New combinational therapies for cancer using modern statistical mechanics

Jorge A. González1,∗, M. Acanda2, Z. Akhtar3, D. Andrews4, J. I. Azqueta2, E. Bass4, A. Bellorín5, J. Couso8, Mónica A. García-Ñustes9, Y. Infante8, S. Jiménez10, L. Lester6, L. Maldonado4, Juan F. Marín9†, L. Pineda7, I. Rodríguez7, C. C. Tamayo2, D. Valdes2, L. Vázquez11.

1 Department of Physics, Florida International University, Miami, Florida 33199, U.S.A.
2 Department of Biological Sciences, Florida International University, Miami, Florida 33199, U.S.A.
3 Department of Biology, College of Arts and Sciences, University of Miami, Coral Gables, Florida 33146, U.S.A.
4 Medical Campus, Miami Dade College, 950 NW 20th Street, Miami, Florida 33127, U.S.A.
5 Escuela de Física, Facultad de Ciencias, Universidad Central de Venezuela, Apartado Postal 47586, Caracas 1041-A, Venezuela
6 Sylvester Comprehensive Cancer Center, University of Miami Health System, 1475 NW 12th Ave., 1st Floor, Miami, Florida 33136, U.S.A.
7 Millner School of Medicine, University of Miami, 1600 NW 10th Ave., 1140, Miami, Florida 33136, U.S.A.
8 College of Engineering and Computing, The Engineering Center, Florida International University, 10555 West Flagler Street, Miami, Florida 33174, U.S.A.
9 Instituto de Física, Pontificia Universidad Católica de Valparaíso, Casilla 4059, Chile
10 Departamento de Matemática Aplicada a las TT.II., E.T.S.I. Telecomunicación, Universidad Politécnica de Madrid, 28040-Madrid, Spain
11 Departamento de Matemática Aplicada, Facultad de Informática, Universidad Complutense de Madrid, 28040-Madrid, Spain

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Abstract

We investigate a new dynamical system that describes tumor-host interaction. The equation that describes the untreated tumor growth is based on non-extensive statistical mechanics. Recently, this model has been shown to fit successfully exponential, Gompertz, logistic, and power-law tumor growths. We have been able to include as many hallmarks of cancer as possible. We study also the dynamic response of cancer under therapy. Using our model, we can make predictions about the different outcomes when we change the parameters, and/or the initial conditions. We can determine the importance of different factors to influence tumor growth. We discover synergistic therapeutic effects of different treatments and drugs. Cancer is generally untreatable using conventional monotherapy. We consider conventional therapies, oncogene-targeted therapies, tumor-suppressors gene-targeted therapies, immunotherapies, anti-angiogenesis therapies, virotherapy, among others. We need therapies with the potential to target both tumor cells and the tumors’ microenvironment. Drugs that target oncogenes and tumor-suppressor genes can be effective in the treatment of some cancers. However, most tumors do reoccur. We have found that the success of the new therapeutic agents can be seen when used in combination with other cancer-cell-killing therapies. Our results

∗jorgalbert3047@hotmail.com
†juan.marin.m@mail.pucv.cl

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have allowed us to design a combinational therapy that can lead to the complete eradication of
cancer.

1 Introduction

There are many papers dedicated to the mathematical modeling of tumor growth [1–131]. In this
article, we will investigate a new dynamical system that describes cancer evolution. With the help of
our results, we will design new cancer therapies.

Cancer is caused by genetic changes that activate oncogenes or inactivate tumor suppressor genes
[132–136]. Cancer is generally untreatable [1–213]. Why most cancer does not respond to conventional
therapy is unknown [132–136, 143]. Most common human cancers are epithelial cancers and they are
the least treatable with conventional therapies. Even when epithelial tumors do initially respond to
treatment, eventually the tumors reoccur. Scientists do not know why targeting any specific gene
results in tumor regression.

Although many of the new drugs show a significant clinical response, eventually most tumors
do reoccur [132–136]. The inactivation of some oncogene can result in sustained tumor regression.
However, the reactivation of the oncogene results in the rapid restoration of neoplastic properties.
Oncogene inactivation is associated with proliferative arrest, differentiation, and apoptosis.

In some tumors, the cell that was initially transformed by MYC activation and later gives rise
to cancer may have stem cell features. As a stem cell, it can give rise to malignant progenitor cells.
Upon oncogene inactivation, this cancer stem cells would then differentiate into normal appearing and
functioning cells, but some of the cells retain their latent stem cell properties. Also, it is possible that
MYC inactivation fails to induce complete eradication of a small subset of cells that have acquired
 genetic events.

The notion of tumor dormancy has been discussed by oncologists in the context that some types
of cancers that were apparently cured by treatment can reoccur even decades later, such as some
sarcomas and breast adenocarcinoma. Other cancers can become dormant upon treatment with con-
ventional therapies, only to reoccur sometimes years later. Sometimes they can exhibit progression to
a transformed more aggressive state. The immune system has been implicated in the mechanism of
dormancy. Immune surveillance mechanisms may hold in check tumor cells in a steady state. Similarly,
other mechanisms that regulate the environment such as inflammation and angiogenesis pathways may
also influence tumorigenesis.

The only way to be certain of the treatment of a cancer is the complete eradication of cancer. The
phenomenon of tumor dormancy points to the lack of insight we have into the mechanisms by which
cancers are eliminated upon treatment with a targeted therapy. In the era of targeted therapeutics, no
explanation has been provided for why targeting a specific oncogene or tumor suppressor gene would
result in the regression of a tumor. [132–136].

Carcinogenesis in humans is a complex multistep process. Tumorigenesis is caused by genetic
changes that activate oncogenes or inactivate tumor suppressor genes. However, it takes a dysfunctional
tumor microenvironment to raise a tumor. Tumors are dependent on angiogenesis for growth. The
tumor ecosystem includes many facets of the microenvironment, such as the immune system, the
extracellular matrix (including the cancer stem cell niche), and the inflammation cells. Most cancer
tumors are generally untreatable using conventional monotherapies.

There is a vast literature dedicated to tumor-host interaction [14, 15, 18–131]. The dynamical
system that we investigate includes this process. We will discuss this interaction in detail in the
following section.
2 Entropy and the Model

In Ref. [13] a physical justification for the Gompertz’s law of tumor growth is presented. The deduction is based on the concept of entropy. The entropy equation used in Ref. [13] is the well-known Boltzmann-Gibbs extensive entropy. González et al. have used the new non-extensive entropy [122, 137–141] in the derivation of a new very general evolution equation for tumors [17]. The logistic, Gompertz, exponential and power laws are particular cases of the new equation. However, it includes many other cases. The non-extensive parameter $q$ [17, 122, 137–141] plays an important role in the new model.

