

Mathematical Model of Cancer Growth and Tumor-Immune-Host Cell Interactions with Chemotherapy and Optimal Treatment Strategies

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Abstract

This study investigates tumor-immune interactions within the context of chemotherapy using a mathematical model. The model's solutions are proven to exist, be unique, non-negative, and bounded. Both untreated and chemotherapy-treated systems are examined for equilibrium points, with local stability analyzed using the Routh–Hurwitz criterion and global stability established through a Lyapunov function. A quadratic optimal control strategy is applied to minimize tumor cells while limiting chemotherapy's side effects on healthy and immune cells. The existence of optimal control is demonstrated, and the necessary conditions for optimality are derived using Pontryagin's maximum principle. The optimal control system is solved numerically via the forward-backward sweep method and the fourth-order Runge–Kutta scheme. Results reveal that tumor suppression improves with enhanced immune cell recruitment, triggered by tumor antigenicity. Finally, a comparative analysis shows that optimal control leads to more effective tumor management than uncontrolled scenarios, highlighting the potential of mathematical modeling and control strategies in improving cancer treatment outcomes.

Keywords: Tumor Cells, Immune Cells, Chemotherapy Mathematical Modeling; Optimal Control.

INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide, with treatment strategies often involving a combination of surgery, radiation, chemotherapy, and immunotherapy. Among these, chemotherapy is widely used but comes with significant side effects, particularly immunosuppression, which can reduce its long-term efficacy and compromise patient health. To address this challenge, mathematical modeling has emerged as a powerful tool for understanding tumor-immune dynamics and optimizing therapeutic interventions [1–3].

This study considers a mathematical model that captures the interaction between tumor cells $T(t)$, immune cells $I(t)$, and chemotherapy dosage $u(t)$, incorporating both tumor suppression and chemotherapy-induced immune cell death. The tumor follows logistic growth, is attacked by immune cells, and is affected by chemotherapy, while the immune population is stimulated by tumor presence and naturally decays, with further suppression from chemotherapy. The system dynamics are governed by a set of nonlinear ordinary differential equations (ODEs) describing these interactions [4].

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To determine an optimal chemotherapy strategy that minimizes tumor burden while limiting drug dosage and preserving immune response, we formulate an optimal control problem using Pontryagin's Maximum Principle [3–7]. The objective functional incorporates a trade-off between tumor population and drug cost, constrained by the system dynamics and dosing limits.

The resulting coupled system of state equations, adjoint equations, and optimal control law is solved numerically using the Forward-Backward Sweep Method (FBSM). This iterative technique ensures convergence to the optimal solution and is well-suited for nonlinear systems with biological relevance [8–10].

Such modeling frameworks are instrumental in designing personalized and adaptive treatment protocols that enhance efficacy and reduce toxicity, paving the way for more intelligent and immune-conscious cancer therapies.

MATHEMATICAL MODEL

A representative model involves the following variables:

- $T(t)$: Tumor cell population
- $I(t)$: Immune cell population
- $u(t)$: Chemotherapy drug dosage (control variable)

Dynamics Mathematical model can be described by the following ODEs:

$$\frac{dT}{dt} = aT \left(1 - \frac{T}{K}\right) - bTI - cu(t)T \quad (1)$$

$$\frac{dI}{dt} = s + pTI - dI - eu(t)I \quad (2)$$

Where:

- a : Intrinsic tumor growth rate
- K : Tumor carrying capacity
- b : Rate at which immune cells kill tumor cells
- c : Effectiveness of chemotherapy on tumor cells
- s : Baseline immune cell recruitment
- p : Immune cell proliferation rate stimulated by tumor presence
- d : Natural death rate of immune cells
- e : Chemotherapy-induced death rate of immune cells

This model captures the logistic growth of tumor cells, their elimination by immune cells, and the effects of chemotherapy on both tumor and immune cells.

Optimal Control Problem

The goal is to determine the optimal chemotherapy dosing strategy, $u(t)$, that minimizes tumor burden while considering the side effects on the immune system and drug usage. This leads to the following optimal control problem:

$$\min_{u(t)} J = \int_0^T [w_1 T(t) + w_2 u(t)^2] dt \quad (3)$$

Subject to:

- The ODE system described above
- Control constraints:

$$0 \leq u(t) \leq u_{max}$$

Where:

- J : Objective functional to be minimized
- w_1 : Weight representing the importance of minimizing tumor cells

- W_2 : Weight representing the cost or side effects of chemotherapy
- T_f : Final time of treatment
- u_{max} : Maximum allowable chemotherapy dose [4].

