

Evolutionary Game Model of Cancer Resistance and Clonal Competition

PANYAWAT HAARSA

Department of Mathematics, Faculty of Science,
Srinakharinwirot University, Bangkok,
THAILAND

Abstract: - Cancer resistance is shaped by clonal competition and treatment-driven selection. This study develops a coupled evolutionary game model for therapy-sensitive and therapy-resistant tumor cells. Frequency-dependent selection is combined with one-way phenotypic switching and resource-limited tumor growth. The full triangular dynamical system is analyzed. Biological admissibility, equilibrium structure, local stability, and long-term tumor-burden behavior are established. Explicit treatment thresholds classify sensitive dominance, resistant dominance, stable coexistence, and bistability. In the switching-free case, the threshold crossings form boundary transcritical bifurcations. Increasing treatment pressure promotes resistance, whereas a larger resistance cost shifts the transition toward higher treatment levels. Phenotypic switching removes the sensitive-only equilibrium and shifts the resistant-state stability boundary toward lower treatment pressure. Numerical simulations confirm the analytical equilibria for representative parameter regimes, with equilibrium errors below 10^{-6} . A finite-time parameter sweep is also consistent with the derived threshold structure. The model provides a qualitative mathematical framework for understanding how treatment pressure, resistance cost, clonal competition, and phenotypic switching shape cancer resistance.

Key-Words: - Evolutionary game theory, cancer resistance, clonal competition, replicator dynamics, treatment thresholds, phenotypic switching.

Received: April 5, 2026. Revised: May 7, 2026. Accepted: June 9, 2026. Published: October 26, 2026.

1 Introduction

Cancer is an evolutionary disease as well as a disease of uncontrolled cell growth. Tumors often contain multiple cell populations with different phenotypes and treatment responses. These populations compete for space, nutrients, and other limited resources [1], [2], [3], [4]. Treatment can alter this competitive environment. It may suppress therapy-sensitive cells while allowing resistant cells to survive and expand [4], [5], [6]. Resistance can therefore emerge through both cellular adaptation and treatment-driven selection.

Drug resistance remains a major obstacle to durable cancer control. Resistant cells may be present before treatment or may emerge during therapy [5], [6]. Their expansion can be promoted when treatment reduces the competitive pressure imposed by sensitive cells [7]. This ecological mechanism is closely related to competitive release. Adaptive therapy was developed in part to exploit such competition. Rather than always seeking maximal tumor reduction, it aims to preserve a population of sensitive cells that can suppress resistant cells [7]. This concept has motivated

mathematical and game-theoretic studies of resistance-aware treatment strategies [8], [9], [10].

Mathematical models provide useful tools for studying tumor growth, treatment response, and resistance evolution [11], [12], [13], [14]. Evolutionary game theory is particularly suitable when cellular fitness depends on population composition. In this framework, tumor phenotypes are represented as competing strategies. Their relative fitness is determined by interactions with other phenotypes and by the treatment environment [15], [16], [17], [18]. Game-theoretic models have been applied to clonal competition, tumor–stroma interactions, cooperation, and treatment response [19], [20], [21], [22], [23]. These studies show that resistance is influenced not only by intrinsic cellular properties but also by frequency-dependent ecological interactions.

Despite this progress, several mathematical issues remain important. Treatment-induced changes in clonal fitness should be linked explicitly to equilibrium and stability conditions. The effects of treatment pressure and resistance cost should also be separated through analytical thresholds. In addition, an analysis based only on clonal frequency

may not fully describe the coupled tumor system. Total tumor burden can have different long-term behavior even when the clonal composition approaches an equilibrium. Phenotypic switching can further modify the equilibrium structure. These features motivate a coupled framework that connects frequency-dependent selection, tumor burden, treatment thresholds, and switching within one dynamical system.

The present study develops such a framework for competition between therapy-sensitive and therapy-resistant tumor cells. Their interactions are described by a two-strategy evolutionary game. Treatment pressure reduces the relative fitness of sensitive cells, whereas resistance carries a fitness cost. The frequency dynamics are coupled to a resource-limited equation for total tumor burden. One-way phenotypic switching from sensitive to resistant cells is also included. The model is intended to describe qualitative dynamical regimes rather than patient-specific outcomes.

The analysis focuses on the full coupled system. First, the biologically feasible region is shown to be positively invariant. The full equilibrium structure and local stability conditions are then characterized. Treatment thresholds are derived to classify sensitive dominance, resistant dominance, coexistence, and bistability. The associated boundary transcritical bifurcations are identified in the switching-free case. The effect of phenotypic switching on the resistant-state stability threshold is also determined. Finally, numerical simulations are used to verify representative analytical equilibria and to compare finite-time behavior with the derived threshold boundaries. The main objective is to provide a compact mathematical description of how treatment pressure, resistance cost, clonal competition, and phenotypic switching shape resistance dynamics.

2 Mathematical Model and Methods

This section formulates the coupled evolutionary tumor model and describes the analytical and numerical methods used in the study. The model combines frequency-dependent competition, treatment pressure, resistance cost, phenotypic switching, and resource-limited tumor growth. The analysis focuses on qualitative dynamical regimes rather than patient-specific prediction.

2.1 Model Framework and Biological Assumptions

We consider a tumor composed of two phenotypes. The first consists of therapy-sensitive cells. The second consists of therapy-resistant cells. Sensitive cells are more affected by treatment. Resistant cells are less affected by treatment, but resistance may carry a fitness cost. This assumption is consistent with mathematical models of cancer resistance and adaptive therapy [7], [12], [13]. Let $S(t)$ denote the density of therapy-sensitive cells at time t . Let $R(t)$ denote the density of therapy-resistant cells. Both populations are assumed to be non-negative. The total tumor burden is $N(t) = S(t) + R(t)$. For $N(t) > 0$, the frequency of sensitive cells is defined by:

$$x(t) = \frac{S(t)}{S(t) + R(t)},$$

The frequency of resistant cells is therefore:

$$1 - x(t) = \frac{R(t)}{S(t) + R(t)}.$$

Hence, $0 \leq x(t) \leq 1$. The state $x = 1$ represents a fully sensitive tumor. The state $x = 0$ represents a fully resistant tumor. An interior state $0 < x < 1$ represents coexistence of the two phenotypes. Thus, $x(t)$ describes tumor composition, whereas $N(t)$ describes total tumor burden. These two variables will form the state variables of the coupled dynamical system.

