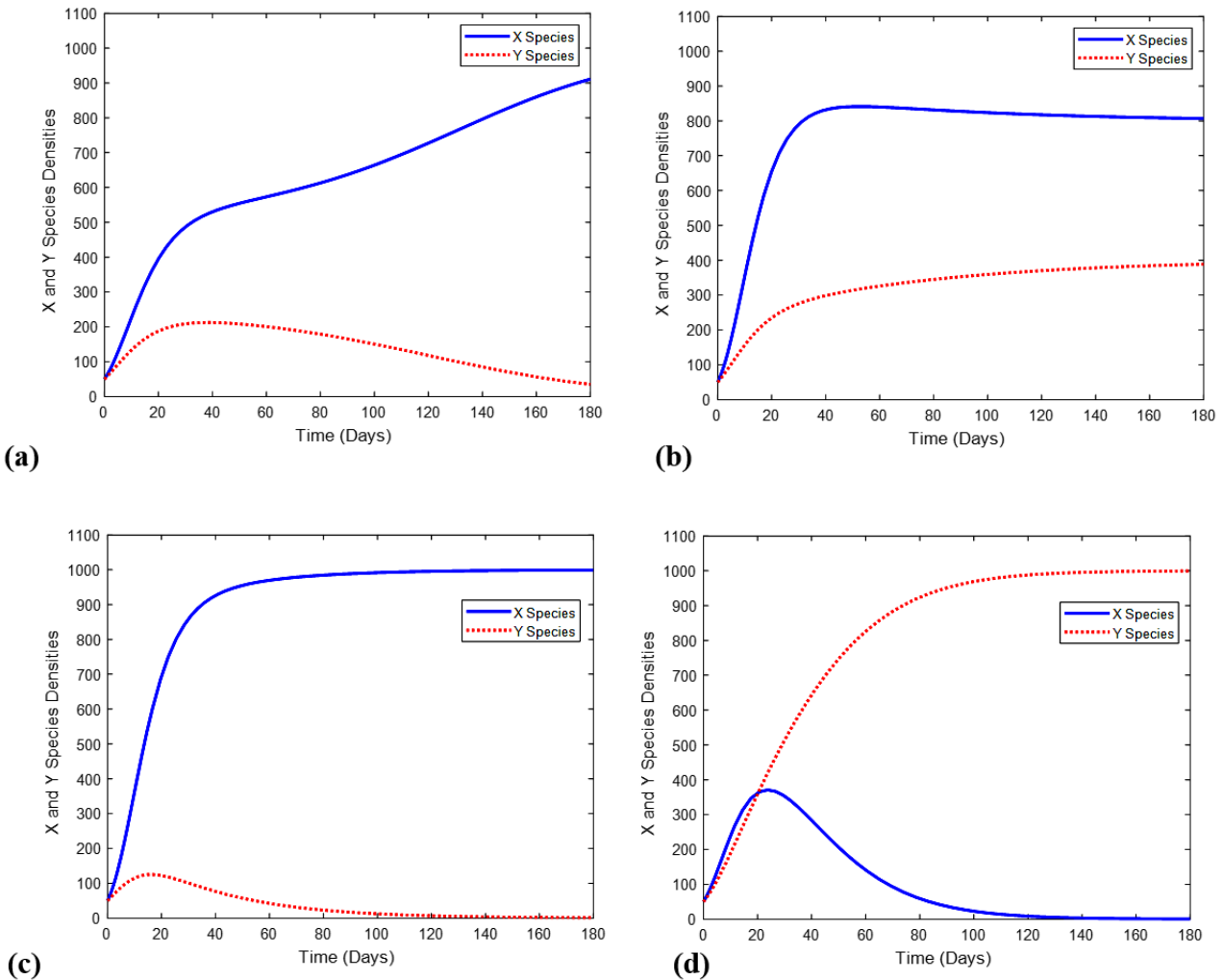
Figure 2. MATLAB numerical results of Gompertz model for the competition dynamics in a two-species system with intrinsic growth rates $r_x = 0.125$ and $r_y = 0.075$. Initial condition is $(100, 100)$.

a) Coexistence of two stable exclusion equilibria: $\alpha_{xy} = 1.5$ and $\alpha_{yx} = 2$.
b) Stable coexistence of an internal equilibrium: $\alpha_{xy} = 0.75$ and $\alpha_{yx} = 0.5$.
c) Only species 1 survives: $\alpha_{xy} = 1.5$ and $\alpha_{yx} = 0.5$.
d) Only species 2 survives: $\alpha_{xy} = 0.5$ and $\alpha_{yx} = 1.5$.