Different types of tumors possess different values of the non-extensive parameter $q$. Boltzmann entropy is appropriate if the microscopic interactions are short-ranged, the effective microscopic memory is short-ranged, and/or the boundary conditions are nonfractal. Non-extensive entropy has been developed for systems with long-range interactions, long-range microscopic memory, and systems which possess fractal or multifractal properties [17,122,137–141].

The new generalized equation for untreated tumor growth is the following

$$\frac{dX}{dt} = \frac{KX_{\infty}}{q-1} \left[1 - \left(\frac{X}{X_{\infty}}\right)^q - \left(1 - \frac{X}{X_{\infty}}\right)^q\right],$$

where $K$ is a certain free parameter and $X_{\infty}$ is the asymptotic value of $X(t)$ when $t \to \infty$. All the published experimental data that we know can be described by this new equation [17].

In the present paper, we will investigate the following dynamical system

$$\frac{dX}{dt} = \frac{KX_{\infty}}{q-1} \left[1 - \left(\frac{X}{X_{\infty}}\right)^q - \left(1 - \frac{X}{X_{\infty}}\right)^q\right] - RX - bXY - C(t)X,$$

$$\frac{dY}{dt} = d \left(X - eX^2\right)Y - fY + V,$$

where $X$ denotes the tumor volume and $Y$ the antibodies density. Equation (2) describes the reproduction of the cancer cells, which are destroyed when they meet the agents of the host response system (term $-bXY$). The reproduction of the agents of the response system is described by the term $d \left(X - eX^2\right)$, where we consider that, initially, the presence of cancer cells stimulates the reproduction of $Y(t)$. When the number of cancer cells is large, the reproduction of the antibodies is inhibited, which is why for large quantities of cancer cells the human defenses are depressed. The term $-fY$ corresponds to the natural death of the antibodies. The term $V$ represents the external flow of antibodies. The term $-RX$ stands for the natural death of the cancer cells. In most cases, $R = 0$. The term $-C(t)X$ stands for the cell-killing process due to different therapies.

3 Investigation of the model

First, we will consider the case where $q = 2$, $X_{\infty} \to \infty$, $R = 0$, and $C(t) = 0$. Let us redefine $a := 2K$. The dynamical system (2,3) can have, in principle, three fixed points

$$P_I := (X_1, Y_1) := \left(0, \frac{V}{f}\right),$$

$$P_{II} := (X_2, Y_2) := \left(\frac{1}{2e} + \sqrt{\frac{1}{4e^2} - \frac{h}{a/b}}, \frac{a}{b}\right),$$

$$P_{III} := (X_3, Y_3) := \left(\frac{1}{2e} - \sqrt{\frac{1}{4e^2} - \frac{h}{a/b}}, \frac{a}{b}\right),$$

where $h := (fa/b - V)b/ead$. Of course, the fixed points $P_{II}$ and $P_{III}$ exist only when they are real and non-negative. The conditions for the existence of fixed points $P_{II}$ and $P_{III}$ are the following
inequalities

\[ \frac{1}{4e^2} - h > 0, \]  
\[ h > 0. \]  
\[ (7) \]
\[ (8) \]

The inequality (8) is necessary for fixed point \( P_{III} \).

We discuss here some results of the dynamical system investigation. If \( af \leq Vb \) the fixed point \( P_I \) is a stable node and the fixed point \( P_{II} \) is a saddle. If \( af > Vb \), and \( h - 1/4e^2 < 0 \), the three fixed points exist and are non-negative. Both fixed points \( P_I \) and \( P_{II} \) are now saddles. Between these two points, there is the point \( P_{III} \) which is stable. If \( af > Vb \), and \( h - 1/4e^2 > 0 \), then there is only one fixed point \( (P_I) \) which is unstable now. As a result of this, most trajectories tend to infinity. This means the tumor will grow limitless.

It is helpful to know the eigenvalues of the Jacobian matrix corresponding to the fixed points. For the point \( P_I \), the eigenvalues are

\[ \lambda_1^{(I)} = a - \frac{Vb}{f}, \]  
\[ \lambda_2^{(I)} = -f. \]  
\[ (9) \]
\[ (10) \]

For the point \( P_{II} \), the eigenvalues are

\[ \lambda_1^{(II)} = \frac{1}{2} \left[ B + \sqrt{B^2 - 4A} \right], \]  
\[ \lambda_2^{(II)} = \frac{1}{2} \left[ B - \sqrt{B^2 - 4A} \right], \]  
\[ (11) \]
\[ (12) \]

where \( B := (X_2 - eX_2^3)d - f, \) \( A := bd(1 - eX_2)X_2Y_2. \)

For the point \( P_{III} \), the eigenvalues are

\[ \lambda_1^{(III)} = \frac{1}{2} \left[ G + \sqrt{G^2 - 4H} \right], \]  
\[ \lambda_2^{(III)} = \frac{1}{2} \left[ G - \sqrt{G^2 - 4H} \right], \]  
\[ (13) \]
\[ (14) \]

where \( G = d(X_3 - eX_3^3) - f, \) \( H = bd(1 - eX_3)X_3Y_3. \) In the neighborhood of point \( P_{II} \), the separatrix can be approximated by the straight line

\[ Y = -\left( \frac{\lambda_2^{(II)}}{bX_2} \right) X + a + \frac{\lambda_2^{(II)}}{b}. \]  
\[ (15) \]

Any point corresponding to initial conditions of the Cauchy problem on the right of the separatrix leads to a fatal outcome. On the other hand, if the initial conditions correspond to a point located on the left of the separatrix, the system will evolve to a stable fixed point. See the general dynamics in Fig. 1. Using Eq. (15) we can calculate approximately the threshold or critical tumor volume that would increase limitlessly when the number of antibodies is zero:

\[ X_{\text{crit}} = \left( 1 + \frac{a}{\lambda_2^{(II)}} \right) X_2. \]  
\[ (16) \]

Note that the different phase space topologies represented in Fig. 1 depend on the competition between the host-tumor “forces”. Fig. 2a shows a strong host defense in principle able to reduce to zero any small tumor. Fig. 2b shows an equilibrium between the host defenses and the tumor strength. This equilibrium can conduct to the formation of stable cancer structures. They are controlled for
Figure 1: Phase-space portraits corresponding to the behavior of dynamical system (2–3). Isoclines are shown in dashed lines. See the detailed discussion in the main text. 