2.2 Evolutionary Payoff Structure

The interaction between the two phenotypes is represented by a two-strategy evolutionary game. The payoff matrix is:

$$A = \begin{pmatrix} a_{SS} & a_{SR} \\ a_{RS} & a_{RR} \end{pmatrix}.$$

The entry a_{SS} is the baseline payoff of a sensitive cell interacting with a sensitive cell. The entry a_{SR} describes a sensitive cell interacting with a resistant cell. Similarly, a_{RS} and a_{RR} describe the corresponding interactions of resistant cells. For a sensitive-cell frequency x , the expected payoff of sensitive cells is:

$$F_S(x) = a_{SS}x + a_{SR}(1 - x) - c,$$

where $c \geq 0$ represents treatment pressure. Treatment reduces the relative fitness of sensitive cells. The expected payoff of resistant cells is:

$$F_R(x) = a_{RS}x + a_{RR}(1-x) - \gamma,$$

where $\gamma \geq 0$ represents the fitness cost of resistance. A larger value of γ gives a greater fitness penalty to the resistant phenotype. The payoff structure is phenomenological. It is not derived from patient-level data or from a detailed mechanistic cancer model. Instead, it provides a minimal representation of frequency-dependent clonal competition. The parameters a_{ij} , c , and γ are therefore interpreted as dimensionless relative-fitness quantities. They are not direct measurements of cellular growth rates. The conversion of payoff differences into a temporal selection rate is introduced in Section 2.3. This distinction preserves dimensional consistency between relative fitness and time-dependent population change. The mean payoff of the tumor population is defined by:

$$\bar{F}(x) = xF_S(x) + (1-x)F_R(x).$$

This quantity links clonal composition to total tumor burden. For $0 < N < K$, a positive value of $\bar{F}(x)$ gives $dN/dt > 0$, whereas a negative value gives $dN/dt < 0$. At a frequency equilibrium x^* , the condition $\bar{F}(x^*) = 0$ can generate additional equilibria in the full system.

2.3 Frequency Dynamics and Selection Rate

The sensitive-cell frequency follows replicator dynamics. The direction of selection is determined by the payoff difference between the two phenotypes [16], [17], [18]. We define:

$$D(x) = F_S(x) - F_R(x).$$

Using the payoff functions in Section 2.2 gives:

$$D(x) = (a_{SS} - a_{RS})x + (a_{SR} - a_{RR})(1-x) - c + \gamma.$$

This expression can be written as:

$$D(x) = qx + h,$$

where $q = a_{SS} - a_{RS} - a_{SR} + a_{RR}$,

and $h = a_{SR} - a_{RR} - c + \gamma$. The payoff quantities are dimensionless. We therefore introduce a selection-rate parameter $s > 0$, with units of inverse time. The frequency equation is:

$$\frac{dx}{dt} = sx(1-x)D(x).$$

Equivalently,

$$\frac{dx}{dt} = sx(1-x)(qx + h).$$

The parameter s converts the dimensionless payoff difference into a temporal rate of selection. A positive value of $D(x)$ favors sensitive cells. A negative value favors resistant cells. The magnitude of s controls the speed of this evolutionary change but does not change the sign of selection. In the absence of phenotypic switching, both boundary states are invariant. Thus, $x=0$ and $x=1$ remain possible states of the frequency dynamics. Interior equilibria may occur when $D(x)=0$. Phenotypic switching is incorporated separately in Section 2.4.

2.4 Phenotypic Switching

We include one-way phenotypic switching from therapy-sensitive to therapy-resistant cells. Let $\mu \geq 0$ denote the switching rate. The parameter μ has units of inverse time. Genetic mutation is not represented by this parameter. The switching process is represented by:

$$\left(\frac{dS}{dt}\right)_{sw} = -\mu S, \text{ and } \left(\frac{dR}{dt}\right)_{sw} = \mu S.$$

Thus, phenotypic switching transfers cells between the two phenotypes. It does not directly change the total tumor burden because the two switching terms sum to zero. Since $x = S/N$, the switching contribution to the sensitive-cell frequency is $-\mu x$. Combining this term with the selection dynamics in Section 2.3 gives:

$$\frac{dx}{dt} = sx(1-x)D(x) - \mu x.$$

Using $D(x) = qx + h$, this equation becomes

$\frac{dx}{dt} = x[s(1-x)(qx + h) - \mu]$. When $\mu = 0$, both boundary states $x=0$ and $x=1$ are invariant. When $\mu > 0$, the state $x=1$ is no longer an equilibrium. The state $x=0$ remains invariant. The formulation also preserves the biologically feasible interval $0 \leq x \leq 1$. Back switching from resistant to sensitive cells is not included. This assumption represents persistent resistance over the time scale considered. Interior equilibria, when they exist, satisfy:

$$s(1-x^*)D(x^*) = \mu.$$

Their existence and stability are analyzed in Section 3.

2.5 Coupled Tumor-burden Dynamics

The frequency equation describes tumor composition. We next include the total tumor burden $N(t)$. A logistic term is used to represent resource-limited tumor growth [24]. The evolutionary state of the tumor modifies this growth through the mean payoff $\bar{F}(x)$. The tumor-burden equation is:

$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K} \right) \bar{F}(x),$$

where $r > 0$ is the baseline growth-rate parameter. It has units of inverse time. The parameter $K > 0$ is the tumor-burden scale associated with resource limitation. Combining this equation with the frequency dynamics gives the full system:

$$\begin{aligned} \frac{dx}{dt} &= sx(1-x)D(x) - \mu x, \\ \frac{dN}{dt} &= rN \left(1 - \frac{N}{K} \right) \bar{F}(x) \end{aligned}$$

where $D(x) = F_S(x) - F_R(x)$. Since $\bar{F}(x)$ is dimensionless, $r\bar{F}(x)$ has units of inverse time. Hence, the tumor-burden equation is dimensionally consistent. The system is triangular because the equation for x does not depend on N . In contrast, the dynamics of N depend on the clonal composition through $\bar{F}(x)$. Because the system is triangular, the frequency dynamics can be analyzed first and then used to study the tumor-burden dynamics. The variables and parameters of the coupled evolutionary tumor model are summarized in Table 1.

The biologically feasible state space is:

$$\Omega = \{(x, N) : 0 \leq x \leq 1, 0 \leq N \leq K\}.$$

The system is continuously extended to $N = 0$ for mathematical analysis. Here, K represents an upper tumor-burden scale. The state $N = K$ is not unconditionally asymptotically stable; its stability depends on the mean payoff $\bar{F}(x)$, as analyzed in Section 3.

Table 1. Variables and parameters of the coupled evolutionary tumor model

Symbol	Meaning
$S(t)$	Density of therapy-sensitive cells
$R(t)$	Density of therapy-resistant cells
$N(t)$	Total tumor burden
$x(t)$	Frequency of therapy-sensitive cells
$1-x(t)$	Frequency of therapy-resistant cells
$a_{SS}, a_{SR}, a_{RS}, a_{RR}$	Dimensionless payoff parameters
c	Dimensionless treatment pressure
γ	Dimensionless fitness cost of resistance
s	Selection-rate parameter, time^{-1}
μ	Sensitive-to-resistant phenotypic switching rate, time^{-1}
r	Baseline tumor growth rate, time^{-1}
K	Tumor-burden scale associated with resource limitation
$D(x)$	Payoff difference, $F_S(x) - F_R(x)$
$\bar{F}(x)$	Mean population payoff

Source: created by the authors

2.6 Analytical Framework

The coupled model is analyzed using standard tools from evolutionary game theory and dynamical systems [16], [17], [18], [25]. The analysis considers both tumor composition and total tumor burden.