As seen in Fig 3, when the initial conditions change from (100,100) to (50,50) and all the other parameters remain at the same values, the solution changes for case (a) because there are two stable equilibrium points. This means that X species wins against Y species, as shown in Fig 3(a) counter to Fig 2(a) when Y species wins against X species. For the rest of the three cases (b-d), choosing the initial conditions does not affect the solution as there is only one stable solution[30], as shown in Fig 3 (b-d), and this matches with Fig 2 (b-d).
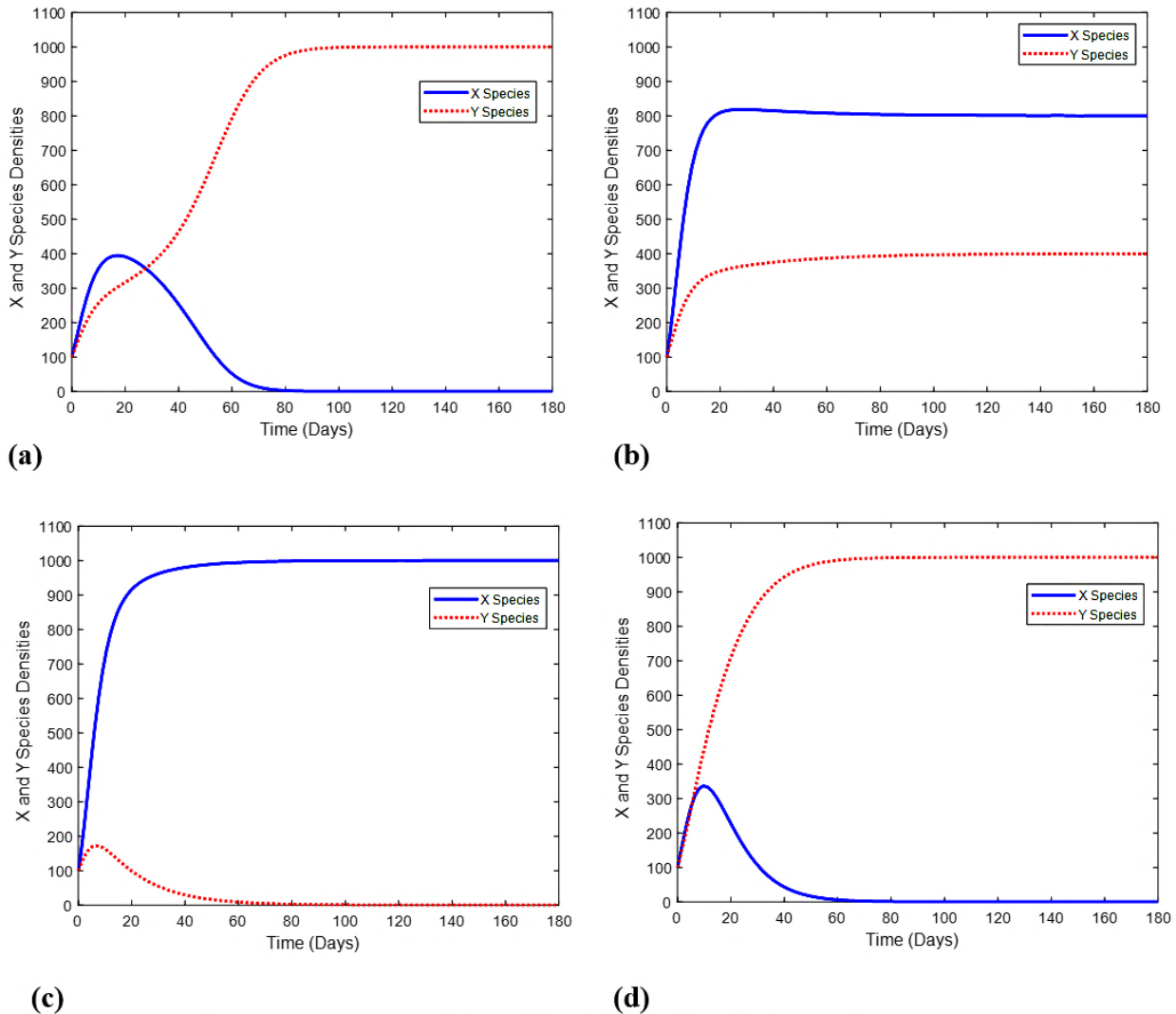
(a)

(b)

(c)

(d)

Figure 3. MATLAB numerical results of Gompertz model for the competition dynamics in a two-species system with intrinsic growth rates $r_x = 0.125$ and $r_y = 0.075$. Initial condition is $(50, 50)$.

    a)   Coexistence of two stable exclusion equilibria: $\alpha_{xy} = 1.5$ and $\alpha_{yx} = 2$.
    b)   Stable coexistence of an internal equilibrium: $\alpha_{xy} = 0.75$ and $\alpha_{yx} = 0.5$.
    c)   Only species 1 survives: $\alpha_{xy} = 1.5$ and $\alpha_{yx} = 0.5$.
    d)   Only species 2 survives: $\alpha_{xy} = 0.5$ and $\alpha_{yx} = 1.5$.