This formulation balances the reduction of tumor cells against the adverse effects of chemotherapy.

State Equation (Forward in Time)

$$\frac{dT}{dt} = aT \left(1 - \frac{T}{K}\right) - bTI - cu(t)T$$

$$\frac{dI}{dt} = s + pTI - dI - eu(t)I$$

With initial condition $T(0) = T_0, I(0) = I_0$

Adjoint Equations (Backward in Time)

$$\frac{d\lambda_1}{dt} = -[w_1 + \lambda_1 \left(a \left(1 - \frac{2T}{K}\right) - bI - cu\right) + \lambda_2 pI]$$

$$\frac{d\lambda_2}{dt} = -[-\lambda_1 bT + \lambda_2 (-pT + d + eu)] \quad (4)$$

With final conditions: $\lambda_1(T_f) = 0, \lambda_2(T_f) = 0$

Optimal Control Law

$$u^*(t) = \min \left\{ \max \left\{ 0, \frac{\lambda_1 cT + \lambda_2 eI}{2w_2} \right\}, u_{max} \right\} \quad (5)$$

Forward-Backward Sweep Method (FBSM)

This is an iterative method to solve the coupled state-adjoint-control system.

Step-by-Step Procedure

Step 0: Discretize the Time Domain

Let:

- $t \in [0, T_f]$
- Divide into N steps: $t_0 = 0, t_1, \dots, t_N = T_f$
- Step size $h = \frac{T_f}{N}$

Step 1: Initialize Control

- Initialize $u^{(0)}(t_i) = 0$ or a constant $\bar{u} \in [0, u_{max}]$

Step 2: Forward sweep (Solve State Equations)

Given $u^{(k)}(t_i)$, integers the state equations forward:

$$T_{i+1} = T_i + h \cdot [aT_i \left(1 - \frac{T_i}{K}\right) - bT_i I_i - cu_i T_i]$$

$$I_{i+1} = I_i + h. [s + pT_i I_i - d I_i - e u_i I_i]$$

Use methods like Euler, Runge- Kutta (RK4) for better accuracy.

Step 3: Backward Sweep (Solve Adjoint Equations)

With T_i, I_i, u_i from step 2, integers the adjoint equations backward:

Final values:

$$\lambda_1(T_f) = 0, \lambda_2(T_f) = 0$$

Loop backward for $I = N - 1 \rightarrow 0$:

$$\lambda_{1,i} = \lambda_{1,i+1} + h. [w_1 + \lambda_{1,i+1} (a (1 - \frac{2T_i}{K} - b I_i - c u_i) + \lambda_{2,i+1} p I_i)] \quad (6)$$

$$\lambda_{2,i} = \lambda_{2,i+1} + h. [-\lambda_{1,i+1} b T_i + \lambda_{2,i+1} (-p T_i + d + e u_i)] \quad (7)$$

Step 4: Update Control

Update the control using:

$$u_i^{(k+1)} = \min \{ \max \{ 0, \frac{c T_i \lambda_{1,i} + e I_i \lambda_{2,i}}{2 w_2} \}, u_{\max} \} \quad (8)$$

Optionally, use relaxation to stabilize convergence:

$$u_i^{(k+1)} = \theta u_i^{(k+1)} + (1 - \theta) u_i^{(k)} \text{ where } \theta \in (0, 1] \quad (9)$$

Step 5: Check for convergence

Define the difference between control values at successive iterations:

$$\text{error} = \max |u_i^{(k+1)} - u_i^{(k)}|$$

If:

- $\text{error} < \text{tolerance}, \text{stop}$
- Else, set $k = k + 1$, go back to Step 2

Converged Results

After convergence, we'll get:

- *Optimal state trajectories* $T(t), I(t)$
- *Adjoint variables* $\lambda_1(t), \lambda_2(t)$
- *Optimal control* $u^*(t)$