Let

$$G(x) = sx(1-x)D(x) - \mu x,$$

and

$$H(x, N) = rN \left(1 - \frac{N}{K} \right) \bar{F}(x).$$

The full system can therefore be written as:

$$\frac{dx}{dt} = G(x), \quad \frac{dN}{dt} = H(x, N).$$

Biological admissibility is examined on the boundary of Ω [24, 25]. Full-system equilibria satisfy $G(x^*) = 0$ and $H(x^*, N^*) = 0$. Local stability is determined from the triangular Jacobian matrix [25]. The frequency equation is further examined using phase-line and bifurcation analyses. Treatment pressure c and resistance cost γ are used as bifurcation parameters to derive analytical thresholds separating the admissible dynamical regimes.

2.7 Numerical Method and Reproducibility

Numerical simulations are used to verify and illustrate the analytical results. The coupled system

is solved in MATLAB using ode45. This solver uses an adaptive Runge–Kutta method and is suitable for nonstiff ordinary differential equations [26], [27]. The relative error tolerance is set to $\text{RelTol}=10^{-9}$. For the state vector (x, N) , component-wise absolute tolerances are used:

$$\text{AbsTol} = \begin{bmatrix} 10^{-11} \\ 10^{-11} K \end{bmatrix}.$$

The time-series simulations are first performed over $0 \leq t \leq 80$. The initial conditions and parameter values used in each experiment are reported with the corresponding numerical results. For verification of isolated equilibria, the numerical solution is compared with the corresponding analytically predicted equilibrium. Let $(x_{\text{num}}, N_{\text{num}})$ denote the final numerical state and let (x^*, N^*) denote the corresponding analytical equilibrium. The normalized equilibrium error is defined by:

$$E_{\text{eq}} = \max \left\{ |x_{\text{num}} - x^*|, \frac{|N_{\text{num}} - N^*|}{K} \right\}.$$

A numerical trajectory is considered converged when $E_{\text{eq}} < 10^{-6}$. The rate tolerance is set to

$\varepsilon_{\text{rate}} = 10^{-8} \text{time}^{-1}$. In addition, the rate residual is required to satisfy:

$$\max \left\{ |G(x)|, \frac{|H(x, N)|}{K} \right\} < \varepsilon_{\text{rate}}.$$

If these conditions are not reached by $t=80$, the integration is continued until the criteria are satisfied or until $t=400$. A tolerance check is also performed for representative parameter sets. These simulations are repeated with $\text{RelTol}=10^{-10}$, and component-wise absolute tolerances:

$$\text{AbsTol} = \begin{bmatrix} 10^{-12} \\ 10^{-12} K \end{bmatrix}.$$

The resulting equilibrium classification is compared with that obtained using the baseline tolerances. For the switching-free two-parameter numerical study, we set $\mu=0$. Treatment pressure is varied over $0 \leq c \leq 1$, and resistance cost is varied over $0 \leq \gamma \leq 0.8$. A uniform 101×81 parameter grid is used. Thus, both parameters are sampled with an increment of 0.01. For each pair (c, γ) , the system is solved to $T=80$. The finite-time resistant-cell frequency $1-x(80)$ is then recorded. This

calculation is interpreted as a finite-time parameter sweep rather than a bifurcation diagram. Analytical threshold curves derived in Section 3 are used separately to identify the mathematical boundaries between dynamical regimes. The numerical sweep is used to examine whether the finite-time solutions are consistent with these analytical predictions. All parameter values, initial conditions, solver tolerances, stopping criteria, and parameter-grid definitions are reported to support reproducibility.

3 Results and Discussion

This section presents the analytical and numerical results of the coupled evolutionary tumor model. The analysis begins with biological admissibility of the state variables. Equilibria and their stability are then examined for the full system. Treatment thresholds and parameter regions are derived analytically. These results are subsequently compared with numerical simulations.

3.1 Biological Admissibility and Invariant Region

A biologically meaningful solution must satisfy $0 \leq x(t) \leq 1$ and $0 \leq N(t) \leq K$. These conditions ensure that the sensitive-cell frequency remains between zero and one. They also ensure that the total tumor burden remains non-negative and within the resource-limited range. Recall that the coupled system is:

$$\begin{aligned} \frac{dx}{dt} &= G(x) = sx(1-x)D(x) - \mu x \\ \text{and} \quad \frac{dN}{dt} &= H(x, N) = rN \left(1 - \frac{N}{K} \right) \bar{F}(x). \end{aligned}$$

The biologically feasible region is $\Omega = \{(x, N) : 0 \leq x \leq 1; 0 \leq N \leq K\}$. The following result establishes the positive invariance of this region. This type of invariant-region argument is standard in population dynamical systems [24], [25].

Proposition 3.1. Assume that $s > 0, r > 0, K > 0$, and $\mu \geq 0$. If $(x(0), N(0)) \in \Omega$, then the solution of the coupled system remains in Ω for all $t \geq 0$.

Proof. We first consider the boundaries of the frequency interval. At $x=0$, $G(0)=0$. Hence, the vector field does not point toward $x < 0$. At $x=1$, $G(1)=-\mu \leq 0$. Thus, the vector field does not point toward $x > 1$. If $\mu=0$, the boundary $x=1$ is

invariant. If $\mu > 0$, the vector field points into the interval. We next consider the tumor-burden boundaries. At $N = 0$, $H(x, 0) = 0$. Therefore, $N(t)$ cannot cross into negative values. At $N = K$, $H(x, K) = 0$. Thus, the boundary $N = K$ is invariant. Solutions starting below this boundary cannot cross it. The right-hand sides of the system are continuously differentiable in (x, N) . Hence, the initial-value problem has a unique local solution [25]. The boundary properties above imply that this solution cannot leave Ω . Therefore, $(x(t), N(t)) \in \Omega$ for all $t \geq 0$. Since the vector field is continuously differentiable and the solution remains in the compact set Ω , the local solution extends to all $t \geq 0$. This proves the proposition. The result confirms that the model preserves biologically admissible states. In particular, negative cell frequencies and negative tumor burdens cannot occur. The upper bound $N = K$ is invariant. However, this does not imply that $N = K$ is always asymptotically stable. Its stability depends on the evolutionary state through $\bar{F}(x)$. This issue is examined in Section 3.3.

3.2 Equilibria of the Full Coupled System

We now determine the equilibria of the full system. An equilibrium (x^*, N^*) must satisfy $G(x^*) = 0$ and $H(x^*, N^*) = 0$. Since

$$H(x, N) = rN \left(1 - \frac{N}{K} \right) \bar{F}(x),$$

the tumor-burden condition gives

$$N^* = 0, \quad N^* = K, \quad \text{or} \quad \bar{F}(x^*) = 0.$$

Thus, the equilibrium structure depends on both the frequency dynamics and the sign of the mean payoff.

