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A Hybrid Plant-Soil Electrical Analogy and Control Engineering Framework for Dynamically Modeling Cancer Cell Growth in an Elastic Environment

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Keywords
Cancer cell growth modeling, Plant-soil analogy, Control engineering, Dynamic mathematical models, Tumor growth simulations, Therapeutic conditions, Nonlinear simulation models

Abstract – This research introduces a novel approach to cancer cell growth modeling by integrating principles from the plant-soil analogy and control engineering. The proposed model offers a flexible alternative to traditional dynamic mathematical models, enabling simulations of tumor growth under therapeutic conditions. The simulator, operational on an annual basis, considers diverse patient characteristics and treatment approaches. Nonlinear simulation models provide a comprehensive comparison, showcasing trajectory and precision improvements relative to conventional time-dependent dynamic mathematical models. The study further proposes an elastic cancer modeling mechanism, exploring optimal drug dosage concentrations and patient resistance to cancer drugs. A dynamic model is introduced to identify optimal dosages and frequencies for cancer drugs, demonstrating enhanced operational flexibility through computer simulations. The proposed elastic modeling mechanism is validated through existing mathematical growth models, revealing its practical value within ethical constraints. This research offers a promising path for developing effective therapeutic strategies in cancer tumor growth.

1. Introduction

In the realm of biomedical research, classical cell lines and animal models have played a pivotal role, significantly advancing our understanding of cellular signaling pathways, drug target identification, and the design of therapeutics for diseases like cancer and infectious diseases during the late 20th and early 21st centuries (Bähr and Wolf, 2012; Brodaczewska et al., 2016; Gurumurthy and Kent Lloyd, 2019; Lee et al., 2018). However, challenges arise in translating findings from model systems to humans, with recent studies emphasizing the importance of human-specific biological processes (Fischer, 2008). In response to these challenges, human in vitro 3D cell culture approaches, particularly organoids, have attracted attention as promising tools to overcome limitations associated with traditional models (Bernard et al., 2012; LaBarbera et al., 2012).

While prior attempts, such as 2D cell cultures, bio-printing, and microfluidic devices, have shown potential in drug screening and disease research, organoids stand out due to their self-organizing 3D structure that closely resembles human organs (Hrynevich et al., 2023; Ma et al., 2018; Mi et al., 2018). Generated from pluripotent or adult stem cells, organoids replicate human development or regeneration, providing valuable insights into these processes, as well as serving as effective models for studying diseases (Hrynevich et al., 2023; Verfaillie, 2002; Young and Black, 2004).

Concurrently, understanding and predicting the growth patterns of solid tumors remain paramount in cancer research (Gerlee, 2013). Despite numerous theories, achieving consensus on these growth patterns has proven elusive. Accurate tumor growth models are essential for evaluating screening methods, optimizing radiation treatment protocols, and making informed decisions about patient treatment (Friberg and Mattson, 1997; Michaelson et al., 1999; Sachs et al., 2001).

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Observing the growth of solid tumors effectively, especially prior to therapeutic interventions, requires volumes exceeding $1mm^3$, representing a critical step in carcinogenesis (Sachs et al., 2001). The expansion to neoplasm size, driven by the upregulation of cell division in malignant cells, is a fundamental observation in cancer studies (Hanahan and Weinberg, 2011).

The multicellular tumor spheroids (MTS) culture technique emerges as a valuable experimental paradigm, providing insights into the prevascular phase of tumor growth without the confounding effects of tumor-host interactions (Sutherland, 1988). This technique facilitates the exploration of three-dimensional cell-cell interactions that regulate tumor growth. Spheroids, by providing oxygen and nutrients through their surface, result in the formation of necrotic cells at the tumor's core (Sutherland, 1988).

The Machine Conception of the Cell (MCC), adopting an analogical approach for cell discussions based on various analogies between machines and organisms, has been instrumental in understanding cellular dynamics (Nicholson, 2019). Mathematical cancer modeling, spanning over five decades, has explored continuous, discrete, or hybrid combinations based on a physical representation of key biological components (Al-Tuwairqi et al., 2020; Altrock et al., 2015; Cunningham et al., 2018; Dhoruri et al., 2020; Hartung et al., 2014; He et al., 2020; Jarrett et al., 2018; Lo et al., 2013; Marušić, 1996; Piantadosi et al., 1983; Rivaz et al., 2019; Vallverdú et al., 2018; West and Newton, 2019).

