A Multi-Scale Computational Framework for Modeling Cancer Chemotherapy

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Abstract

Mathematical modeling is a powerful tool for understanding the complex dynamics of cancer-immune interactions and optimizing therapeutic strategies. Traditional models, often based on Ordinary Differential Equations (ODEs), provide a deterministic, "mean-field" approximation of these interactions. However, they lack the ability to capture the critical roles of biological randomness and spatial heterogeneity. This paper presents a multi-scale computational framework that extends a foundational ODE model (Lestari et al., 2019) into two progressively more realistic models: (1) a Stochastic Differential Equation (SDE) model that introduces probabilistic noise to capture random biological fluctuations, and (2) a novel Network-Hybrid model that replaces the bulk tumor population with an agent-based, spatial graph. This hybrid model introduces new, spatially-aware rules for immune attack (surface vs. core) and chemotherapy penetration (a vascular-based gradient). We demonstrate that while the SDE model provides a richer, probabilistic forecast, its mean-field assumption remains a limitation. The Network-Hybrid model reveals emergent behaviors, demonstrating that spatial heterogeneity can protect a tumor "core" from immune attack, allowing the tumor to persist even under conditions where the mean-field models predict its complete elimination.

1 Introduction

Cancer remains a leading cause of mortality worldwide, characterized by the uncontrolled proliferation of abnormal cells [1]. The dynamic interplay between tumor cells, the host immune system, and therapeutic interventions like chemotherapy is immensely complex [1]. Mathematical modeling has emerged as a critical methodology for dissecting these dynamics, analyzing treatment efficacy, and predicting therapeutic outcomes [2].

A common and effective approach involves systems of Ordinary Differential Equations (ODEs), which model the "predator-prey" battle between immune effector cells and tumor cells [1]. A foundational model in this area is presented by Lestari et al. (2019), which

describes the bulk, mean-field interactions between three populations: Effector (immune) cells (E), Tumor cells (T), and Chemotherapy drug concentration (M) [1]. This deterministic model (Figure 1) provides valuable insights into the stability of the system, identifying conditions that may lead to tumor-free or cancer-persistence states [1].

However, this ODE model relies on two major simplifying assumptions:

1. **It is Deterministic:** It predicts a single, smooth trajectory, ignoring the inherent randomness (stochastic noise) of biological events like cell division and death [2].

2. **It is Mean-Field:** It assumes all populations are "well-mixed," meaning every immune cell can interact with every tumor cell, and drug concentration is uniform. This is biologically unrealistic for solid tumors, which possess a complex spatial structure.

To address these limitations, we developed a multi-scale framework by progressively enhancing the foundational Lestari et al. model. This paper details the formulation and analysis of three distinct models:

1. **Model 1: The Deterministic ODE (Baseline):** The original Lestari et al. (2019) model [1].

2. **Model 2: The Stochastic SDE (Temporal):** An extension of the ODE system into a Stochastic Differential Equation (SDE) model. This introduces probabilistic noise to capture random fluctuations and allows for the calculation of metrics like "tumor extinction probability" [2].

3. **Model 3: The Network-Hybrid (Spatial):** A novel hybrid model that replaces the bulk tumor population T with a spatial, agent-based network. This model introduces new, spatially-aware rules for immune attack and drug penetration, providing a more realistic simulation of a solid tumor.

By comparing the outputs of these three models under identical parameters, we demonstrate how adding layers of biological realism—first stochasticity, then spatial structure—fundamentally alters the predicted outcomes of therapeutic intervention.

2 Model Formulation and Methodology

Our framework is built upon the three-variable system from Lestari et al. (2019) [1].

2.1 Model 1: The Deterministic Foundation (ODE)

The baseline model is the deterministic, mean-field system of Ordinary Differential Equations (ODEs) presented as System (11) by Lestari et al. [1]. The system (Figure 1) describes the interactions between Effector cells (E), Tumor cells (T), and Chemotherapy drug concentration (M) [1].

The parameters, detailed in Table 1, represent established biological processes such as immune cell source (s), immune recruitment (p), tumor logistic growth (r, b), immune cleanup (a, g), and drug clearance (γ) [1].

This model's primary limitation is its deterministic, mean-field nature.

$$\frac{dE}{dt} = s + p\frac{ET}{h+T} - mET - \mu E - K_E ME$$
$$\frac{dT}{dt} = rT(1-bT) - a\frac{ET}{T+g} - K_T MT$$
$$\frac{dM}{dt} = -\gamma M + V_M(t)$$

Figure 1: The Lestari et al. (2019) ODE System (11) [1].

Table 1: Key Model Parameters and Definitions [1].