We first consider the frequency component. For $\mu = 0$, $G(x) = sx(1-x)(qx+h)$. The two boundary equilibria are $x_R = 0$ and $x_S = 1$. If $q \neq 0$, an interior equilibrium is $x_C = -(h/q)$. It is biologically feasible when $0 < x_C < 1$. If $q = 0$ and $h \neq 0$, no interior equilibrium exists. The case $q = h = 0$ is degenerate because every $x \in [0, 1]$ is a frequency equilibrium. This nongeneric case is not used in the parameter classification below. For $\mu > 0$, the sensitive-only state $x = 1$ is no longer an equilibrium. The resistant state $x_R = 0$ remains an equilibrium. Any interior equilibrium satisfies

$$s(1-x)(qx+h) = \mu.$$

For $q \neq 0$, this condition becomes

$$qx^2 + (h-q)x + \left(\frac{\mu}{s} - h \right) = 0.$$

Hence,

$$x_{\pm} = \frac{q-h \pm \sqrt{\Delta}}{2q},$$

where $\Delta = (q+h)^2 - (4q\mu/s)$. An interior equilibrium exists only when $\Delta \geq 0$ and at least one root lies in $(0, 1)$. If $q = 0$ and $h > 0$, the interior equilibrium reduces to $x^* = 1 - (\mu/sh)$. This equilibrium is feasible when $0 < \mu < sh$. We can now describe the equilibria of the full system.

Proposition 3.2. *Let $x^* \in [0, 1]$ be an isolated equilibrium of the frequency equation, so that $G(x^*) = 0$. If $\bar{F}(x^*) \neq 0$, then the corresponding isolated equilibria of the full system are*

$$E_0 = (x^*, 0) \text{ and } E_K = (x^*, K).$$

If $\bar{F}(x^*) = 0$, then every point (x^*, N) , $0 \leq N \leq K$ is an equilibrium.

Proof. The first equation of the system requires $G(x^*) = 0$. The second equation requires

$$rN \left(1 - \frac{N}{K} \right) \bar{F}(x^*) = 0.$$

If $\bar{F}(x^*) \neq 0$, this equation gives only $N^* = 0$ or $N^* = K$. If $\bar{F}(x^*) = 0$, the tumor-burden equation vanishes for every $N^* \in [0, K]$. Hence, a continuous equilibrium set is obtained. This proves the proposition. At $N = 0$, the frequency x has no direct biological interpretation because the tumor burden is absent. It is retained as a limiting composition coordinate of the mathematical system. Positive-burden equilibria are therefore of greater biological interest. The equilibria of the full coupled system and their corresponding existence conditions are summarized in Table 2.

Table 2. Equilibria of the full coupled system and their existence conditions

Frequency state	Existence condition	Full-system equilibrium
Resistant state $x_R=0$	$\mu \geq 0$	$(0,0), (0,K)$; continuum $(0,N)$ if $\bar{F}(0)=0$
Sensitive state $x_S=1$	$\mu = 0$	$(1,0), (1,K)$; continuum $(1,N)$ if $\bar{F}(1)=0$
Coexistence $x_C=-(h/q)$	$\mu=0, q \neq 0, 0 < x_C < 1$	$(x_C,0), (x_C,K)$; continuum if $\bar{F}(x_C)=0$
Switching equilibrium $x_\pm$	$\mu > 0, q \neq 0, \Delta \geq 0, 0 < x_\pm < 1$	$(x_\pm,0), (x_\pm,K)$; continuum if $\bar{F}(x_\pm)=0$

Source: created by the authors

For $q=0$ and $\mu > 0$, the interior switching equilibrium is $x^* = 1 - (\mu/sh)$, provided that $h > 0$ and $0 < \mu < sh$. The result shows that the full system contains more equilibrium possibilities than the scalar frequency equation alone. In particular, the condition $\bar{F}(x^*)=0$ generates a non-isolated equilibrium set. The stability of the isolated equilibria is examined in Section 3.3.

3.3 Local Stability and Long-Term Behavior

We next examine the stability of the full coupled system. Standard linearization arguments for autonomous dynamical systems are used, [25].

Recall that

$$G(x) = sx(1-x)D(x) - \mu x, \text{ and}$$

$$H(x, N) = rN \left(1 - \frac{N}{K}\right) \bar{F}(x).$$

The Jacobian matrix is:

$$J(x, N) = \begin{pmatrix} G'(x) & 0 \\ rN \left(1 - \frac{N}{K}\right) \bar{F}'(x) & r \left(1 - \frac{2N}{K}\right) \bar{F}(x) \end{pmatrix},$$

where $G'(x) = s[(1-2x)D(x) + x(1-x)q] - \mu$. Because the Jacobian is triangular, its eigenvalues are given by the diagonal entries. Consider first an equilibrium $E_0 = (x^*, 0)$, where $G(x^*)=0$ and $\bar{F}(x^*) \neq 0$. The eigenvalues are $\lambda_1 = G'(x^*)$, $\lambda_2 = r\bar{F}(x^*)$. Hence, E_0 is locally asymptotically stable when $G'(x^*) < 0$ and $\bar{F}(x^*) < 0$. Now consider $E_K = (x^*, K)$. The corresponding eigenvalues are $\lambda_1 = G'(x^*)$, $\lambda_2 = -r\bar{F}(x^*)$.

Therefore, E_K is locally asymptotically stable when $G'(x^*) < 0$ and $\bar{F}(x^*) > 0$. These conditions are summarized in the following result.

Theorem 3.1. *Let x^* be an isolated equilibrium of the frequency equation and assume that $\bar{F}(x^*) \neq 0$. Then $E_0 = (x^*, 0)$ is locally asymptotically stable if $G'(x^*) < 0$ and $\bar{F}(x^*) < 0$. The equilibrium $E_K = (x^*, K)$ is locally asymptotically stable if $G'(x^*) < 0$ and $\bar{F}(x^*) > 0$. If either eigenvalue has positive real part, the corresponding equilibrium is unstable.*

Proof. At $N=0$, the Jacobian has diagonal entries $G'(x^*)$ and $r\bar{F}(x^*)$. At $N=K$, the diagonal entries are $G'(x^*)$ and $-r\bar{F}(x^*)$. Since $r > 0$, the stated conditions follow directly from the signs of the two eigenvalues [25]. This proves the theorem. The result shows that $N=K$ is not unconditionally asymptotically stable.

For the interior switching equilibria derived in Section 3.2, their frequency stability can be characterized explicitly. Let

$$x_\pm = \frac{q - h \pm \sqrt{\Delta}}{2q}, \quad \Delta = (q+h)^2 - \frac{4q\mu}{s},$$

with $q \neq 0$. At an interior equilibrium x^* , the equilibrium condition $s(1-x^*)(qx^*+h) = \mu$ gives $G'(x^*) = sx^*[(q-h) - 2qx^*]$. Hence, when $\Delta > 0$, $G'(x_+) = -sx_+ \sqrt{\Delta} < 0$, $G'(x_-) = sx_- \sqrt{\Delta} > 0$, whenever the corresponding roots lie in $(0,1)$.

Therefore, a feasible x_+ is locally asymptotically stable in the frequency direction, whereas a feasible x_- is unstable. When $\Delta = 0$, the two roots coalesce and $G'(x^*) = 0$, so the resulting equilibrium is non-hyperbolic. Accordingly, when $\bar{F}(x_+) \neq 0$, Theorem 3.1 determines whether the corresponding stable full-system equilibrium is $(x_+, 0)$ or (x_+, K) according to the sign of $\bar{F}(x_+)$. In contrast, any full-system equilibrium associated with a feasible x_- is unstable because $G'(x_-) > 0$. For the special case $q=0$ and $0 < \mu < sh$, the interior switching equilibrium $x^* = 1 - (\mu/sh)$ satisfies $G'(x^*) = -shx^* < 0$. Hence, it is locally

asymptotically stable in the frequency direction. If $\bar{F}(x^*) \neq 0$, Theorem 3.1 then determines the stability of the corresponding full-system equilibria.