The highly nonlinear and multimodal nature of cancer tumor growth and treatment poses significant challenges, particularly in therapeutic conditions (Friberg and Mattson, 1997). Identifying optimal or sub-optimal solutions in the same system becomes complex due to multiple constraints and competing objectives (Guocheng et al., 2011; Yang et al., 2021)

Despite extensive efforts, accurately simulating tumor progression remains a formidable challenge (Buosi et al., 2024; Das et al., 2024; Hussein et al., 2024; Zhang et al., 2024). Various growth functions have been proposed in ecological and epidemiological research (Sethanan et al., 2023), yet a comprehensive model for cancer cell growth through computer simulations is still elusive (Hanahan and Weinberg, 2011).

This study endeavors to address this complexity by considering personal and therapeutic variables, employing an electrical simulation across a broad spectrum. The proposed three-layered electrical model, analogous to cancer cell growth in the MTS culture technique, symbolizes cancer cell growth as an electrical circuit comprising resistors, capacitors, and inductors. Inspired by the soil-plant model, the electrical analogy provides an effective means to convert non-electrical systems into electrical systems for accurate and efficient solutions (Anayochukwu, 2013; Hunt et al., 1991; Jakubaszek and Stadnik, 2019; Molz and Remson, 1970; Ruggiero et al., 1999; Stirzaker and Passioura, 1996; van Bavel, 1996)

This article is structured as follows: Section 2 presents the problem formulation, materials and methods, including discussions on mathematical derivations of cancer cell growth models based on electrical analogies, electrical model structure, and similarities with the plant-soil method, and advancements in cancer cell growth. Section 3 graphically represents simulation results and discusses simulator performance. Section 4 delves into the model's results and potential advantages in depth, and Section 5 provides concluding observations and recommendations for future research.

This comprehensive exploration integrates diverse aspects of biomedical research, ranging from advanced cell culture techniques and tumor growth dynamics to mathematical modeling and electrical analogies, aiming to contribute to our understanding of cancer and pave the way for improved treatment strategies.

2. Problem Formulation and Methodology

The understanding of mathematical concepts governing complex systems, despite their pivotal role in comprehending natural phenomena, remains incompletely deciphered. Drawing inspiration from Newton's principles, the application of mathematical models encompassing physical, chemical, and biological aspects is deemed essential for a comprehensive understanding of any system (Ducheyne, 2005). Real-world challenges, particularly in biological processes, exhibit intricate complexity. Diverse mathematical models, varying in complexity from basic to highly elaborate, have been formulated to accurately represent these processes, guided by the dynamics of the system and specific modeling requirements (Rivaz et al., 2019).

Initiating the mathematical modeling process involves defining functional specifications, including the purpose, accuracy, boundaries, and time scaling, essential for constructing an effective model. While achieving an exact replication of "actual" behavior through mathematical models is often unfeasible, establishing modeling objectives aids in understanding the requirements and determining the necessary degree of precision (Piantadosi et al., 1983; Stare et al., 2006; West and Newton, 2019) Subsequently, computer simulations are employed to observe the behavior of these models.

2.1. Classical mathematical models

In the realm of tumor growth analysis, classical mathematical models focus on changes in tumor volume over time, employing first-order ordinary differential equations based on initial assumptions. This section presents commonly referenced tumor growth models found in the literature.

2.1.1. Exponential and Malthusian model

One such model is the exponential growth model shown in Figure 1, which approximates tumor growth for small time values. Equations incorporating intrinsic growth rates, such as the widely used Malthusian model, represent the simplest form of a differential equation describing tumor growth.

$$\frac{\mathrm{dV}}{\mathrm{dt}} = \mathrm{r}V \tag{1}$$

$$\mathrm{V(t)} = \mathrm{V_0}e^{\mathrm{rt}} \tag{2}$$

The solution for $\mathrm{V(t)} = \mathrm{V_0}e^{\mathrm{rt}}$, where $\mathrm{V_0}$ is the volume at time 0.

The Malthusian model, initially introduced by Collins (Collins et al., 1956) and extensively applied in various systems, was subsequently employed in the context of cancer cell growth. The utilization of tumor doubling time (DT = (ln 2)/r) served as a quantification of growth rates in their study.