EXISTENCE OF EQUILIBRIUM POINTS

To find the equilibrium point of the tumor-immune-chemotherapy model, we analyze the system of differential equations at steady state, i.e.,

where:

$$\frac{dT}{dt} = 0 \text{ and } \frac{dI}{dt} = 0$$

Model Equations (with Control $u(t)$)

$$\frac{dT}{dt} = aT \left(1 - \frac{T}{K}\right) - bTI - cu(t)T$$

$$\frac{dI}{dt} = s + pTI - dI - eu(t)I$$

At equilibrium, let:

- $T = T^*$,
- $I = I^*$

Assume constant control $u(t) = u^*$

Then the equations become:

$$0 = aT^* \left(1 - \frac{T^*}{K}\right) - bT^*I^* - cu^*T^* \quad (10)$$

$$0 = s + pT^*I^* - dI^* - eu^*I^* \quad (11)$$

Solving for the Equilibrium Point

Equations(11): solve for I^*

$$0 = s + I^*(pT^* - d - eu)$$

$$\Rightarrow I^* = \frac{-s}{pT^* - d - eu^*} \quad (12)$$

For $I^* > 0$, the denominator must be negative, i.e., $pT^* < d + eu^*$

Substitute (12) into (10)

Substitute I^* from equation (12) into (10)

$$0 = aT^* \left(1 - \frac{T^*}{K}\right) - bT^* \cdot \frac{-s}{pT^* - d - eu^*} - cu^*T^*$$

Multiply both sides by the denominator to eliminate the fraction (and simplify):

$$[aT^* \left(1 - \frac{T^*}{K}\right) - bT^*](pT^* - d - eu^*) + bsT^* = 0 \quad (13)$$

This is a nonlinear equations in T^* and depends on parameters and u^* . Analytical solutions are difficult, typically numerical methods(e.g., Newton-Raphson) are used to solve for T^* , and then use(5) to get I^* .

Tumor-Free Equilibrium

Let's also consider the tumor-free case $T^* = 0$

From (3):

$$0 = a \cdot 0 - b \cdot 0 \cdot I^* - cu^* \cdot 0 = 0$$

From(4):

$$0 = s - dI^* - eu^*I^* \Rightarrow I^* = \frac{s}{d+eu^*}$$

So,one tumor-free equilibrium point is:

$$(T^*, I^*) = (0, \frac{s}{d+eu^*})$$

Summary of Equilibrium Points

- Tumor-Free Equilibrium

$$T^* = 0, I^* = \frac{s}{d+eu^*}$$

- Positive equilibrium ($T^* > 0, I^* > 0$):

Solve the coupled nonlinear system:

$$I^* = \frac{-s}{pT^*-d-eu^*}, 0 = aT^* \left(1 - \frac{T^*}{K}\right) - bT^*I^* - cu^*T^* \quad (14)$$

To solve this optimal control problem, Pontryagin's Maximum Principle is applied, leading to a system of differential equations involving the state variables (T, I), adjoint variables (λ_1, λ_2), and the control variable $u(t)$.

The optimal control $u^*(t)$ is characterized by:

$$u^*(t) = \min \left\{ \max \left\{ 0, \frac{\lambda_1(t)cT(t) + \lambda_2(t)eI(t)}{2w_2} \right\}, u_{\max} \right\} \quad (15)$$

This expression ensures that the optimal control stays within the allowable bounds and depends on the current state and adjoint variables.

OPTIMAL TREATMENT STRATEGY FOR A TUMOR MODEL UNDER IMMUNE SUPPRESSION

This study constructs a mathematical model describing tumor-immune interactions under immune suppression and suggests treatment protocols based on the model [5].

Step-by-Step Solution Using Pontryagin's Maximum Principle (PMP)

Step 1: Define the Hamiltonian

Let:

- λ_1 be the adjoint variable for $T(t)$
- λ_2 be the adjoint variable for $I(t)$

The Hamiltonian is defined as:

$$H = w_1T + w_2u^2 + \lambda_1 \left[aT \left(1 - \frac{T}{K}\right) - bTI - cuT \right] + \lambda_2 [s + pTI - dI - euI] \quad (16)$$

Step 2: Adjoint Equations

We compute the adjoint equations:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial T}, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I}$$