When $G(x^*) = 0$ and $\bar{F}(x^*) = 0$, the equilibrium is non-isolated. At any point (x^*, N^*) on the equilibrium set, the Jacobian has eigenvalues $\lambda_1 = G'(x^*)$, $\lambda_2 = 0$. If $G'(x^*) > 0$, the equilibrium set is unstable in the frequency direction. If $G'(x^*) < 0$, perturbations in the frequency direction decay locally. Individual points on the equilibrium set are not asymptotically stable because arbitrarily close points on the same set are also equilibria. For isolated equilibria with $\bar{F}(x^*) \neq 0$, the long-term tumor-burden behavior depends on the sign of the mean payoff. A stable frequency equilibrium with $\bar{F}(x^*) > 0$ supports convergence toward K , whereas $\bar{F}(x^*) < 0$ favors tumor decline. The triangular structure also permits a direct analysis of the long-term tumor burden. For $0 < N(t) < K$, the tumor-burden equation can be written as:

$$\frac{d}{dt} \ln \left(\frac{N}{K - N} \right) = r \bar{F}(x(t)).$$

Integration gives:

$$\frac{N(t)}{K - N(t)} = \frac{N(0)}{K - N(0)} \exp \left(r \int_0^t \bar{F}(x(\tau)) d\tau \right)$$

This expression gives a useful convergence criterion.

Proposition 3.3. Assume that $0 < N(0) < K$ and that $x(t) \rightarrow x^*$ as $t \rightarrow \infty$. If $\bar{F}(x^*) > 0$, then $N(t) \rightarrow K$. If $\bar{F}(x^*) < 0$, then $N(t) \rightarrow 0$.

Proof. If $\bar{F}(x^*) > 0$, continuity implies that $\bar{F}(x(t))$ remains positive and bounded away from zero for sufficiently large t . Hence,

$$\int_0^t \bar{F}(x(\tau)) d\tau \rightarrow +\infty.$$

The explicit relation above then gives $N(t) \rightarrow K$. If $\bar{F}(x^*) < 0$, the integral tends to $-\infty$. Therefore, $N(t) \rightarrow 0$. This proves the proposition. When $\bar{F}(x^*) = 0$, the preceding conclusion does not

apply. This is a non-hyperbolic case and may correspond to the continuous equilibrium sets identified in Section 3.2.

3.4 Treatment Thresholds and Parameter-Region Classification

Treatment pressure changes the relative fitness of the two phenotypes. The corresponding invasion thresholds can be derived directly from the payoff difference. This type of threshold analysis is standard in evolutionary game dynamics [15], [16], [17], [18]. For $\mu = 0$, $D(x) = qx + h$, where $h = a_{SR} - a_{RR} - c + \gamma$. At the resistant state $x = 0$, $D(0) = h$. Sensitive cells can invade this state when $D(0) > 0$.

Hence,

$c < a_{SR} - a_{RR} + \gamma$. We define the sensitive-invasion threshold as $c_S^{\text{crit}} = a_{SR} - a_{RR} + \gamma$. Thus, the resistant frequency state is locally stable when $c > c_S^{\text{crit}}$. At the sensitive state $x = 1$, $D(1) = q + h = a_{SS} - a_{RS} - c + \gamma$. Resistant cells can invade when $D(1) < 0$. Therefore, $c > a_{SS} - a_{RS} + \gamma$. We define the resistant-invasion threshold as $c_R^{\text{crit}} = a_{SS} - a_{RS} + \gamma$. The two thresholds satisfy $c_R^{\text{crit}} - c_S^{\text{crit}} = q$. This relation determines the ordering of the thresholds and the qualitative structure of the model. When $q < 0$, we have $c_R^{\text{crit}} < c_S^{\text{crit}}$. Three parameter regions arise. If $c < c_R^{\text{crit}}$, the sensitive state is stable and the resistant state is unstable. For $0 < x(0) < 1$, the frequency dynamics converge to the sensitive state $x = 1$. Thus, this region corresponds to sensitive dominance for interior initial conditions. If $c_R^{\text{crit}} < c < c_S^{\text{crit}}$, both boundary states are unstable. The interior equilibrium $x_C = -(h/q)$ lies in $(0, 1)$. Since $q < 0$, this equilibrium is locally asymptotically stable. For $0 < x(0) < 1$, trajectories converge to the interior equilibrium x_C . This region therefore corresponds to stable coexistence for interior initial conditions. If $c > c_S^{\text{crit}}$, the resistant state is stable and the sensitive state is unstable. For $0 < x(0) < 1$, the frequency dynamics converge to the resistant state $x = 0$. Thus, this region corresponds to resistant dominance for interior initial conditions. When $q > 0$, the threshold ordering is reversed: $c_S^{\text{crit}} < c_R^{\text{crit}}$. If $c < c_S^{\text{crit}}$, only the sensitive boundary state is stable. For $0 < x(0) < 1$,

trajectories converge to the sensitive state $x=1$. For $c_S^{\text{crit}} < c < c_R^{\text{crit}}$, both boundary states are locally stable. The interior equilibrium exists but is unstable because $q > 0$. This region is therefore bistable. The interior equilibrium x_C separates the two basins of attraction. For $0 < x(0) < x_C$, trajectories converge to the resistant state $x=0$, whereas for $x_C < x(0) < 1$, they converge to the sensitive state $x=1$. If $x(0) = x_C$, the solution remains at the unstable interior equilibrium. If $c > c_R^{\text{crit}}$, only the resistant boundary state is stable. For $0 < x(0) < 1$, trajectories converge to the resistant state $x=0$. The analytical parameter-region classification for the switching-free frequency dynamics is summarized in Table 3. The case $q=0$ is degenerate. In this case, $c_R^{\text{crit}} = c_S^{\text{crit}} = c_0^{\text{crit}}$. If $c < c_0^{\text{crit}}$, sensitive cells are favored for all $0 < x < 1$. If $c > c_0^{\text{crit}}$, resistant cells are favored. At $c = c_0^{\text{crit}}$, $D(x) = 0$. Hence, every $x \in [0, 1]$ is an equilibrium of the switching-free frequency dynamics. The payoff difference vanishes throughout the frequency interval. Phenotypic switching modifies these classifications. For $\mu > 0$, the state $x=1$ is no longer an equilibrium. The stability of the resistant state $x=0$ is determined by

$$G'(0) = sh - \mu.$$

Hence, $x=0$ is locally stable when $sh < \mu$.

Equivalently,

$$c > a_{SR} - a_{RR} + \gamma - \frac{\mu}{s}.$$

Thus, one-way switching shifts the resistant-state stability boundary toward lower treatment pressure by μ/s . It also removes exact sensitive-only persistence. Interior switching equilibria are determined by the conditions derived in Section 3.2.