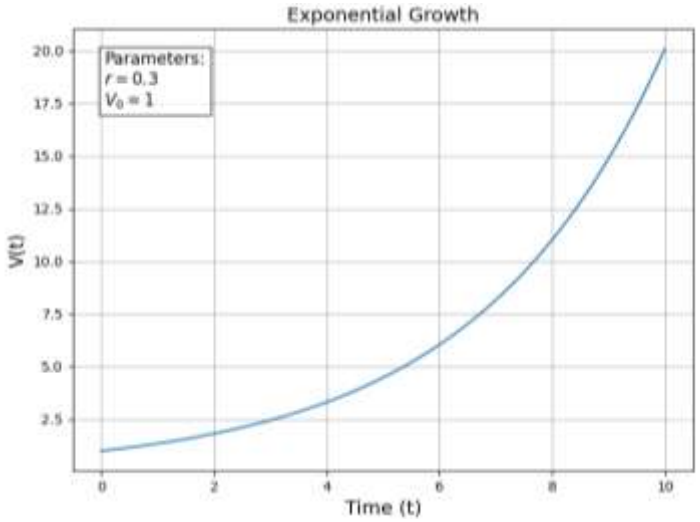

Figure 1. Exponential growth model

The exponential growth law has been found applicable in modeling leukemia, and an investigation involving over 300 untreated lung cancers similarly demonstrated the suitability of exponential growth modeling (Friberg and Mattson, 1997). Particularly advantageous for simulating early tumor growth, this model, however, lacks consideration for spatial limitations and constraints arising from dependencies on nutrients and oxygen (Talkington and Durrett, 2015).

2.1.2. The power law model

Proposed approximately five decades ago (Dethlefsen et al., 1968), the power law differential equation asserts that the rate of increase is proportionate to the volume raised to the power of α, shown in Figure 2.

$$\frac{\mathrm{dV}}{\mathrm{dt}} = \mathrm{r}V(t)^{\alpha} \tag{3}$$

When α is equal to 1, this model transforms into an equivalent of the exponential growth model. However, for cases where α is less than 1, the equation takes on a different form.

$$\mathrm{V(t)} = \mathrm{V_0}^{1-\alpha} + ((1-\alpha)rt)^{1/(1-\alpha)} \tag{4}$$

The power law with linear death formed as follows;

$$\frac{\mathrm{dV}}{\mathrm{dt}} = \mathrm{r}V(t)^{\alpha} - r\frac{\mathrm{V(t)}}{\mathrm{K}^{1-\alpha}} = \mathrm{r}V^{\alpha}\left(1 - \left(\frac{\mathrm{V}}{\mathrm{K}}\right)^{1-\alpha}\right) \tag{5}$$

Comprehending the assumptions and ramifications of these models is essential, as they frequently serve as the underpinning for more intricate tumor growth models (Forys and Marciniak-Czochra, 2003).

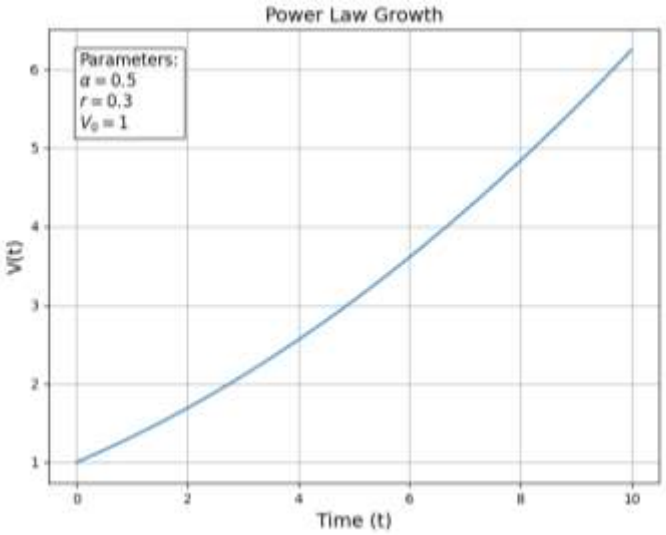

Figure 2. Power law growth model

2.1.3. The Gompertz model

Benjamin Gompertz's research primarily centered on mortality curves in humans, while Wright recognized the suitability of the Gompertz model for biological growth (Gompertz B., 1825) demonstrated in Figure 3. The Gompertz model, as proposed by Gompertz, gained prominence in cancer research, with Laird demonstrating its effectiveness. Wright expressed the alteration in tumor volume through the formulation of a differential equation.