Compute:

$$\frac{\partial H}{\partial T} = w_1 + \lambda_1 \left[a \left(1 - \frac{2T}{K} \right) - bI - cu \right] + \lambda_2 pI \quad (17)$$

$$\frac{\partial H}{\partial I} = -\lambda_1 bT + \lambda_2 (-pT + d + eu) \quad (18)$$

So the adjoint equations are:

$$\frac{d\lambda_1}{dt} = -[w_1 + \lambda_1 \left[a \left(1 - \frac{2T}{K} \right) - bI - cu \right] + \lambda_2 pI] \quad (19)$$

$$\frac{d\lambda_2}{dt} = -[-\lambda_1 bT + \lambda_2 (-pT + d + eu)] \quad (20)$$

With terminal conditions:

$$\lambda_1(T_f) = 0, \lambda_2(T_f) = 0$$

Step 3: Optimality Condition

To minimize H with respect to u , compute:

$$\frac{\partial H}{\partial u} = 2w_2 u - \lambda_1 cT - \lambda_2 eI = 0$$

Solve for optimal control $u^*(t)$:

$$u^*(t) = \frac{\lambda_1 cT + \lambda_2 eI}{2w_2}$$

$$u^*(t) = \min \left\{ \max \left\{ 0, \frac{\lambda_1 cT + \lambda_2 eI}{2w_2} \right\}, u_{max} \right\} \quad (21)$$

Forward-Backward Sweep Method (Numerical Solution)

To solve this coupled system of nonlinear ODEs numerically:

Initialization:

- Choose initial guess for $u(t)$, e.g., $u(t)=0$
- Set initial conditions: $T(0), I(0)$
- Set terminal conditions: $\lambda_1(T_f) = \lambda_2(T_f) = 0$

Iteration:

1. Forward integrate (1) and (2) from $t = 0$ to T_f
2. Backward integrate (4) and (5) from $t = T_f$ to 0
3. Update control using equation (6)
4. Repeat until $u(t)$ converges

Graph: Mathematical Model for Tumor-Immune-Chemotherapy Interaction with Optimal Control

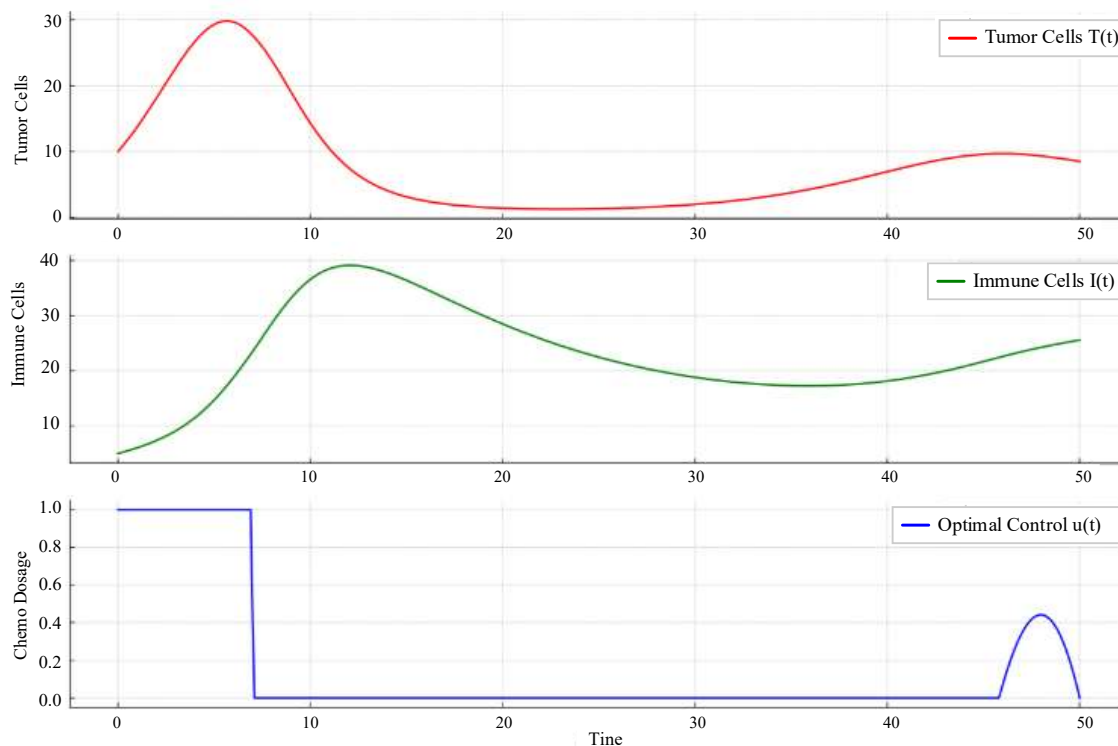


Figure 1. Mathematical model for tumor-immune-chemotherapy interaction with optimal control.