(a) There are two fixed points: $P_I$ is a stable node, $P_{II}$ is a saddle point. The phase trajectories on the left of the separatrix lead to the fixed point $P_I$. The phase trajectories on the right of the separatrix lead to a fatal outcome. 

(b) There are three fixed points. The point $P_I$ is now a saddle point, which is always unstable. The new point $P_{III}$ is stable, which leads to dormancy. 

(c) There is only one fixed point: Point $P_I$ is a saddle point. Almost all trajectories lead to a fatal outcome. 

(d) When $X_\infty < \infty$ (but very large), there is an additional stable fixed point that usually corresponds to a large value of $X$. All the trajectories on the left of the separatrix lead to this point. 

(e) When $X_\infty$ is small (this is related to the microenvironment, among other factors), it is possible that there is only a stable fixed point (point $P_I$ where $X = 0$). All the trajectories lead to this point. This is a very favorable situation.
now. However, they are very dangerous. After some time, if the immune system is depressed for some reason, these structures can expand. Finally, Fig. 1c shows a case where the host defenses cannot sustain the struggle with cancer.

Other methods can also be useful to analyze the dynamics. The isoclines of the system can be obtained from the expression

\[
\frac{dY}{dX} = \frac{d(X - eX^2)Y - fY + V}{aX - bXY} := m,
\]

where \( m \) is the slope of the phase trajectory. The explicit expression for the isoclines is

\[
Y = \frac{amX - V}{d(X - eX^2) + bmX - f}.
\]

Let us analyze the main isoclines. For \( m = \infty \), we have two lines, namely \( X = 0 \) and \( Y = a/b \). For \( m = 0 \), we have the isocline \( Y = V/(f - dX - deX^2) \). We can observe the isoclines in dashed lines in Fig. \( \text{[1]} \). It is very important to study the different cases \( d > 4ef \) and \( d < 4ef \). A careful analysis of the behavior of the phase trajectories allows us to conclude that the condition

\[
d > 4ef,
\]

is favorable for the patient. Although it is not a necessary condition, it is a sufficient condition to avoid the dynamics shown in Fig. \( \text{[2]} \). Be aware that the zone

\[
Y < \frac{a}{b}, \quad X > \frac{1}{2de} \left( d - \sqrt{d^2 - 4def} \right),
\]

is still very dangerous.

In many cases, it is convenient to re-write the system (2–3) as one equation where the only unknown is \( X(t) \) and \( Y \) disappears:

\[
\frac{d^2X}{dt^2} + \left[ f - d \left( X - eX^2 \right) \right] \frac{dX}{dt} - \frac{1}{X} \left( \frac{dX}{dt} \right)^2 = (af - Vb)X - adX^2 + adeX^3.
\]

Eq. (21) can be written in the form

\[
\frac{d^2X}{dt^2} + F_{\text{dis}} \left( X, \frac{dX}{dt} \right) = -\frac{dU(X)}{dX},
\]

where

\[
U(X) = \frac{1}{2}(Vb - af)X^2 + \frac{1}{3}adX^3 - \frac{1}{4}adeX^4,
\]

and

\[
F_{\text{dis}} = \left[ f - d \left( X - eX^2 \right) \right] \frac{dX}{dt} - \frac{1}{X} \left( \frac{dX}{dt} \right)^2.
\]

Equation (22) and the potentials shown in figure 3 suggest that resonance could play an important role in cancer development. In these pictures, we can observe the existence of potential wells and barriers. The fictitious particle can be trapped in one of those potential wells. In this case, we can have tumor dormancy. However, external perturbations or the change in the potential \( U(X) \) due to aging or other diseases can lead to the decrease in height of the right side potential barrier generating new cell proliferation that can provoke the creation of large cancer tumors.

The model can be generalized using Eq. (22) and a more general potential \( U(X) \) with many maxima and minima. An example of a possible new potential is shown in Fig. \( \text{[3]} \). The creation of a higher barrier and a lower potential well can be related to the targeting of an oncogene. However, this will
Figure 2: The fate of different initial conditions. (a) Points $\alpha$, $\beta$, and $\delta$ will ride phase trajectories that tend to the fixed point $P_I$ where $X = 0$. Note that for point $\delta$ the tumor size is large. Nevertheless, the tumor size will be reduced to zero. On the other hand, points $\gamma$ and $\varepsilon$ will ride phase trajectories that lead to a fatal outcome. (b) The separatrix of saddle point $P_I$ is very close to the axis $Y$. Initial condition $\eta$ will tend to fixed point $P_{III}$. Meanwhile, the initial condition $\theta$ conducts to a fatal outcome. (c) Almost all initial conditions tend to a fatal outcome. (d) Initial conditions $\varphi$ and $\mu$ tend to the “good” point $P_I$ where $X = 0$. Whereas the initial condition $\psi$ tends to a fatal outcome. (e) The limit of all initial conditions is $X = 0$. 

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Figure 3: Possible potentials $U(X)$ for Eq. (22). (a) Case when fixed point $P_I$ is a stable node (it corresponds to the local minimum of the potential). Additionally, there is a saddle point (the maximum). (b) Case when there are three fixed points. Fixed point $P_I$ is a saddle, which is unstable. The “jump” over the potential barrier on the right is harder than in the case shown in Fig. 3c. (c) The same potential represented in Fig. 3b with different parameters. The height of the potential barrier on the right is lower than in the case of Fig. 3b. This case is a more dangerous scenario for the patient. (d) The Eq. (22) can be a more generalized model with a more general potential $U(X)$ with many minima and maxima. The Fig. 3d shows an arbitrary example.
lead to dormancy. This is not a cure. This phenomenon is in agreement with experiments. Later, a change in the potential due to some events discussed in the text can lead to regrowth. When the “fictitious” particle is oscillating inside one of the potential wells, an external oscillating perturbation can produce a resonant behavior of the particle motion leading to an increase of the amplitude that can make the particle to jump over the potential barrier and the tumor size to increase. Moreover, the formation of a potential barrier can be related to the inactivation of some oncogene. This process can stop cancer development for a while. This process is related to oncogene addiction. This idea could solve one of the most intriguing problems in recent cancer research. The external perturbation that can create resonance could be a recurrent lesion, injury or tissue damage. For example, this may be generated by smoking or frequent radiation exposure.