$$\frac{\mathrm{dV}}{\mathrm{dt}} = \alpha(t)\mathrm{V(t)} \text{ where } \frac{\mathrm{d}\alpha}{\mathrm{dt}} = -\mathrm{r}\alpha(t) \tag{6}$$

This equation is solved as follows:

$$V(t) = \mathrm{V_0}\exp\left(\frac{\alpha_0}{\mathrm{r}}(1 - e^{rt})\right) \tag{7}$$

To derive the logistic growth, the first differential equation is

$$\frac{\mathrm{dV}}{\mathrm{dt}} = r\mathrm{V(t)}\log(K/V(t)) \tag{8}$$

where K= $\mathrm{V_\infty}$=$\lim_{t\to\infty}(V(t))$

The solution of this equation is:

$$V(t) = \mathrm{V}_0 \exp\left(A(1 - e^{-rt})\right) \tag{9}$$

where A=log (V_∞ /V_0)

$$A = \ln(10^{12}) = 27.631 \tag{10}$$

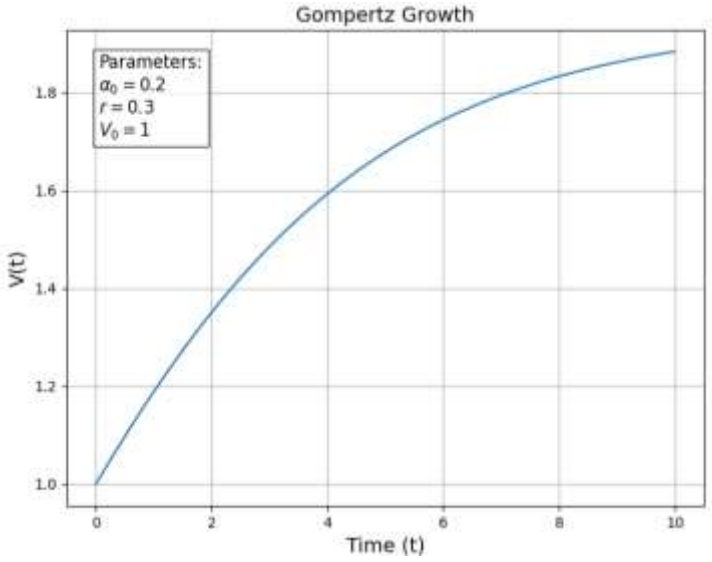

Figure 3. Gompertz growth model

2.1.4. The generalized logistic

The generalization of the logistic model is achieved through interpolating between the Gompertz and logistic models.

$$\frac{\mathrm{dV}}{\mathrm{dt}} = r\mathrm{V(t)}\ (1 - \mathrm{V(t)}/K)^{\beta} \tag{11}$$

The solution to this equation is:

$$V(t) = K(1 + Qexp(-\beta rt))^{-1/\beta} \tag{12}$$

where $Q = \left[(K/\mathrm{V}_0)^{\beta} - 1\right]$ and K is the carrying capacity, r is the growth rate and V_0 is the initial volume.

When $\beta = 1$, the generalized logistic model simplifies to the standard logistic model. The equation becomes:

$$V(t) = K(1 + Qexp(-rt))^{-1} \tag{13}$$

with Q reducing to:

$$Q = [(K/\mathrm{V}_0) - 1] \tag{14}$$

This paper illustrates diverse graphical representations of models sourced from the literature depicting the progression of tumor mass or volume over time. A spectrum of growth prediction models is accessible, spanning from the elementary single-parameter Exponential model to sophisticated ones such as the Gompertz and Generalized Logistics models (Forys and Marciniak-Czochra, 2003). Additionally, the Fractional Logistic Equation presents another model alternative (Varalta et al., 2014).