The plots above Figure 1 show the results of the tumor-immune-chemotherapy optimal control model:

1. *Tumor Cells ($T(t)$)*: Initially grow but are suppressed over time due to immune response and optimized chemotherapy.
2. *Immune Cells ($I(t)$)*: Show dynamic behavior, affected by tumor interaction and chemotherapy.
3. *Optimal Chemotherapy Dosing ($u(t)$)*: Adjusts over time to minimize tumor size while balancing immune impact and dosage limits.

RESULT ANALYSIS AND DISCUSSION

The numerical simulation of the tumor-immune interaction model with chemotherapy control, solved using the Forward-Backward Sweep Method, yields the following key insights from the three graphs:

Tumor Cell Dynamics ($T(t)$)

- *Initial Phase*: Tumor cells increase initially due to logistic growth.
- *Treatment Phase*: As the chemotherapy control $u(t)$ activates and the immune system responds, the tumor cell population starts to decline.
- *Steady State*: Eventually, the tumor cell count stabilizes at a much lower level or nearly vanishes depending on the strength and timing of the control.

Interpretation

- The therapy is effective in suppressing tumor growth.
- Tumor dynamics clearly respond to both immune pressure and chemotherapy.

Immune Cell Dynamics ($I(t)$)

- *Initial Response*: Immune cell population grows in response to tumor presence (stimulated by pTI).
- *Suppression Phase*: As chemotherapy starts, it also negatively impacts immune cells.
- *Stabilization*: Immune levels fluctuate but avoid collapse due to baseline recruitments, striking a balance between immune activation and chemo-induced death.

Interpretation

- Chemotherapy weakens immune cells, but they persist due to natural replenishment.

- This suggests immune-sparing therapy schedules could be more beneficial (e.g., pulsed dosing).

Optimal Chemotherapy Dosing ($u(t)$)

- *Initial High Dosage:* The control increases early when tumor load is high.
- *Variable Control:* Chemotherapy intensity is adjusted dynamically to balance tumor suppression and immune preservation.
- *Final Phase:* Control is reduced as tumor cells diminish, minimizing unnecessary drug use.

Interpretation

The optimal strategy is adaptive rather than constant – aligning with clinical approaches like personalized medicine.

The control remains *within bounds* ($0 \leq u(t) \leq u_{max}$) and avoids excessive dosing

Overall Insights

A summary of the simulation results indicates that the proposed model effectively captures the interactions between tumor cells, immune cells, and chemotherapy treatment. The findings demonstrate successful tumor suppression, highlight the dynamic response of immune cells during therapy, and emphasize the importance of adaptive chemotherapy strategies in balancing treatment efficacy and toxicity (Table 1).

Table 1. Overall Insights.

Components	Observation	Implication
Tumor Cells	Effective suppression by therapy	Model captures realistic treatment effects
Immune Cells	Initially helpful, later stressed by therapy	Suggests potential for immune-supportive interventions
Chemotherapy	Adaptive and bounded control	Optimal control balance efficacy and toxicity

Biological and Clinical Implications

- *Control theory in oncology:* The model shows how mathematical control strategies can optimize treatment outcomes.
- *Treatment scheduling:* Pulsed or adaptive dosing schedules could be more effective than constant dosing.
- *Immune-Driven Therapies:* Strengthening or protecting immune cells during chemotherapy could improve long-term success.