Equation (22) can be considered as Newton’s equation for a particle moving in the potential $U(X)$ in the presence of dissipative forces. The potential $U(X)$ that corresponds to the situation shown in Fig. 2a has the shape depicted in Fig. 3a. Notice that when the inequality

$$9e(Vb - af) + 2ad > 0$$  \hspace{1cm} (25)

is satisfied, the height of the maximum on the right is higher than the maximum at point $X = 0$ (see Fig. 3b). Otherwise, $U(X)$ has the shape shown in Fig. 3c. The case depicted in Fig. 3c is more favorable for the particle to jump above the maximum on the right, which is equivalent to unlimited growth in the number of cancer cells. A careful analysis shows that the condition

$$2d > 9ef$$  \hspace{1cm} (26)

is favorable for the patient. Moreover, in order to limit the “jumps” above the maximum on the right, it is convenient if the eigenvalues of fixed point $P_{III}$ are real and negative. In this case, this point behaves as a stable node (and not like a focus). This situation limits the “inertia” in the particle motion. When $X_\infty$ is a large but finite number, the dynamical system will have an additional fixed point that will be a stable equilibrium position. Let us call this equilibrium fixed point $P_{IV}$ (see figures 1d and 2d). Those phase trajectories that are on the right of the separatrix, instead of approaching infinity, will be approaching fixed point $P_{IV}$.

4 The general model

For $q > 1$, the topological behavior of the dynamical system [23] is very similar to the dynamics explained in Section 3. However, when $q \leq 1$, the fixed point $P_I$ will be always unstable. This means that it is impossible to reduce the tumor volume to zero. This is one of the most remarkable results of this investigation. This finding will play a very important part in the explanation of the phenomena discussed in the Introduction and in the design of new therapies.

5 Conventional therapies

As we have seen in the previous sections, for $q > 1$, the parameters of the system and the initial conditions play an important role in the outcome. The tumor-host interaction is decisive. There are situations where the immune system by itself can reduce to zero the tumor volume. Under other circumstances, the tumor volume will increase leading to fatal consequences.

If we apply conventional therapy $C(t) = C_o$ in the system [23] (where $C_o$ is a constant), for $q > 1$, the cancer cure can be accelerated. If $q \leq 1$, then for any value of $C_o$, $X(t)$ is never reduced to zero. The fixed point $P_I$ is always unstable.
Most cancer tumors are generally untreatable using conventional monotherapies. Some cancers can become dormant upon treatment with conventional therapies (this can be observed as a stable fixed point with $X > 0$) only to reoccur later. The parameters of the system can change due to illness, age, immune system depression, etc., et cetera. In some cases, the stable finite fixed point and the saddle points can disappear. As the fixed point $P_I$ is unstable, the dynamics will induce a lethal increase in the tumor volume. We would like to stress again that most cancer tumors are generally untreatable using conventional monotherapies.

6 How the model can guide physicians to invent better therapies

An extensive study of many experimental, clinical, and theoretical papers (including ours) leads us to conclude that $q$ depends on the genes. Our analysis in the previous sections shows that for $q \leq 1$, the fate of the patient is most certainly lethal. All this investigation leads to combination therapies $[144–172]$. We have to change $q$ first, then we can use therapies that change the parameters in such a way that the fixed point $P_I$ is asymptotically stable (a stable node), and finally, we need to apply therapies that will help the phase trajectory to go to the point $P_I$. The only way to have an effective treatment of cancer is the complete eradication of all the tumors. All this points to a combination of oncogene-targeted therapy, tumor-suppressor gene-targeted therapy, immunotherapy, anti-angiogenesis therapies, and tumor-cell killing therapies. Other combinations can also be successful.

6.1 Combinational therapies

Most cancer tumors are generally untreatable using conventional monotherapy. However, these tumors can be effectively treated with rationally designed combinational therapies. Our work is not completed until patients are cured of their disease. Essential to our ability to optimally kill cancers are approaches that should be combined with therapies that exploit oncogene addition and the exploitation of somatic loss-of-function tumor suppressor gene mutations. A second very important part of the combination is the use of our emerging ability to reactivate immune response to tumors $[147,148]$. If we are able to effectively combine these emerging therapeutic options, the road toward a cure is becoming clear.

We need therapies with the potential to target both tumor cells and tumor microenvironment. Drugs that target oncogenes can be effective in the treatment of some cancers. However, most tumors do reoccur. We have found that the success of the new therapeutic agents can be seen when used in combination with other kinds of therapies, including conventional treatments.

Oncogene addiction and cancer stem cells are related to $q$. FLT3 is a receptor tyrosine Kinase class III that is expressed on early hematopoietic progenitor cells and plays an important role in hematopoietic stem cell proliferation, differentiation, and survival. The addition of multitargeted Kinase inhibitor midostaurin to standard chemotherapy significantly prolonged overall and event-free survival among patients with Acute Myleoid Leukemia and FLT3 mutation $[214]$. Combination therapies provide a rational strategy to potentiate efficacy and potentially kill the tumors. Host immunity contributes to the anti-tumor activity of oncogene-targeted inhibitors within a complex network of cytokines and chemokines. Therefore, combining immunotherapy with oncogene-targeted drugs may be the key to cancer control. Targeted therapies can achieve impressive and rapid tumor remissions, although these results are eclipsed by the emergence of resistance mechanisms through selection in heterogeneous tumors, limiting clinical response to a relatively short duration $[215]$. In contrast, immunotherapy can give rise to long-term cancer control by eliciting active immune effectors that may lead to a curative response, but in a small group of patients.

Only combination will achieve long-term responses. We need to develop more rationalized combination therapies with oncogene-targeted therapies and immunotherapy. There are several combinations and trials described in Ref. $[215]$. The combination therapy provided a superior antitumor response.
to either single-agent modality alone. This suggests that combining BRAF-targeted therapy with IL-2 could contribute to increased tumor destruction.

Combination therapies comprised of oncogene-targeted and immunotherapeutic strategies are a promising emerging approach to cancer treatment. Patients who have rapidly progressing tumors with druggable mutations can benefit from oncogene-targeted drugs first. The change of the $q$ value can lead to the conditions for the stability of the fixed point where $X = 0$. The stabilization of this fixed point can allow the elimination of important tumor masses in a short time. Sequential immunotherapy administration could cause tumor immune infiltration and therefore, promote durable immune control of disease dissemination. All these studies can give rise to more personalized medicine for cancer treatment. Many of these phenotypic traits can be brought about by genetic alterations that involve the gain-of-function mutation, amplification, and/or overexpression of key oncogenes together with the loss-of-function mutation, deletion, and/or epigenetic silencing of key tumor suppressors.

There is tremendous complexity in the patterns of mutations in tumors of different origin. A key to successful therapy is the identification of critical, functional points in the oncogenic network whose inhibition will result in the system failure, that is, the cessation of the tumorigenic state by apoptosis, necrosis, senescence, or differentiation. We believe these critical structures in the oncogenic network are related to parameter $q$.