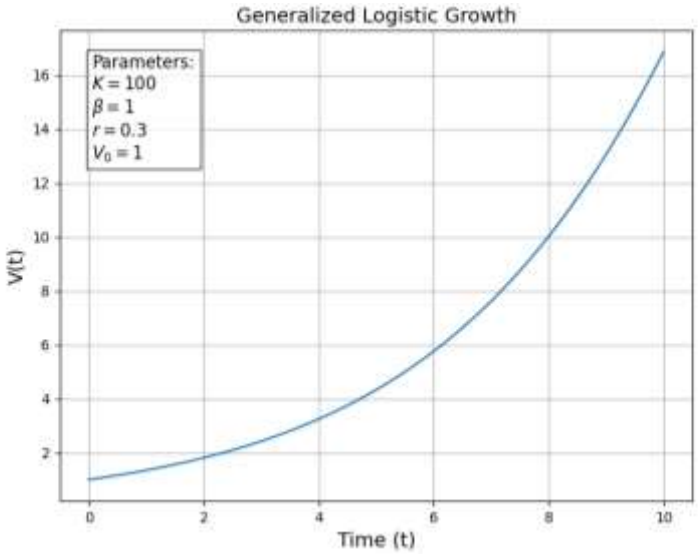

Figure 4. Logistic growth model

Researchers and practitioners often find the generalized logistic differential equation valuable due to its ability to capture more complex growth patterns compared to simpler models. Its application extends to fields such as ecology, where it is used to model population dynamics, and epidemiology, where it may describe the spread of diseases within a population. The generalized logistic differential equation serves as a powerful tool for modeling diverse growth processes, providing a balance between simplicity and flexibility as shown in Figure 4. Its parameters allow for fine-tuning the model to match specific scenarios, making it a valuable asset in the study of dynamic systems across various disciplines.

2.1.5. Bertalanffy growth model

The Bertalanffy Growth Model, proposed by Ludwig von Bertalanffy, is a mathematical representation designed to capture the growth patterns of organisms over time. Introduced as an alternative to simplistic linear or exponential growth models, Bertalanffy's model accounts for the biological principle that growth rates tend to decrease as an organism approaches maturity. This model has found applications in fields such as biology, ecology, fisheries science, and even in understanding the growth trajectories of individual organisms illustrated in Figure 5.

The Bertalanffy Growth Model is typically expressed as:

$$W(t) = W_{\infty}\left(1 - e^{-k(t-t_0)}\right) \tag{15}$$

This model is particularly useful when studying the growth of fish, where it has been extensively applied to estimate growth parameters and predict the size distribution of populations. The asymptotic maximum length L∞ provides insight into the potential size an organism could reach under optimal conditions, while the growth rate constant k determines how quickly an organism approaches this maximum length.

One notable feature of the Bertalanffy Growth Model is its ability to accommodate non-linear growth patterns, which is often observed in organisms that experience changing environmental conditions or resource availability. This makes it a valuable tool for researchers seeking a more realistic representation of growth dynamics in natural populations.

The Bertalanffy Growth Model has proven to be a versatile and widely applicable tool in the study of biological growth. Its consideration of the asymptotic limit and the decelerating growth rate aligns more closely with the biological realities of many organisms, making it a valuable asset in various scientific disciplines. Researchers continue to refine and adapt this model to address specific challenges and gain deeper insights into the complex dynamics of growth in living organisms.

The von Bertalanffy Growth Model, adapted for fisheries, stands as a cornerstone in fisheries biology, offering a robust framework to comprehend the growth dynamics of fish populations. This model has been tailored to the specific characteristics of fish growth, rendering it a vital tool in fisheries science. Its application extends to the estimation of critical parameters such as asymptotic weight, growth rate, and age at which growth commences