As seen in Fig 4, changing the intrinsic growth rates, for example, changing r_x from 0.125 to 0.25 and r_y from 0.075 to 0.15, does not affect the numerical solution or the behavior of the solution. However, it affects the speed at which the solution is reached.

The higher the growth rate, the faster the solution is reached. From Figs 2 and 4, it is observed that, for cases (a), (b), (c), and (d), the speed to reach the solution changed from 160 to 80 days, 40 to 20 days, 140 to 70 days, and 120 to 60 days, respectively.

Figure 4. MATLAB numerical results of Gompertz model for the competition dynamics in a two-species system with intrinsic growth rates $r_x = 0.25$ and $r_y = 0.15$. Initial condition is $(100, 100)$.

    a)   Coexistence of two stable exclusion equilibria: $\alpha_{xy} = 1.5$ and $\alpha_{yx} = 2$.
    b)   Stable coexistence of an internal equilibrium: $\alpha_{xy} = 0.75$ and $\alpha_{yx} = 0.5$.
    c)   Only species 1 survives: $\alpha_{xy} = 1.5$ and $\alpha_{yx} = 0.5$.
    d)   Only species 2 survives: $\alpha_{xy} = 0.5$ and $\alpha_{yx} = 1.5$.

Conclusion

In this paper, tumor growth was discussed; how it originates and spreads in cells and then to the organs as well as how to use the Gompertz model to solve a mathematical model. The mathematical model was defined and the stabilization points were found. In Gompertz's growth, there were three fixed points. In addition, numerical applications were used to see what the solution looks like and where stability happens. This was illustrated in a number of forms.

From the work of special programs in MATLAB and MATHEMATICA applications, it was found that if both $\alpha_{xy} > 1$ and $\alpha_{yx} > 1$, the coexistence of two stable exclusion equilibria occurs. Whereas if $\alpha_{xy} < 1$ and $\alpha_{yx} < 1$, then stable coexistence of an internal equilibrium occurs. If $\alpha_{xy} > 1$ and $\alpha_{yx} < 1$, then species extinction occurs, type one survival, and type two extinction. Finally, it was found that if $\alpha_{xy} < 1$

and $\alpha_{yx} > 1$, species extinction takes place, wherein type two survival and type one extinction. The Gompertz model is the most accurate sigmoid model to use for growth tumor data. The research can be

developed and expanded to include the system to an n of equations that illustrates competing cancer cells. Furthermore, for genetic mutations occurring in single species, the concept of quasi-species can be explored in future work.

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been

included with the necessary permission for re-publication, which is attached to the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Baghdad.

Authors' Contribution Statement

This work was carried out in collaboration between A. K. Jr. and H. M.AS. The Gompertz model is presented for two species of cells, performing a linear stability analysis. This model is

extended to describe the competition between two types of cancer cells. The behavior of the two species is elucidated using linear stability analysis and simulations in addition to the numerical findings.

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النمذجة الرياضية لنمو الأورام: نموذج قائم على المنافسة وفق نموذج كَومبيرتز في البعدين

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الخلاصة

بالنسبة لهذه المقالة، تمت دراسة المنافسة بين الخلايا السرطانية داخل جسم الإنسان اعتمادًا على نمو جومبيرتز. تعتمد هذه النماذج على نوعين من الخلايا السرطانية، وتنمو هذه الخلايا إلى حد ما يسمى بالقدرة الاستيعابية. يتم أخذ القدرة الاستيعابية في الاعتبار وتعريفها على أنها عدد الخلايا الذي يصل اليه الورم في النهاية. عندما يحدث هذا، يتقلب معدل النمو، إما أن يكون أعلى قليلاً أو أقل قليلاً من القدرة الاستيعابية. ستغطي هذه الدراسة جوانب النمذجة الرياضية لنمو جومبيرتز وطريقة لتحديد كيفية المنافسة لنموالورام وما إذا كانت تؤدي إلى الاستقرار أو عدم الاستقرار. يتضمن البحث معادلات نمو تظهر نوعين متنافسين يؤديان إلى الانقراض أو التعايش أو ظهور نوع متفوق على الآخر.

الكلمات المفتاحية: المنافسة، التعايش، نقاط التوازن، الانقراض، نموذج كَومبيرتز.