Param.	Definition	Param.	Definition
s	Growth rate of effector cells	r	Rate of tumor growth
p	Degree of effector cell recruitment	b	Inverse of tumor carrying capacity
h	Saturation for effector recruitment	a	Parameter of cancer cleanup by E cells
m	Inactivation of E cells by T cells	g	Half-saturation for cancer cleanup
μ	Natural death rate of E cells	γ	Clearance rate of chemotherapy drug
K_E	Chemo kill-rate on E cells	K_T	Chemo kill-rate on T cells

2.2 Model 2: The Stochastic Extension (SDE)

Biological systems are inherently stochastic, or random [2]. To capture this, we first converted the deterministic ODE system into a system of Stochastic Differential Equations (SDEs) [2].

An SDE augments the deterministic equation (the **"drift"**) with a new term that represents random noise (the **"diffusion"**) [2]:

$$dY = f(Y)dt + G(Y)dW(t)$$

Here, Y is the state vector $\begin{bmatrix} E & T & M \end{bmatrix}^T$. $f(Y)$ is the "drift" vector, which is identical to the original set of ODEs from Model 1 [1]. $dW(t)$ is the **Wiener Process**, a mathematical construct representing a "perfect random walk" that provides the stochastic "jolt" at each time step [2]. $G(Y)$ is the **Diffusion Matrix**, or "noise amplifier," which scales the random jolt $dW(t)$ based on the current state of the system [2].

Based on a common heuristic for biological systems, we define $G(Y)$ as a diagonal matrix where the noise magnitude for each variable is the square root of the sum of the absolute values of its corresponding reaction rates. The resulting SDE system is:

$$dE = (s + p\frac{ET}{h+T} - mET - \mu E - K_E ME)dt + \sqrt{s + p\frac{ET}{h+T} + mET + \mu E + K_E ME}\, dW_1(t),$$
$$dT = (rT(1-bT) - a\frac{ET}{T+g} - K_T MT)dt + \sqrt{|rT(1-bT)| + a\frac{ET}{T+g} + K_T MT}\, dW_2(t),$$
$$dM = (-\gamma M + V_M(t))dt + \sqrt{\gamma M + V_M(t)}\, dW_3(t).$$

The full system is solved numerically using the standard **Euler-Maruyama method** [2]. This model, while still "mean-field," can now capture random fluctuations and produce a *distribution* of possible outcomes, allowing for the calculation of clinically relevant metrics like **Tumor Extinction Probability** [2].

2.3 Model 3: The Network-Hybrid (Spatial) Model

The SDE model fixes the problem of determinism but not the problem of spatial structure. Solid tumors are not "well-mixed" bags of cells; they are complex, heterogeneous structures.

To model this, we developed a novel **Network-Hybrid** model. This model maintains E (immune cells) and M (chemotherapy) as global, well-mixed variables governed by the SDEs from Model 2. However, it replaces the single T (tumor) variable with a **spatial graph** (using the `networkx` library), where each node is an individual **agent** (a tumor cell).

This multi-scale architecture allows for new, spatially-aware rules:

1. **Network Generation:** At the start, N tumor cell nodes are placed randomly in a 2D space. Edges (physical adjacency) are created between any two cells within a specified `radius`, forming the tumor's physical contact network .

2. **Immune Attack (Surface vs. Core):** We replace the mean-field immune attack. At each time step, the model identifies "surface nodes" (nodes with a connection count, or degree, at or below the network average) . The global E cell population attacks *only* these surface nodes, leaving the high-degree "core" nodes shielded .

3. **Chemo Penetration (Gradient):** We designate a `source_node` in the graph to represent a blood vessel . The global chemo concentration M is not applied uniformly. Instead, each node receives a `local_M` dose that decays exponentially based on its network distance (`shortest_path_length`) from the source . Cells deep in the tumor core receive a far lower dose than cells near the blood vessel.

4. **Agent-Based Proliferation:** The Lestari model's logistic growth term ($rT(1-bT)$) [1] is re-interpreted at the agent level. Each living tumor node is given a probability of division at each time step, calculated as $P_{divide} = r \times (1 - N_{alive}/K) \times dt$ (where $K = 1/b$) [1]. When a node divides, a new, connected node is added to the graph, realistically embedding it into the spatial structure.

5. **Feedback Loop:** The model creates a true feedback loop. The count of "surface nodes" ($T_{surface}$) from the network is fed *back* into the global dE/dt SDE to calculate immune cell recruitment and inactivation.

This hybrid model simulates the spatial and stochastic battle, capturing emergent behaviors that are impossible to observe in mean-field models.