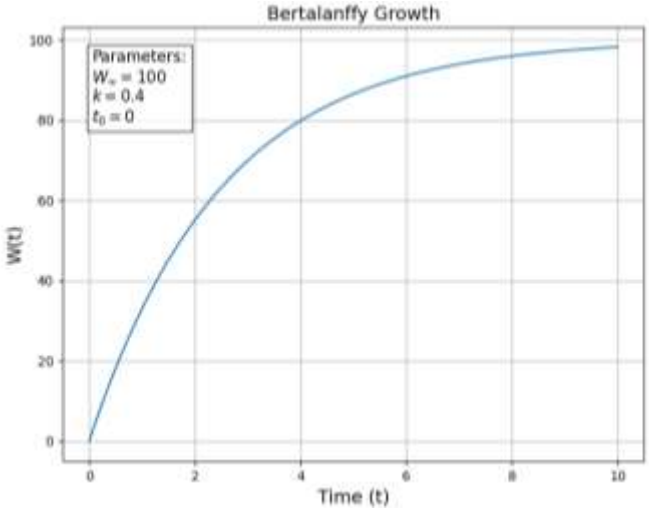

Figure 5. The von Bertalanffy Growth Model

This model plays a pivotal role in elucidating the growth patterns of fish populations over time. Through the estimation of its parameters from observed weight-at-age data, scientists gain valuable insights for fisheries management. The von Bertalanffy Growth Model enables the determination of sustainable harvest levels, evaluation of population structure, and prediction of future size distributions.

2.2. Reaction-diffusion models

Reaction-diffusion models represent a powerful class of mathematical frameworks widely employed to elucidate the spatiotemporal dynamics of various biological phenomena, including cancer tumor growth. These models integrate the effects of local interactions (reaction) and movement across space (diffusion) to capture the complex patterns emerging in biological systems. In this academic text, we delve into the fundamentals and applications of reaction-diffusion models, with a specific focus on their relevance to the understanding of cancer biology.

Reaction-diffusion models are partial differential equations (PDEs) that describe how the concentrations of interacting substances change over both time and space. In the context of cancer biology, these models prove invaluable in simulating the spread of tumor cells and capturing the emergent patterns arising from interactions with the microenvironment.

The general form of a one-dimensional reaction-diffusion equation is given by

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + f(u) \tag{16}$$

Here, $u(x,t)$ represents the concentration of a substance (e.g., tumor cells), D is the diffusion coefficient, and $f(u)$ describes the local reaction, often representing processes such as cell proliferation, death, or migration.

2.2.1. Fisher-KPP equation

The Fisher-KPP equation is a classic reaction-diffusion model frequently applied to describe the invasion of a new population into a spatial domain. In the context of tumor biology, this equation is particularly relevant for capturing the spread of cancer cells within tissues. The Fisher-KPP equation is given by:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + ru\left(1 - \frac{u}{K}\right) \tag{17}$$

Here, r represents the net growth rate of the tumor cells, and K is the carrying capacity.

Reaction-diffusion models in cancer research offer a valuable tool for investigating the interplay between local cell behaviors and spatial constraints. These models aid in predicting tumor invasion patterns, understanding the impact of different microenvironmental factors, and evaluating potential therapeutic strategies.

Reaction-diffusion models stand as a valuable and versatile tool in the realm of cancer biology. Their ability to bridge the gap between molecular-level interactions and macroscopic patterns provides a nuanced understanding of tumor growth dynamics, paving the way for more informed strategies in cancer treatment and intervention. As research continues to advance, the refinement and application of reaction-diffusion models will undoubtedly contribute to unraveling the intricacies of cancer biology.

3. Soil-Plant model analogy for cancer cell growth electrical circuit model

The application of mathematical modeling, drawing inspiration from the electrical analogy of water flow through the soil-plant system, can help to gain profound insights into the complex dynamics of cancer tumor growth. By adapting the principles of fluid dynamics and electrical conductivity to the tumor microenvironment, we aim to provide a quantitative framework for understanding nutrient transport, resistance factors, and their impact on cancer cell proliferation.

The concept of plant water uptake was devised to enrich our comprehension of the water transport process from the soil to the leaf. This concept delineates a physiological cycle that unfolds under typical conditions. Various factors, including plant configuration, soil water potential, root circulation, and climatic variables, collectively contribute to the non-steady transient flow within this framework (Zhuang et al., 2014).

In the soil-plant system, the electrical analogy represents water flow through the soil as an electrical concept. Adapting this analogy to cancer biology, we equate nutrient transport within the tumor microenvironment to fluid dynamics, where the movement of nutrients is analogous to the flow of water. A comprehensive mechanistic delineation of transient water uptake is yet to be established. Consequently, a non-steady state biophysical model, rooted in the Electrical Circuit Analogous to Water Flow RLC circuit, has been formulated, as illustrated in Figure 6.