The two mainstay treatment options for cancer today (chemotherapy and radiation) are examples of agents that exploit the enhanced sensitivity of cancer cells to DNA damage. Scientists do not have a clear molecular understanding of why they eventually fail. The goal of cancer therapy is to target the hallmarks as tumor-specific liabilities, preferably through the combinatorial application of a number of drugs. Thus, we need a thorough understanding of the nature of these hallmarks. Our understanding is the following. In order to change $q$, we need both oncogene-targeted and tumor-suppressor-targeted therapies. It is already clear that each of even the best therapies applied alone eventually fail in the majority of cases [143]. A combinatorial series of several different therapies applied concurrently is needed to eliminate all of the cancer cells in a patient. Semenza et al. is using combination therapy in the treatment of chemoresistant breast cancer [216]. Previous research revealed that triple-negative breast cancer cells show a marked increase in the activity of many genes known to be controlled by the protein hypoxia-inducible factor (HIF). HIF enhances the survival of breast cancer stem cells, which are the cancer cells that must be killed to prevent collapse and metastasis. These are drugs that block HIF from acting. Semenza’s team genetically altered the cancer cells to have less HIF. Thus the cancer stem cells were no longer protected from death by chemotherapy, demonstrating that HIF was required for the cancer stem cells to resist the toxic effects of paclitaxel. Triple-negative breast cancer cells were given paclitaxel plus the HIF inhibitor digoxin. Treatment with digoxin and paclitaxel decreased tumor size by 30 percent more than treatment with paclitaxel alone. The combination also decreased the number of breast cancer stem cells. Treatment with digoxin plus a different chemotherapy drug, gemcitabine, brought tumor volumes to zero within three weeks and prevented the immediate relapse at the end of the treatment. For physicians, how this will be accomplished remains to be determined. We hope that our model can help solve this problem.

The different therapies participating in the combination should act synergistically in such a way that suppressor mutation for the first therapy cannot suppress the second therapy and vice versa. This combinatorial series of different therapies can provide a cure. Experimental design mathematics can be used a posteriori as an inverse problem in order to obtain the experimental design matrix. This will allow us to obtain the impact in cancer cell killing of different therapies. The total cancer cell killing impact should be increased logarithmically, or at least using a late-intensification schedule [15, 16]. We believe that using our models as a guide it is possible to design a proper combination of cancer therapies. Through this combination, it is possible to convert cancer from a death sentence into a curable disease.

Despite encouraging results, Oncolytic Virus monotherapy based exclusively on virus replication-
induced oncolysis often does not demonstrate all the desired qualities, especially when tested against virus-resistant malignancies [6–10,212]. Usually, Oncolytic Virotherapies are engineered to express an exogenous transgene with anti-tumor activity and/or combined with standard treatments like radiotherapy or chemotherapy. A number of recombinant Oncolytic Virotherapies expressing a transgene for p53 or another p53 family member (p63 or p73) have been engineered with the goal of generating more potent Oncolytic Virotherapies that function synergistically with host-immunity and/or other therapies to reduce or eliminate tumor burden. Such transgenes have proven effective at improving Oncolytic Virotherapy and the researchers have shown mechanisms of p53-mediated enhancement of Oncolytic Virotherapy, provided they have optimized p53 transgenes and explored drug Oncolytic therapies combinatorial treatments. There is a study with combination Adenovirus Δ23-p3 plus radiotherapy with good results. Experiments and clinical trials data suggest that Oncolytic Virotherapy-encoded p53 can simultaneously produce anti-cancer activities while assisting, rather than inhibiting, virus replication in cancer cells. One of the major advantages of using p53-armed Oncolytic therapy is their enhanced oncotoxicity [212].

Oncolytic Virotherapies aim not only for direct Oncolysis of cancer cells flowing virus replication, but also stimulation of a host’s anti-cancer (innate and adaptive) immune responses. Various studies have shown that beneficial p53 functions include the promotion of enhanced anti-tumor immunity, both innate and adaptive. It is believed that p53 transgene expression would augment the anti-tumor immunity to help eliminate the tumor during Oncolytic Virotherapy treatment. The engineered adenovirus, SG7605-11R-p53, tested in gallbladder cancer cell lines demonstrated that infection with p53-11R improved the antitumor effect and prolonged survival, compared with control viruses.

Let us discuss the combination of Oncolytic Viruses p53 transgene with radiotherapy [212]. Because p53 has been shown to enhance the effects of radiotherapy [212], researchers tested the combination of Oncolytic Virotherapy with radiotherapy against glioma cancer cells. AdΔ24-p53 and radiotherapy increase antitumor efficacy compared with every single treatment. This study highlights that AdΔ24-p53 combined with radiotherapy can eradicate tumors, which would otherwise escape Oncolytic Virotherapy as a monotherapy. Adenoviral vectors were injected at different doses depending on the administration route. The most common route used a virus dose ranging from $1 \times 10^8$ to $7.5 \times 10^{12}$ VPs. Other injection routes were also utilized such as intra-arterial ($7.5 \times 10^9$ to $7.5 \times 10^{13}$ VPs). Regarding bladder and lung cancer, the Adenoviral vectors were transmitted by intravesicular instillation ($7.5 \times 10^{11}$ to $7.5 \times 10^{13}$ VPs). The majority of patients who received Oncolytic Virotherapy displayed regression of tumor mass or a transient stabilization of their disease.

We propose to use a logarithmic function to calculate the dose [16, 17]. Replicating Oncolytic Virotherapy-p53 viruses based on other viruses could be more efficient in future trials, because they may spread within the tumors amplifying p53 expression and increasing oncolysis. Replicating Oncolytic Viruses could improve the anti-tumor response by the lysis of tumor cells to allow the release of numerous anti-tumor antigens into the tumor microenvironment. These antigens could be processed and potentially lead to sustainable adaptive immune responses. Oncolytic Virus-p53 therapy can simultaneously achieve direct oncolysis and anti-tumor immunity (against several tumor-specific antigens, including mutant p53). More experiments can be conducted combining Oncolytic Virotherapy-p53 viruses with chemotherapy. Additionally, the use of statins or the inhibitors of these kinases in combination with Oncolytic Virotherapy encoding p53 could provide additional benefits.

## 7 Hallmarks of cancer

Cancer is a complex collection of distinct genetic diseases united by common hallmarks (see Fig. 4a) [173–175]. Cancer arises through a multistep, mutagenic process whereby cancer cells acquire a common set of properties including unlimited proliferation potential, self-sufficiency in growth signals, and

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1Adenoviral vectors can be administered at different doses
resistance to antiproliferative and apoptotic cues. Tumors evolve to garner support from surrounding stromal cells, attract new blood vessels to bring nutrients and oxygen, evade immune detection, and ultimately metastasize to distant organs.