Increasing γ shifts both critical treatment levels upward. A larger resistance cost therefore requires stronger treatment pressure before resistance becomes selectively favored. In contrast, increasing c moves the system toward the resistant-dominant region. These analytical boundaries provide the basis for the bifurcation diagram in Section 3.5.

Table 3. Analytical parameter regions for the switching-free frequency dynamics

Payoff regime	Treatment region	Stable frequency outcome
$q < 0$	$c < c_R^{\text{crit}}$	Sensitive dominance
$q < 0$	$c_R^{\text{crit}} < c < c_S^{\text{crit}}$	Stable coexistence
$q < 0$	$c > c_S^{\text{crit}}$	Resistant dominance
$q > 0$	$c < c_S^{\text{crit}}$	Sensitive dominance
$q > 0$	$c_S^{\text{crit}} < c < c_R^{\text{crit}}$	Bistability
$q > 0$	$c > c_R^{\text{crit}}$	Resistant dominance

Source: created by the authors

3.5 Bifurcation Structure in Treatment Pressure and Resistance Cost

We now examine how treatment pressure and resistance cost change the equilibrium structure. The analysis is first performed for $\mu = 0$. Standard one-dimensional bifurcation arguments are used [25]. Recall that the interior equilibrium is $x_C = -(h/q)$, where $h = a_{SR} - a_{RR} - c + \gamma$. The two critical treatment levels are $a_{SS} - a_{RS} + \gamma$ and $a_{SR} - a_{RR} + \gamma$. At $c = c_R^{\text{crit}}$, we have $D(1) = q + h = 0$. Hence, $x_C = 1$. The interior equilibrium therefore meets the sensitive boundary equilibrium. At $c = c_S^{\text{crit}}$, we have $D(0) = h = 0$. Hence, $x_C = 0$. The interior equilibrium therefore meets the resistant boundary equilibrium.

Proposition 3.4. Assume that $\mu = 0$ and $q \neq 0$. The frequency dynamics undergo boundary transcritical bifurcations at $c = c_R^{\text{crit}}$ and $c = c_S^{\text{crit}}$. At each threshold, an interior equilibrium collides with a boundary equilibrium and the two branches exchange stability.

Proof. The equilibrium branches are $x=0$, $x=1$, and $x_C = -(h/q)$. Since h depends linearly on c , the interior branch varies continuously with treatment pressure. At $c = c_R^{\text{crit}}$, we obtain $x_C = 1$. At $c = c_S^{\text{crit}}$, we obtain $x_C = 0$. The stability results in Section 3.4 show that the corresponding equilibrium branches exchange stability as each threshold is crossed. More explicitly, let

$$f(x, c) = sx(1-x)[qx + h(c)], \quad h'(c) = -1.$$

At $(0, c_S^{\text{crit}})$, $f = f_x = f_c = 0$, while $f_{xc} = -s \neq 0$ and $f_{xx} = 2sq \neq 0$.

At $(1, c_R^{\text{crit}})$, $f = f_x = f_c = 0$, while $f_{xc} = s \neq 0$ and $f_{xx} = -2sq \neq 0$.

Hence, the standard nondegeneracy conditions for a transcritical bifurcation are satisfied when $q \neq 0$. These crossings therefore have the structure of transcritical bifurcations [25]. This proves the proposition.

Only threshold values lying in the admissible treatment domain $c \geq 0$ are biologically relevant. The bifurcation structure depends on the sign of q . When $q < 0$, $c_R^{\text{crit}} < c_S^{\text{crit}}$. Increasing c moves the frequency subsystem from sensitive dominance to stable coexistence and then to resistant dominance. The two transitions occur at c_R^{crit} and c_S^{crit} , respectively. When $q > 0$, $c_S^{\text{crit}} < c_R^{\text{crit}}$. The intermediate region is bistable. In this region, both boundary equilibria are locally stable. The interior equilibrium is unstable and separates their basins of attraction. The resistance cost γ shifts both bifurcation thresholds linearly. In the (c, γ) -plane, the two threshold curves are $\gamma = c - (a_{SS} - a_{RS})$ and $\gamma = c - (a_{SR} - a_{RR})$. Both curves have slope one. Their separation is determined by q . Increasing γ shifts the transitions toward larger treatment pressure. Thus, a larger resistance cost delays the transition toward resistant dominance. For the baseline payoff values used in the numerical experiments,

$$\begin{aligned} a_{SS} &= 0.70, & a_{SR} &= 1.00, \\ a_{RS} &= 1.00, & a_{RR} &= 0.60, \end{aligned}$$

we obtain $q = -0.70$. Hence, the relevant ordering is $c_R^{\text{crit}} < c_S^{\text{crit}}$. The corresponding threshold curves are $c_R^{\text{crit}} = \gamma - 0.30$ and $c_S^{\text{crit}} = \gamma + 0.40$. The region between these curves corresponds to stable coexistence whenever it lies within the admissible parameter domain. The resulting analytical bifurcation regions in the (c, γ) -plane are shown in Figure 1. When $\mu > 0$, the sensitive boundary state $x=1$ is removed. The resistant state remains an equilibrium. Its stability changes when $G'(0) = 0$. This gives the shifted threshold

$$c_\mu^{\text{crit}} = a_{SR} - a_{RR} + \gamma - \frac{\mu}{s}.$$

Thus, one-way phenotypic switching shifts the resistant-stability boundary toward lower treatment pressure. The exact interior equilibrium structure

then depends on the discriminant derived in Section 3.2.

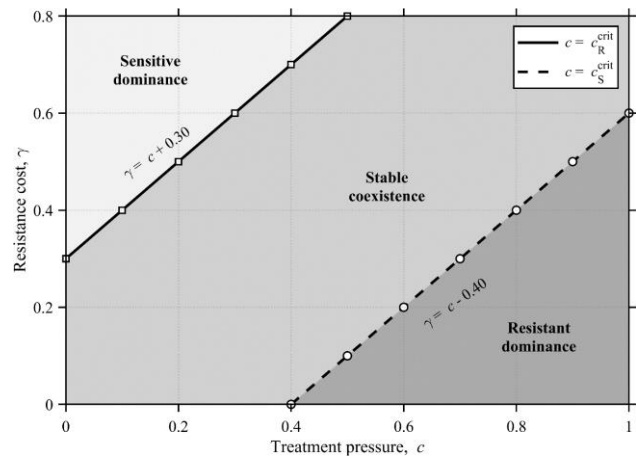


Fig. 1: Analytical bifurcation regions in the (c, γ) -plane for the switching-free model $\mu = 0$.

Source: created by the authors

The solid line, $\gamma = c + 0.30$, represents the threshold $c = c_R^{\text{crit}}$, whereas the dashed line, $\gamma = c - 0.40$, represents the threshold $c = c_S^{\text{crit}}$. These boundaries separate the parameter plane into three regimes: sensitive dominance, stable coexistence, and resistant dominance.