3 Results and Comparative Analysis

We ran all three models using the scenarios defined by Lestari et al. (2019) to observe the impact of increasing model complexity [1]. The initial conditions were $E(0) = 30,000$,

$T(0) = 40,000$, and $M(0) = 0$ [1].

Simulation Scenarios:

- **Scenario 1:** Low tumor growth ($r = 0.00431$), constant chemo ($V = 0.5$).
- **Scenario 2:** High tumor growth ($r = 0.47$), constant chemo ($V = 0.5$).
- **Scenario 3:** High tumor growth ($r = 0.47$), higher chemo ($V = 0.6$).

3.1 Model 1 (ODE) Results

The deterministic ODE model produces single, smooth trajectories (Figure 2).

- **Scenario 1:** The combination of low tumor growth and chemotherapy is highly effective, driving the tumor population to **complete elimination** (Tumor = 0).
- **Scenario 2:** The high tumor growth rate overwhelms the therapy, and the tumor population grows exponentially.
- **Scenario 3:** Increasing the chemo dose ($V = 0.6$) successfully controls the high-growth tumor, but it is **not eliminated**, persisting at a high population.

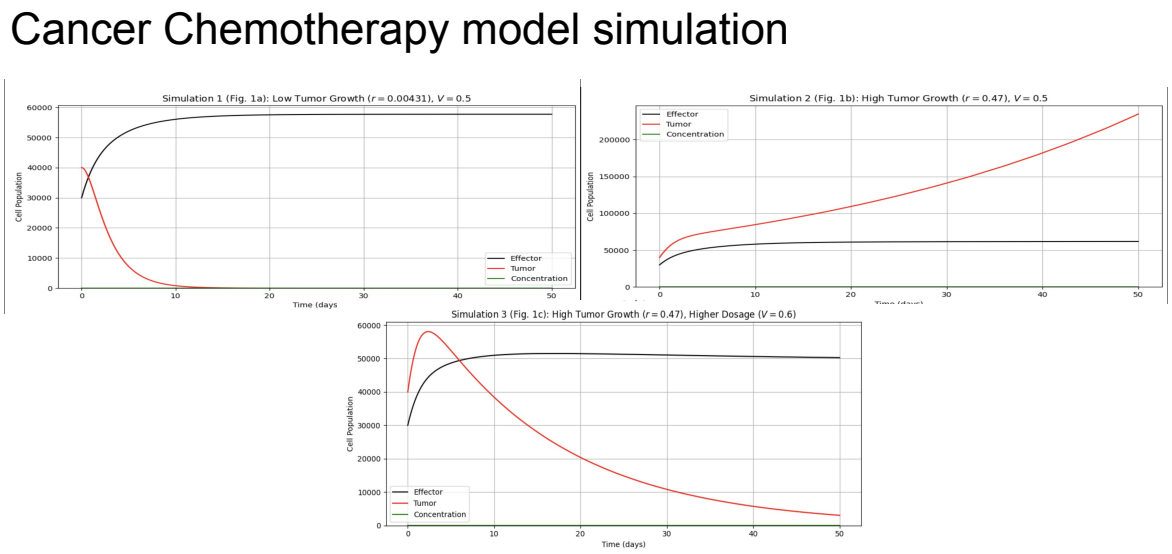

Figure 2: Deterministic ODE model results for Scenarios 1 (left), 2 (middle), and 3 (right).

3.2 Model 2 (SDE) Results

The SDE model produces a distribution of outcomes (Figure 3). The plots show the *mean* (solid line) and *standard deviation* (shaded area) of an ensemble of 50 simulations.

- **Scenario 1:** The *mean* tumor population is **eliminated**, consistent with the ODE model. The shaded area shows some variability, but all paths converge to extinction.
- **Scenario 2:** The *mean* tumor population grows, consistent with the ODE.
- **Scenario 3:** The *mean* tumor population is controlled, consistent with the ODE.

While the *mean* behavior of the SDE mirrors the ODE, its true value lies in the *distribution*. For example, in a scenario where the ODE predicts persistence, the SDE ensemble could show that 15