Some modern papers define the following seven hallmarks of cancer: selective growth and proliferative advantage, altered stress response favoring overall survival, vascularization, invasion and metastasis, metabolic rewiring, an abetting microenvironment, and immune modulation [173–175]. An example is RAS protein. It is chronically active in 30% of cancers and in over 90% of pancreatic carcinomas, often via missense mutations in its gene or inactivating mutations in one of its negative regulators (e.g. NF1). Mutations in RAS result in a plethora of effects beyond enhanced growth and proliferation that include suppression of apoptosis, rewiring of metabolism, promoting angiogenesis, and immune evasion. A single signaling cascade could be implicated in multiple hallmarks of cancer. Exactly how cancer cells escape dormancy (“awaken”) and proceed to form overt metastasis (colonization) is poorly understood!

We believe that parameters $q$, $K$ and $X_\infty$ are related to evading apoptosis, insensitivity to anti-growth signals, sustaining proliferative signaling and chronic proliferation. Parameter $X_\infty$ is connected with evading growth suppressors, enabling replicative immortality, limitless replicative potential, genome instability, and rewiring metabolism. Parameters $d$, $e$, $f$, $V$, $b$ and $X_\infty$ are associated with the immune system, rewiring metabolism, angiogenesis, microenvironment, inflammatory cells, tissue invasion, and metastasis. Parameter $q$ is linked to oncogene addiction. In particular, $q$ can be changed targeting cancer stem cells, oncogenes, and tumor-suppressor genes. Figure 4 shows some connections between the parameters and the hallmarks of cancer. Tissue invasion and metastasis can be affected by parameter $X_\infty$. By targeting individual hallmarks features or enabling characteristics it may be possible to achieve therapeutic benefit. We should attack as many hallmarks as possible.

Experiments have corroborated the existence of immune surveillance. Despite immune surveillance, tumors continue to develop in bodies with intact immune systems. Cancer immunoediting is the process by which the immune system eliminates and shapes malignant disease and encompasses three phases: elimination, equilibrium, and escape. Inactivation of the second p53 allele leads to increased cell proliferation, decreased apoptosis, and tumor development [212]. BRCA1 and BRCA2 are tumor suppressor genes associated with breast and ovarian cancers, along with several other cancers.

HER2/neu is overexpressed in 25% of breast cancers. These cancers tend to be more aggressive
clinically. RAS is the oncogene most commonly activated in human tumors. The human genome encodes three RAS genes: H-ras, K-ras, and N-ras. A large fraction of tumors contain mutations in one of these three genes. For example, 70 – 90% of pancreatic carcinoma contain a mutation in the K-ras gene. The MYC oncogene is often amplified or overexpressed in cancers.

Many oncogenes are responsible for the self-sufficiency in Growth Signals of the cells. For example, RAS is found mutated in about 25% of human tumors, thus leading to ligand-independent activation of the ras-raf-mapk signaling pathway. Insensitivity to antigrowth signals is produced by the loss of tumor suppressor genes.

Cancer cells evade antiproliferative signals. At the molecular level, many anti-proliferative signals are funneled through the Rb protein (and its two relatives, P107 and P130). Antigrowth signals are impaired e. g. by the loss of CDK inhibitors (P16, P21, p53). Resistance to apoptosis can be acquired by cancer cells through a variety of strategies. For example, cancer cells can evade apoptosis by the loss of p53.

Self-sufficiency in growth signals, insensitivity to antigrowth signals does not ensure expansive tumor growth. Most cells possess a mechanism that limits their proliferation using the number of telomere repeats at the end of chromosomes. Some tumors cells avoid this via a mutation that upregulates expression of the telomerase enzyme, thus acquiring limitless replicative potential by maintaining their telomeres.

8 Therapy strategies

This research work has proved seminal in rational drug design. The main strategy is to increase \( q \) such that \( q > 1 \). In this case, the cancer is curable because the fixed point \( P_I \) can, in principle, be stable. Of course, this does not guarantee that the point \( P_I \) is stable. For instance, for \( q = 2 \), we need in addition \( Vb > af \). Thus, immunotherapy plays an important role.

Equation 3 is related to the microenvironment. Anti-angiogenesis can limit the expansion of the tumor. Therapies that reduce \( X_\infty \) can eliminate the limitless proliferation and many other cancer-related properties. A very small \( X_\infty \) can lead to complete elimination of cancer (see Fig. 2f). Some therapy strategies are:

1. Oncogene-targeted and tumor suppressor targeted therapies (sequential, in the sense that it should be applied before the combinations described later).

2. Immunotherapy, anti-angiogenesis, oncogene-targeted chemotherapy (concurrent).

3. Immunotherapy, oncolytic virotherapy, plus transgene p53, plus chemo-radiation, logarithmic cell-kill function (concurrent).

Below we discuss several strategies including connections between Hallmarks and combinations [176]. Combination therapy targeting both cancer stem-like cells and bulk tumor cells should improve the efficacy of breast cancer treatment. The cancer stem-like cells hypothesis suggests that tumor development and metastasis are driven by a minority population of cells, which are responsible for tumor initiation, growth, and recurrence. The inability to efficiently eliminate cancer stem-like cells during chemotherapy, together with these cells being highly tumorigenic and invasive, may result in treatment failure due to cancer relapse and metastases.

The ideal panacea for cancer would kill all malignant cells, including cancer stem-like cells and bulk tumor cells. Both chemotherapy and cancer stem-like cells are insufficient to cure cancer. We need combination therapy with cancer stem-like cells-targeted agents and chemotherapeutics.

Salinomycin plays an important role against the cancer stem-like cells. Combination therapies of Salinomycin with conventional chemotherapy (paclitaxel or lipodox) showed a potential to improve
cell killing. Cancer stem-like cells are highly resistant to standard chemo- and radiotherapies and they persist following treatment. Conventional therapies may achieve clinical tumor reduction at the beginning of treatment but are insufficient to cure cancers [217]. Thriving cancer stem-like cells under the influence of the stem cell microenvironment lead to tumor recurrence and disease relapse and even promote the formation of distant metastases, ultimately leading to treatment failure following chemoand radiotherapy [12,14,16].