3.6 Numerical Verification

Numerical experiments are used to verify the analytical classification derived above. The purpose is not to estimate patient-specific parameters. Instead, the simulations examine whether the trajectories approach the equilibria predicted by the mathematical analysis. The numerical procedure and stopping criteria are described in Section 2.7. We first consider the switching-free case. The baseline payoff parameters are:

$$\begin{aligned} a_{SS} &= 0.70, & a_{SR} &= 1.00, \\ a_{RS} &= 1.00, & a_{RR} &= 0.60. \end{aligned}$$

For the numerical verification, we set $s = r = K = 1$, $x(0) = 0.5$, and $N(0) = 0.5$. For these values, $q = -0.70 < 0$. Hence, the analytical results predict three treatment regimes. These are sensitive dominance, stable coexistence, and resistant dominance. The transition boundaries are:

$$c_R^{\text{crit}} = \gamma - 0.30 \text{ and } c_S^{\text{crit}} = \gamma + 0.40.$$

Representative parameter sets are selected from each region. For each case, the numerical solution is compared with the corresponding analytical

equilibrium. Agreement is assessed using the equilibrium error E_{eq} defined in Section 2.7.

Table 4. Comparison between analytical equilibria and numerical approximations for representative parameter regimes

Regime	c	γ	μ	Analytical equilibrium (x^*, N^*)	Numerical equilibrium m (x_{num}, N_{num})	E_{eq}
Sensitive dominant ce	0.1	0.5	0	(1, 1)	(0.99999998, 1)	1.6456 $\times 10^{-8}$
Stable coexisten ce	0.5	0.4	0	(0.42857143, 1)	(0.42857143, 1)	2.4864 $\times 10^{-9}$
Resistant dominant ce	0.9	0.3	0	(0, 1)	(0.00000003, 1)	2.9886 $\times 10^{-8}$

Source: created by the authors

The numerical results in Table 4 agree closely with the analytical predictions for all three parameter regimes. In each case, $E_{eq} < 10^{-6}$, and the tighter-tolerance computations give the same equilibrium classification. This agreement supports the analytical regime classification. When $\mu > 0$, the sensitive-only state is no longer an equilibrium, while the stability boundary of the resistant state is shifted to

$$c_{\mu}^{crit} = a_{SR} - a_{RR} + \gamma - \frac{\mu}{S}.$$

For $\mu > 0$, the possible equilibrium states include the resistant boundary and feasible interior switching equilibria derived in Section 3.2. For direct comparison with the switching-free analytical thresholds, a two-parameter finite-time study is performed with $\mu = 0$ over $0 \leq c \leq 1$, $0 \leq \gamma \leq 0.8$. For each pair (c, γ) , the resistant-cell frequency $1 - x(80)$ is recorded. The resulting finite-time resistant-cell frequency over the (c, γ) -plane is shown in Figure 2. This calculation represents a finite-time parameter sweep. It is not used as a bifurcation diagram. The analytical threshold curves from Section 3.5 are superimposed to permit direct comparison between finite-time behavior and asymptotic regime boundaries.

The analytically derived threshold curves are superimposed for comparison. Contour lines and distinct line styles are included to ensure interpretation in grayscale and improve color-vision accessibility

The analytical boundaries provide the asymptotic classification, whereas the numerical sweep represents the system at the finite observation time $T = 80$. Differences near the analytical thresholds may therefore occur because of slow convergence. The tighter-tolerance computations for representative parameter sets yield the same equilibrium classification, supporting the robustness of the numerical results.

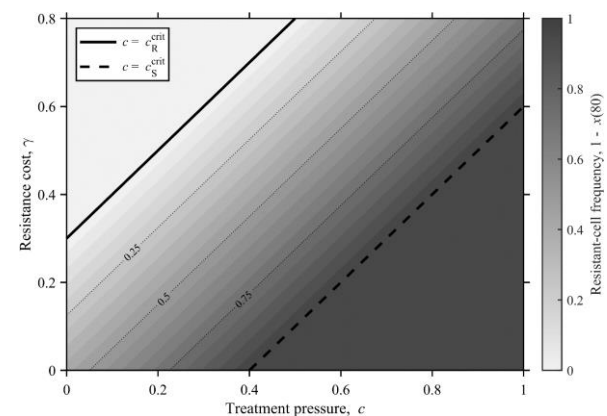


Fig. 2: Finite-time resistant-cell frequency $1 - x(80)$ over the (c, γ) -plane

Source: created by the authors

3.7 Biological Interpretation and Limitations

The analytical results clarify how treatment pressure and resistance cost shape clonal competition. Increasing c shifts the frequency-selection balance toward resistance. In contrast, increasing γ raises the treatment level required for resistant cells to gain a selective advantage. The resistance cost can therefore delay the transition toward a resistant-dominated state. In the absence of phenotypic switching, $q < 0$ produces a region of stable coexistence through negative frequency dependence. Neither phenotype dominates throughout this region. This behavior is consistent with the ecological principle underlying adaptive therapy. Maintaining competition between sensitive and resistant cells may influence the evolutionary response to treatment [7], [8], [9], [10]. The present model provides a mathematical interpretation of this mechanism rather than a clinical treatment rule. Phenotypic switching also changes the equilibrium structure. When $\mu > 0$, the sensitive-only state is no longer an equilibrium. The stability boundary of the resistant state shifts toward lower treatment pressure. Thus, one-way switching can increase the range of conditions under which resistance persists. The tumor-burden dynamics add another level of interpretation. Clonal composition alone does not

determine the long-term tumor size. The sign of the mean payoff $\bar{F}(x^*)$ is also required. If $x(t) \rightarrow x^*$ and $0 < N(0) < K$, then $\bar{F}(x^*) > 0$ implies $N(t) \rightarrow K$, whereas $\bar{F}(x^*) < 0$ implies $N(t) \rightarrow 0$. This distinction shows why analysis of the full coupled system is necessary. Several limitations should be noted. The payoff matrix is phenomenological and is not derived from patient-specific measurements. The parameter values are used to represent qualitative dynamical regimes. They should not be interpreted as clinically calibrated estimates. The model also assumes constant treatment pressure. Only one-way phenotypic switching is included. Genetic mutation is not modeled explicitly. Spatial heterogeneity, stochastic effects, and time-dependent treatment schedules are also outside the present framework.

Despite these limitations, the model provides a tractable framework for linking clonal competition, treatment pressure, resistance cost, and tumor burden. Its main contribution is the characterization of biologically admissible equilibria and their stability, together with an analytical classification of treatment-driven frequency regimes and their transitions. The results may provide a basis for future extensions involving adaptive treatment schedules, spatial interactions, stochastic resistance, and optimal control.

4 Conclusion

This study developed a coupled evolutionary game model for competition between therapy-sensitive and therapy-resistant tumor cells. The model combines frequency-dependent selection, phenotypic switching, and resource-limited tumor growth. The analysis was performed for the full triangular dynamical system. Biologically admissible equilibria and their local stability were characterized. The role of the mean population payoff in determining long-term tumor burden was also identified.

Treatment pressure and resistance cost generate explicit thresholds that separate distinct evolutionary regimes. In the switching-free case, negative frequency dependence can produce stable coexistence, whereas positive frequency dependence can generate bistability. Increasing treatment pressure favors resistance, while a larger resistance cost shifts the transition toward higher treatment levels. One-way phenotypic switching removes the sensitive-only equilibrium and shifts the resistant-

state stability boundary toward lower treatment pressure.