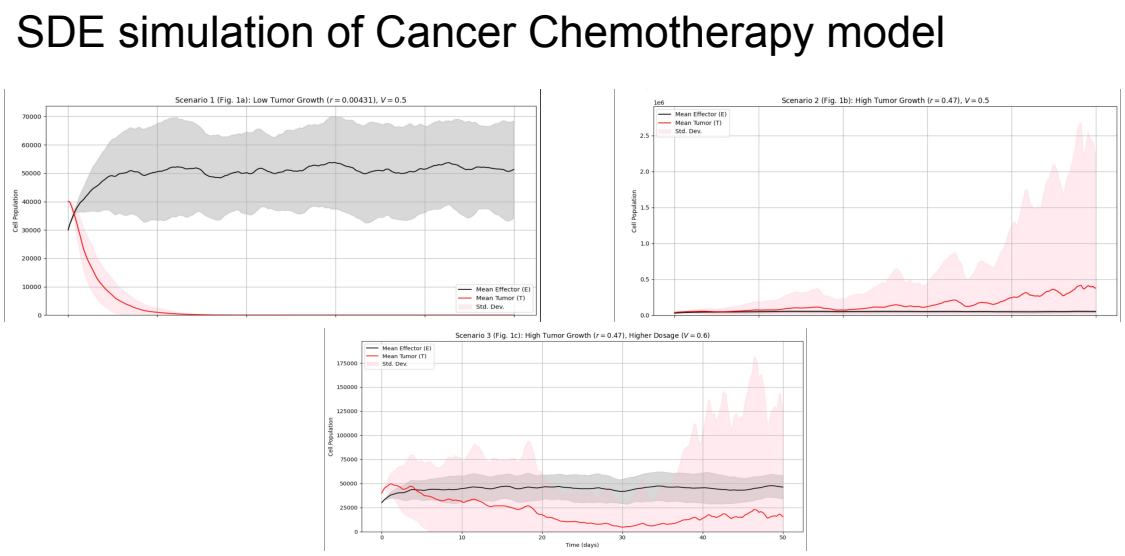

Figure 3: Stochastic SDE model results (mean ± std. dev.) for Scenarios 1 (top-left), 2 (bottom-left), and 3 (right) .

3.3 Model 3 (Network-Hybrid) Results

The Network-Hybrid model reveals a stark divergence in outcomes (Figure 4).

- **Scenario 1 (Low Growth):** This is the most critical result. In Model 1 (ODE) and Model 2 (SDE), this scenario led to **complete tumor elimination** (Figures 2 & 3, left). In the Network-Hybrid model, under the *exact same parameters*, the **tumor persists**.

- **Analysis:** The plot in Figure 4 (left) shows *why*. The "T (Total Living Cells)" line remains high, while the "T (Surface Cells)" line is much lower. The immune system (E) is effectively killing the exposed surface cells, but the tumor's spatial structure **shields the "core"** (high-degree nodes) from immune attack. This protected core allows the tumor to survive and maintain a stable, persistent population, demonstrating a spatial-based treatment resistance that mean-field models cannot capture.

- **Scenario 3 (High Growth, High Chemo):** The right plot in Figure 4 shows the network model under high growth and higher chemo. The chemo, with its `source_node` gradient, "cores out" the tumor, while the immune cells attack the surface. The result is a dynamic, persistent state, again highlighting the spatial nature of the battle.

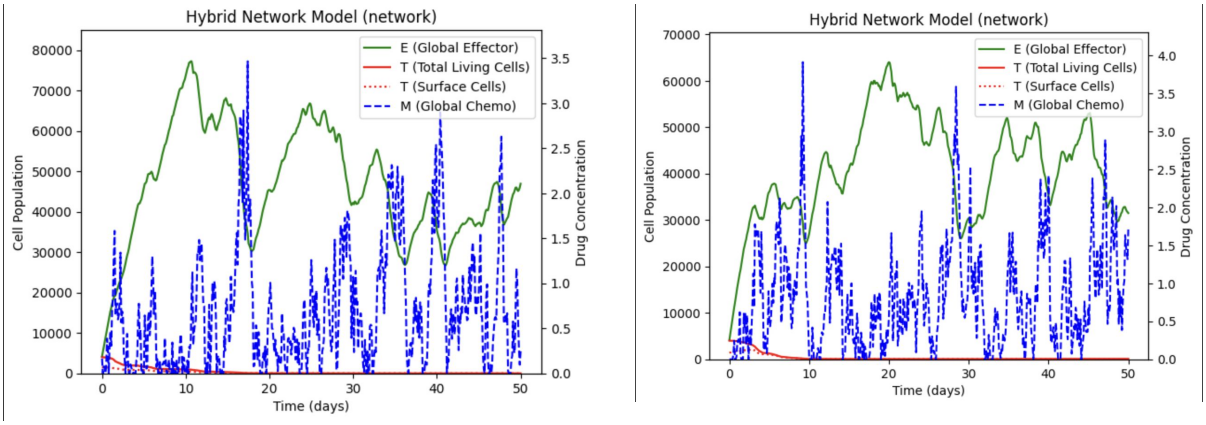

Figure 4: Network-Hybrid model results for Scenario 1 (left) and a high-growth/high-chemo scenario (right).