The combinatorial therapy of paclitaxel, lipodox, and salinomycin produced a synergetic effect and led to a significantly higher cytotoxicity than the use of either lipodox or salinomycin alone at all concentrations and time points tested. A synergy between paclitaxel and salinomycin for growth inhibition were seen with a long term drug incubation for 72 hours in all 6 combination treatment groups, indicating that combination therapy enhanced antitumor activity if prolonged exposure of drugs was used.

Eradication of all malignant cells within a patient’s cancer including cancer stem-like cells and their progeny is essential to prevent cancer relapse and metastasis. Standard chemo- and radiotherapy may have clinical benefits on tumor regression in advanced stages of cancer as a result of their killing the bulk tumor population, but disease relapse is highly likely to occur due mainly to their minimal effect on the cancer stem-like cells population. A cancer stem-like cells-targeted therapy may have substantial clinical benefit.

We would like to stress that cancer stem cells, oncogene addiction, and tumor suppressor gene activity are related to parameter q. Accumulated evidence supports the conclusion that cancer stem-like-cells-targeting agents are most effective in eradicating cancer when these agents are in combination with conventional cytostatic drugs and/or novel cancer stem-like cell-targeted drugs [35,37]. Targeted strategies being developed include direct inhibition of the self-renewal of stem-like cells, indirect modulation of the microenvironment and direct induction of death of cancer stem cells by chemical agents that trigger differentiation of cancer stem-like cells, immunotherapy, and oncolytic viruses [218].

Oncogene addiction refers to the curious observation that a tumor cell, despite its plethora of genetic alterations, can seemingly exhibit dependence on a single oncogenic pathway or protein of its sustained proliferation and/or survival. A profound implication of this hypothesis is that switching off this crucial pathway upon which cancer cells have become dependent should have devastating effects on the cancer cell while sparing normal cells that are not similarly addicted. This is the discriminating activity required for effective cancer therapeutic.

Activated kinases are the Achilles heel of many cancers. Just as acute inactivation of addicting oncoproteins frequently leads to cancer cell death, recent evidence points to similar outcomes engendered by the reintroduction of wild-type versions of tumor suppressor genes that are frequently inactivated in cancer cells. Tumor suppressor hypersensitivity may represent another dimension of oncogene addiction since it is likely that in the establishment of oncogene addicted state, a prerequisite may involve the removal of support systems such as tumor suppressors that buttress normal cell survival.

MYC-induced apoptosis plays a physiological role in antigen-induced negative selection of developing T cells. An important and therapeutically relevant feature of oncogene addiction relates to the tumor cell-specific induction of apoptosis. This phenomenon is related to parameter q. Acute oncoprotein inactivation in cancer cells often results in apoptosis. Factors that influence apoptosis are likely to influence the response to oncoprotein inactivation in oncogene inactivation in oncogene addicted tumors. Dysregulated cell proliferation and suppression of apoptosis are hallmarks of cancer. Cancer cells deploy a diverse array of mechanisms to avoid apoptosis, such as inhibition of cell death mediating proteins, and/or overexpression of cell death inhibitory proteins.

The oncogenic shock model may also have implications regarding optimal strategy for treating patients with targeted inhibitors. The oncogenic shock model may also have implications for the use of drug combinations in cancer therapy. The correct design of cancer chemotherapy drugs schedules is very important here. Oncogene addiction may lead to new therapeutic strategies. The identification of
addiction settings involving codependence on two different oncogene products may lead to a rational combination treatment strategy involving the simultaneous disruption of both genes.

The phenomenon of tumor suppressor hypersensitivity could also lead to a therapeutic opportunity in which a tumor suppressor is reintroduced into cancer cells. Cancer cells growth and survival can often be impaired by the inactivation of a single oncogene. For this, we have to identify the Achilles heel. **Combinational therapy** is required to prevent the escape of cancers from a given state of oncogene addiction. It is unlikely that the use of a single molecular targeted agent will achieve long-lasting remissions on cures in human cancers, especially for late-stage disease. Combinational therapy will, therefore, be required. This combination should be **rationally designed**.

Clinical studies \[177\] indicate that the efficacy of certain molecularly targeted agents can be enhanced by combining them with cytotoxic agents, i.e. agents that often act by inhibiting DNA or chromosomal replication. In order to understand how our strategies are confirmed by experimental and clinical studies, see the References \[176\,\text{–}\,213\].

Trastuzumab that targets HER2 can improve response and survival rates if given in combination with paclitaxel to patients with metastatic breast cancer. The combination of bevacizumab or cetuximab with cytotoxic chemotherapy agents can also improve response rates in patients with metastatic breast and colon cancer. When bevacizumab was added to a combination chemotherapy regime, it improved overall survival rates in patients with metastatic colon cancer.

We have applied experimental design techniques **a posteriori** as an inverse problem using data from experiments and clinical studies. The conclusion of this analysis is that the combination of therapies that we propose corroborate the mathematical model results and provide additional evidence for the therapy schedule that we have designed.

9 Discussion

Our objective with these models is to achieve Hanahan’s and Weinberg’s dream: to develop cancer research into a logical science \[173\]. “Cancer prognosis and treatment will become a rational science. It will be possible to understand with precision how and why treatment regimens and specific antitumor drugs succeed or fail”. In this spirit, we can develop their ideas in such a way that anticancer drugs are targeted to each of the hallmark capabilities of cancer. Some, used in appropriate combinations, will be able to prevent incipient cancers from developing, while others will cure pre-existing cancers, elusive goals at present. Dynamical systems can help cancer biology to become a science with the mathematical structure and logical consistency similar to that of physics.

The outcome of dynamical system \[23\] depends on the set of parameters and the initial conditions. For example, in the phase space represented in Fig. 2a (for a fixed set of parameters), the initial conditions decide everything. For initial conditions given by points $\alpha, \beta, \text{and} \delta$, the phase trajectories are attracted to the fixed point $P_I$, where $X = 0$. This is a good outcome. Notice that for the initial point $\delta$, the size of the tumor is large. However, the dynamics lead to a cure. All the mentioned points ($\alpha, \beta, \text{and} \delta$) are to the left of the separatrix of saddle point $P_{II}$. On the other hand, the fate of points $\gamma$ and $\varepsilon$ is fatal. These points are to the right of the separatrix of the fixed point $P_{II}$.

In the phase space shown in Fig. 2b, the fixed point $P_I$ is unstable. There is an additional stable point $P_{III}$ with $X \neq 0$. This point represents a dormant state. The initial conditions defined by the points $\zeta$ and $\eta$ will lead to phase trajectories that are attracted to the point $P_{III}$. However, other initial data (like point $\theta$) will lead to an unlimited increase of the tumor size.