The numerical results agree with the analytical predictions for representative parameter regimes. The finite-time parameter sweep also supports the analytical threshold structure. These results provide a qualitative mathematical framework for studying treatment-driven clonal competition. The model is not intended for patient-specific prediction. Future work may incorporate time-dependent treatment, spatial interactions, stochastic resistance, and optimal control.

Acknowledgement:

The author would like to thank the Department of Mathematics, Faculty of Science, Srinakharinwirot University, for academic support.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, the author(s) utilized artificial intelligence (AI) technologies solely for the purpose of linguistic refinement and grammatical correction. Following the application of these tools, the author(s) comprehensively reviewed, verified, and edited the resulting text. The author(s) maintain full accountability and responsibility for the accuracy, integrity, and final content of the publication.

References:

- [1] P. C. Nowell, The clonal evolution of tumor cell populations, *Science*, Vol. 194, No. 4260, 1976, pp. 23-28.
- [2] L. M. F. Merlo, J. W. Pepper, B. J. Reid and C. C. Maley, Cancer as an evolutionary and ecological process, *Nature Reviews Cancer*, Vol. 6, No. 12, 2006, pp. 924-935.
- [3] I. Kareva, Biological stoichiometry in tumor micro-environments, *PLOS ONE*, Vol. 8, No. 1, 2013, Article e51844.
- [4] C. C. Maley, A. Aktipis, T. A. Graham, A. Sottoriva, A. M. Boddy, M. Janiszewska, A. S. Silva, M. Gerlinger, Y. Yuan, K. J. Pienta, K. S. Anderson, R. A. Gatenby, C. Swanton, D. Posada, C.-I. Wu, J. D. Schiffman, E. S. Hwang, K. Polyak, A. R. A. Anderson, J. S. Brown, M. Greaves and D. Shibata, Classifying the evolutionary and ecological features of neoplasms, *Nature Reviews Cancer*, Vol. 17, No. 10, 2017, pp. 605-619.
- [5] M. Greaves and C. C. Maley, Clonal evolution in cancer, *Nature*, Vol. 481, No. 7381, 2012, pp. 306-313.

- [6] C. Holohan, S. Van Schaeybroeck, D. B. Longley and P. G. Johnston, Cancer drug resistance: an evolving paradigm, *Nature Reviews Cancer*, Vol. 13, No. 10, 2013, pp. 714-726.
- [7] R. A. Gatenby, A. S. Silva, R. J. Gillies and B. R. Frieden, Adaptive therapy, *Cancer Research*, Vol. 69, No. 11, 2009, pp. 4894-4903.
- [8] K. Stankova, J. S. Brown, W. S. Dalton and R. A. Gatenby, Optimizing cancer treatment using game theory: a review, *JAMA Oncology*, Vol. 5, No. 1, 2019, pp. 96-103.
- [9] C. McGehee and Y. Mori, A mathematical framework for comparison of intermittent versus continuous adaptive chemotherapy dosing in cancer, *npj Systems Biology and Applications*, Vol. 10, 2024, Article 140.
- [10] J. West, F. Adler, J. Gallaher, M. Strobl, R. Brady-Nicholls, J. Brown, R. Robertson-Tessi, E. Kim, R. Noble, Y. Viossat, D. Basanta and A. R. A. Anderson, A survey of open questions in adaptive therapy: bridging mathematics and clinical translation, *eLife*, Vol. 12, 2023, Article e84263.
- [11] P. M. Altrock, L. L. Liu and F. Michor, The mathematics of cancer: integrating quantitative models, *Nature Reviews Cancer*, Vol. 15, No. 12, 2015, pp. 730-745.
- [12] A. Yin, D. J. A. R. Moes, J. G. C. van Hasselt, J. J. Swen and H.-J. Guchelaar, A review of mathematical models for tumor dynamics and treatment resistance evolution of solid tumors, *CPT: Pharmacometrics & Systems Pharmacology*, Vol. 8, No. 10, 2019, pp. 720-737.
- [13] T. Azizi, Mathematical modelling of cancer treatments, resistance, and optimization, *AppliedMath*, Vol. 5, No. 2, 2025, Article 40.
- [14] A. R. A. Anderson and V. Quaranta, Integrative mathematical oncology, *Nature Reviews Cancer*, Vol. 8, No. 3, 2008, pp. 227-234.
- [15] J. Maynard Smith, *Evolution and the Theory of Games*, Cambridge University Press, 1982.
- [16] J. Hofbauer and K. Sigmund, *Evolutionary Games and Population Dynamics*, Cambridge University Press, 1998.
- [17] M. A. Nowak, *Evolutionary Dynamics: Exploring the Equations of Life*, Harvard University Press, 2006.
- [18] J. W. Weibull, *Evolutionary Game Theory*, MIT Press, 1995.
- [19] I. P. M. Tomlinson, Game-theory models of interactions between tumour cells, *European Journal of Cancer*, Vol. 33, No. 9, 1997, pp. 1495-1500.
- [20] D. Basanta and A. Deutsch, A game theoretical perspective on the somatic evolution of cancer, *In Silico Biology*, Vol. 8, No. 3-4, 2008, pp. 397-410.
- [21] M. Archetti, Evolutionary game theory of growth factor production: implications for tumour heterogeneity and resistance to therapies, *British Journal of Cancer*, Vol. 109, No. 4, 2013, pp. 1056-1062.
- [22] M. Archetti and K. J. Pienta, Cooperation among cancer cells: applying game theory to cancer, *Nature Reviews Cancer*, Vol. 19, No. 2, 2019, pp. 110-117.
- [23] D. Basanta, J. G. Scott, M. N. Fishman, G. Ayala, S. W. Hayward and A. R. A. Anderson, Investigating prostate cancer tumour-stroma interactions: clinical and biological insights from an evolutionary game, *British Journal of Cancer*, Vol. 106, No. 1, 2012, pp. 174-181.
- [24] J. D. Murray, *Mathematical Biology I: An Introduction*, 3rd ed., Springer, 2002.
- [25] L. Perko, *Differential Equations and Dynamical Systems*, 3rd ed., Springer, 2001.
- [26] E. Hairer, S. P. Nørsett and G. Wanner, *Solving Ordinary Differential Equations I: Nonstiff Problems*, 2nd ed., Springer, 1993.
- [27] W. H. Press, S. A. Teukolsky, W. T. Vetterling and B. P. Flannery, *Numerical Recipes: The Art of Scientific Computing*, 3rd ed., Cambridge University Press, 2007.

Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

The sole author contributed to all stages of the present research, including the formulation of the problem, the analysis, the interpretation of the results, and the preparation of the final manuscript.

Sources of Funding for Research Presented in a Scientific Article or Scientific Article Itself

No funding was received for conducting this study.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

Creative Commons Attribution License 4.0 (Attribution 4.0 International, CC BY 4.0)

This article is published under the terms of the Creative Commons Attribution License 4.0

https://creativecommons.org/licenses/by/4.0/deed.en_US