Algorithm 1: Hybrid Tumor–Immune–Chemo Model

Input : Parameters $p, E, M, dt, t_{\text{end}}$
Output: Temporal evolution of $(E, M, N_{\text{alive}}, T_{\text{surface}})$
$G \leftarrow$ generate_tumor_network(N_0, radius) ;
for $t \leftarrow 0$ **to** t_{end} dt **do**
  living_nodes $\leftarrow$ get_living_nodes(G) ;
  if *living_nodes* $= \emptyset$ **then**
    Update E, M using SDE with $T_{\text{surface}} = 0$;
  surface_nodes $\leftarrow$ identify_surface_nodes(living_nodes) ;
  $T_{\text{surface}} \leftarrow |\text{surface\_nodes}|$;
  $(E, M) \leftarrow$ EulerMaruyamaStep$(E, M, p, T_{\text{surface}})$;
  kill_surface_cells(surface_nodes, E, p) ;
  kill_by_chemo(living_nodes, M, path_len, p) ;
  proliferate_alive_cells(living_nodes, p, K_{cap}) ;
  record_history$(t, E, M, N_{\text{alive}}, T_{\text{surface}})$;

Biological Interpretation:

- Immune cells attack only tumor surface nodes.
- Chemotherapy diffuses from a source node, decaying with distance.
- Tumor core remains shielded, enabling persistence.

4 Conclusion

This research successfully developed a multi-scale computational framework to analyze cancer chemotherapy. By starting with a foundational deterministic ODE model [1], we first introduced stochasticity (Model 2, SDE) and then spatial heterogeneity (Model 3, Network-Hybrid).

Our findings demonstrate that:

1. **Stochasticity is essential:** SDE models provide more realistic, probabilistic forecasts of treatment success (e.g., "extinction probability") compared to the single, deterministic outcome of an ODE [2].
2. **Spatial structure is dominant:** The mean-field assumption, shared by both ODE and SDE models, is a significant limitation. Our Network-Hybrid model revealed that a tumor's spatial structure can create emergent resistance. We showed that a tumor can **persist** by shielding its core from immune attack, even when the equivalent mean-field models predict **complete elimination**.

This work provides a robust, agent-based platform for future research. It can be used to test hypotheses that are inaccessible to simpler models, such as the effect of tumor topology (e.g., "clumped" vs. "stringy" tumors) on treatment efficacy, or the optimal timing of spatially-targeted therapies to synergize immune and chemical attacks.

5 References

References

[1] Lestari, D., Sari, E. R., & Arifah, H. (2019). Dynamics of a mathematical model of cancer cells with chemotherapy. *Journal of Physics: Conference Series, 1320*, 012026.

[2] Kim, K. S., Kim, S., & Jung, I. H. (2016). Dynamics of tumor virotherapy: A deterministic and stochastic model approach. *Stochastic Analysis and Applications, 34*(3), 483–495.

[3] *Modeling Cancer Chemotherapy — Research Paper (Code Repository)*. Available at: `https://github.com/kanis777/A-Multi-Scale-Computational-Framework-for-Modeling-Cancer-Chemotherapy/`

[4] Yin, A., He, Z., Zhang, C., & Gao, H. (2024). A Review of Mathematical Models for Tumor Dynamics and Drug Resistance. *Computational and Systems Oncology, 3*(1), e12012.

[5] Cogno, N., de Andres, J. L., & Zubiarrain-Laserna, A. (2024). Agent-based approaches for biological modeling in oncology. *Frontiers in Systems Biology, 4*, 1365872.

[6] Alsakaji, H. J., & Khasawneh, F. A. (2023). Stochastic tumor–immune interaction model with external treatments. *Mathematical Biosciences, 358*, 109997.

[7] Aderyani, S. R., Rahman, M., & Latif, S. (2025). Mathematical modeling of tumor–immune dynamics: deterministic and stochastic perspectives. *Scientific Reports, 15*(1), 4512.

[8] Nave, O., & Osman, I. (2022). A mathematical model for treatment using chemo-immunotherapy. *Results in Applied Mathematics, 15*, 100292.

[9] Guo, E., Kim, T., & Li, X. (2023). Mathematical Modeling of Oncolytic Virus Therapy Reveals Optimal Infection and Cytotoxicity Parameters for Tumor Elimination. *Journal of Theoretical Biology, 564*, 111412.

[10] Poleszczuk, J., Enderling, H., & Hahnfeldt, P. (2016). Agent-Based Modeling of Cancer Stem Cell Driven Solid Tumor Growth. *Physical Biology, 13*(4), 045003.