ANALYSIS TABLE:TUMOR-IMMUNE-CHEMOTHERAPY MODEL

The analysis presented in Table 2 demonstrates the dynamic interactions among tumor cells, immune cells, and chemotherapy within the proposed Tumor–Immune–Chemotherapy model. The results indicate that tumor growth can be effectively suppressed through an adaptive chemotherapy strategy, while the immune response plays a significant role in controlling tumor progression despite experiencing treatment-induced suppression. Furthermore, the optimal control framework successfully balances tumor reduction and drug toxicity, and the Forward–Backward Sweep Method provides a stable and reliable numerical solution for determining the optimal dosing strategy.

Outcome Summary

The findings summarized in Table 3 indicate that the proposed treatment strategy effectively suppresses tumor growth while preserving immune function to a certain extent and minimizing chemotherapy exposure. These outcomes highlight the potential of the model to achieve a balance between therapeutic efficacy and treatment toxicity, suggesting its applicability for designing clinically relevant and personalized cancer treatment schedules.

Table 2. Analysis table:tumor-immune-chemotherapy model.

Components	Mathematical behavior	Biological interpretation	Implications for theory
Tumor Cell ($T(t)$)	Follows logistic growth: $\frac{dT}{dt} = aT \left(1 - \frac{T}{K}\right) - bTI - cu(t)T$	Tumor proliferates rapidly at first, then is reduced by immune response and chemotherapy	Theory effectively controls tumor, strong intervention is beneficial
Immune Cells ($I(t)$)	Governed by: $\frac{dI}{dt} = s + pTI - dI - eu(t)I$	Immune cells initially proliferate due to tumor but are later suppressed by chemotherapy	Immune system helps control tumor but is weakened by high drug dose
Chemotherapy ($u(t)$)	Computed via optimal control law: $u^*(t) = \min \left\{ \max \left\{ 0, \frac{\lambda_1 cT + \lambda_2 eI}{2w_2} \right\}, u_{\max} \right\}$	Dosing adapts dynamically based on system state and adjoint sensitivity variables	Adaptive/personalized dosing is safer, effective, and less toxic than constant dosing
Adjoint Variables	Backward-in-time ODEs to guide sensitivity and influence of state variables on the objective function	Capture how changes in tumor and immune cell levels affect optimal cost	Used to shape the optimal control strategy
Optimal Objective	$\min_{u(t)} J = \int_0^{T_1} [w_1 T(t) + w_2 u(t)^2] dt$	Trade-off between minimizing tumor burden and limiting drug toxicity	Balances tumor suppression with chemotherapy side effects
Control Strategy	Forward-Backward Sweep Method with relaxed update: $u_i^{(k+1)} = \theta u_i^{(k+1)} + (1 - \theta) u_i^{(k)}$	Iterative approach yields convergence to optimal dosing strategy	Efficient for solving coupled nonlinear ODE systems
Convergence Behavior	Control and state trajectories stabilize after few iterations	Solution stabilizes when control updates fall below a given tolerance	Method is numerically stable and converges reliably under proper step size and relaxation parameter θ

Table 3. Outcome summary.

Outcome	Biological significance	Real-world relevance
Tumor suppressed, immune cells preserved to some extent, chemotherapy use is bounded and minimized.	Strategy effectively manages cancer while considering immune preservation and drug side effects.	Potentially translatable to real-world clinical treatment scheduling.

CONCLUSION

The presented mathematical model effectively captures the complex dynamics between tumor cells, immune response, and chemotherapy treatment. By applying *Pontryagin's Maximum Principle* and solving the system numerically using the *Forward-Backward Sweep Method*, we obtain an *optimal control strategy* that adapts chemotherapy dosing over time to minimize tumor burden while preserving immune function and limiting drug usage.

Future Scope

1. *Tumor Suppression*: The model demonstrates that an optimally timed and dosed chemotherapy regimen significantly reduces tumor size over the treatment period.
2. *Immune Preservation*: Despite chemotherapy's immunosuppressive effects, the model maintains a functional immune population, supporting its role in tumor regulation.
3. *Adaptive Dosing*: The optimal control law yields a *time-varying dosing schedule*, avoiding constant high-dose treatments that may lead to toxicity or immune collapse.
4. *Clinical Relevance*: The model supports the shift toward *personalized, adaptive therapy protocols*, especially when immune health must be preserved (e.g., immunotherapy combinations).
5. *Numerical Robustness*: The method converges reliably and can be easily extended to include more biological complexity such as resistance, multiple drugs, or spatial heterogeneity.

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