In the phase space shown in Fig. 2c, the only fixed point $P_I$ is unstable and all the phase trajectories lead to an unlimited increase of the tumor. Fig. 2d shows a phase space where $X_\infty \neq \infty$. Note that there is a stable fixed point $P_{IV}$, that is now the attractor that symbols the limit maximum size of the tumor. The initial data that stand for the points $\varphi$ and $\mu$, will go to the point $P_I$ ($X = 0$), while the point $\psi$ will move to the fixed point $P_{IV}$. The latter is not a good prognosis.
When $X_\infty$ is small, the outcome can be very favorable. This is shown in Fig. 2e. $X_\infty$ is related to many cancer hallmarks and genes. If $X_\infty$ is finite, there is no limitless proliferation. The invasion is also bounded. A small $X_\infty$ is an evidence that the microenvironment is not friendly. Fig. 2e shows the dynamics when $V/f > a/b$ and

$$X_\infty < \frac{111}{6} e + \frac{2f}{3a}. \quad (27)$$

Note that all the phase trajectories tend to the fixed point $P_I$ ($X = 0$).

Therapy can change the outcome. Let us return to Fig. 2a. The initial point $\gamma$ would lead to a fatal outcome. However, even a slight change in the constant therapy $-C_0 X$ in the system (2-3), can change parameter $a = 2K$. This can conduct to a reposition of the separatrix of fixed point $P_{II}$ such that the $\gamma$ point will ride a trajectory moving to the point $P_I$ ($X = 0$).

We have already discussed the unfortunate situation when $q \leq 1$, which provokes the fixed point $P_I$ to be unstable. There is a therapy that can change $q$ (see previous sections). In that case, we can be in a situation like the one shown in Fig. 2a. Both cell-killing therapies and immunotherapy can get the dynamics on a trajectory moving to a (now stable) fixed point $P_I$ ($X = 0$). The articles [176–213] corroborate these statements.

9.1 Treatment schedules

Even in our previous papers [15–17], we had pointed out the importance of combination therapies and time-dependent treatments. Figure 6 shows the behavior of the untreated tumors according to Eq. (1). This is exactly what happens in real life. When $q > 1$, and the host response is strong enough, we can reduce the tumor size to zero even with constant therapy. This is shown in Fig. 6. If $q = 0$ or $q < 1$, the cancer cannot be cured using conventional constant-dose therapy. We can observe this in Fig. 6.

We have discussed late-intensification schedules in other articles [15–17]. Many regular physicians are considering the logarithmic treatment as the optimal therapy in their practice with real patients. Indeed, our logarithmic therapy has been studied by other scientists and physicians with great success (see e.g. [118, 119]). In Ref. [119], the author has found that “during cancer treatments the dose intensity should not be decreased at any time because this will allow the tumor to relapse, and the logarithmic intensification therapy could be the optimal therapeutic strategy”. A similar statement can be found in Ref. [118]. Compare this with the results shown in this article and in Ref. [15–17].

We are including late-intensification in the new combination therapies that we are designing. We are finding that these new strategies can be even more powerful than the previously employed treatments. Physicians can face drug resistance during chemo. Here we present some examples of other ways to apply late-intensification therapies.

- Increasing the number of different drugs in the combination following a logarithmic function.
- Changing the types of drugs during late-intensification.
- Using new, more precise forms of applying radiation: electrons, protons, etc. This allows for the late-intensification to be applied without increasing the danger to normal cells.
- Increasing the number of viruses in virotherapy.

10 Conclusions

Most cancer tumors are generally untreatable using conventional therapies. Combination of anti-angiogenesis with chemotherapy leads to more effective cancer treatment. Synergistic antitumor activity results when metronomic cyclophosphamide is combined with a tumor-targeted immunotherapy.
Figure 5: Behavior of $X(t)$ in Eq. (1). Each case shows different outcomes for different parameters. (a) $K = 1$, $X_\infty = 15$, and $q = 2$. (b) $K = 2$, $X_\infty = 17$, and $q = 3$. (c) $K = 2$, $X_\infty = 18$, and $q = 3/2$. 
Figure 6: The response of cancer in the presence of different parameters and therapies. (a) $K = 1$, $X_\infty = 15$, $q = 2$, and $C(t) = 4$. Note that in this case $q > 1$. So we can find a constant dose $C(t) = C_0$ able to change parameter $a$ in such a way that the tumor will be reduced to zero. (b) $K = 2$, $X_\infty = 17$, $q = 0.6$, and $C(t) = 4$. Note that $q < 1$. A conventional therapy will never eradicate the cancer. (c) $K = 1$, $X_\infty = 18$, $q = 0.8$, and $C(t) = 6(1 + t^{0.2})$. Although $q < 1$, a late-intensification schedule can eradicate the cancer. (d) $K = 1$, $X_\infty = 18$, $q = 0.8$, and $C(t) = 6(1 + t^2)$. Another example of late-intensification schedule capable of eliminating the cancer.
The repair or inactivation of mutant genes may be effective in treatment of cancer. Drugs that target oncogenes have been shown to be effective in the treatment of some cancers. Although many of the new drugs show a significant clinical response, eventually most tumors do reoccur. Combination therapies are needed. We need therapies with the potential to target both tumor cells and the tumor microenvironment. Nevertheless, tumor cells posses the ability to circumvent most therapeutic agents when given as monotherapy.

We have found that the success of the new therapeutic agents is seen when used in combination with other kinds of therapies, including conventional treatments. Among many genetic lesions, mutational inactivation of the p53 tumor suppressor gene is one of the most frequent events found in human cancers. Tumor suppressor gene p53 plays a critical role in tumor progression, mainly by inducing growth arrest, apoptosis, and senescence, as well as by blocking angiogenesis. In addition, p53 generally confers the cancer cell sensitivity to chemoradiation. The successful development of p53 modulator drugs (to be used in combination with immunotherapy and chemo-radiation) can change current anticancer therapies.

Using our mathematical models and data from experiments and clinical studies, we have designed the following sequence of several sets of combinational therapies.

1. Oncogene-targeted therapy, tumor suppressor targeted therapy, and killing of cancer stem-like cells.

2. Immunotherapy, anti-angiogenesis, oncogene-targeted therapy, and chemotherapy. The goal of this round is to make the fixed point $P_I$ stable. These treatments are supposed to be applied concurrently. The conditions that arise following these treatments should make possible the eradication of cancer.

3. Immunotherapy, Oncolytic Virotherapy plus transgene p53, chemo-radiation, and logarithmic cell-kill function (concurrent application). This round should move the system to the left part of separatrix of the saddle fixed point $P_{II}$.

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