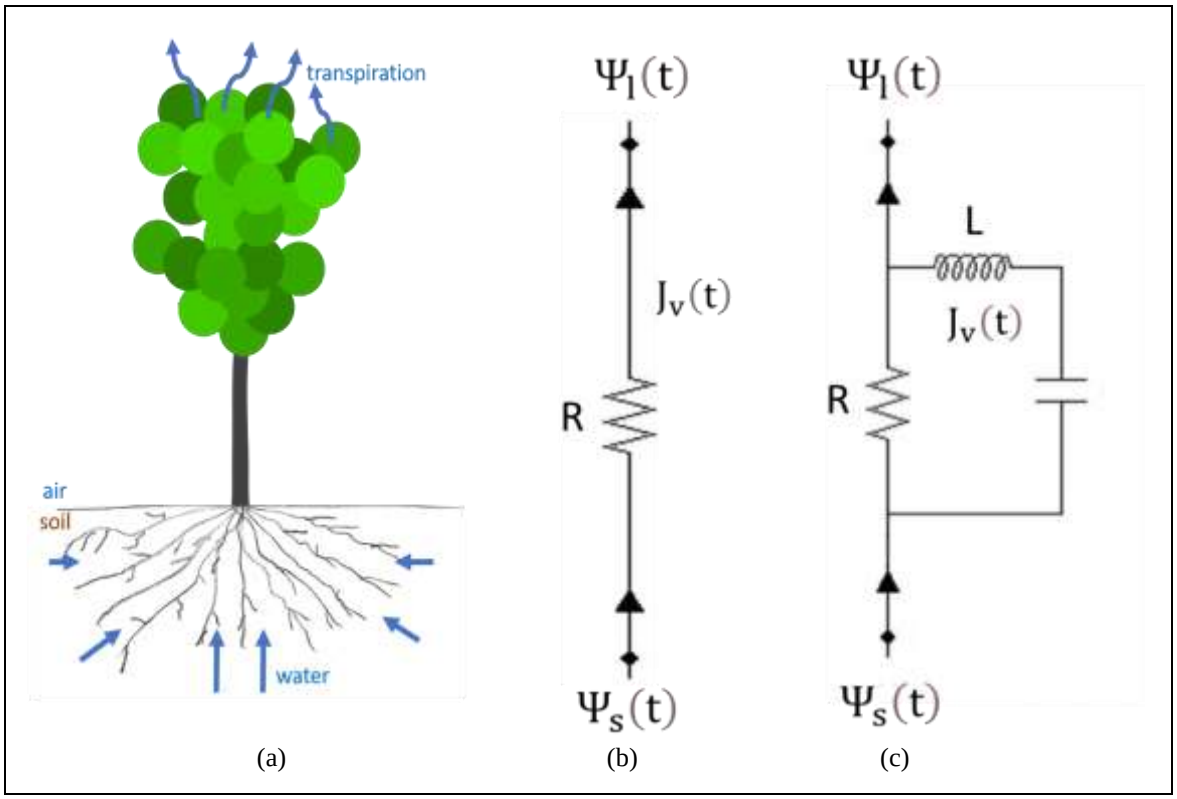

Figure 6. An electrical analogy of water flow through the soil-plant system: (a) soil-plant system, (b) traditional steady state model, and (c) non-steady state model.

Measuring the physiological properties of plants or trees, such as cell wall extensibility, hydraulic resistance, and hydraulic capacitance, poses considerable challenges. Models derived from the electrical analogy of the soil-plant hydraulic method incorporate variable capacitors, inductors, and resistors (Chapman et al., 2012; De Pauw et al., 2008; Hunt et al., 1991). Figure 6 illustrates the water potential difference (Ψ), depicting a positive correlation between soil and leaf water uptake. The observed hysteresis in plant water uptake indicates retardation. A mechanistic approach allows the analysis of changes in uptake rates in response to water stress. In the electrical analogy, resistances influence the flow of current. Similarly, in cancer biology, resistances to nutrient diffusion play a crucial role. These resistances can be mathematically represented as barriers impacting the movement of nutrients within the tumor microenvironment.

Similar to the soil-plant model, the Multicellular Tumor Spheroid (MTS) system, depicted in Figure 7, comprises three layers: the necrotic core (I), quiescent (non-proliferating) cells (II), and proliferating cells (III). The growth curves of tumor spheroids can be accurately determined through dense measurements and high precision (Freyei and Sutherland, 1986). In this study, these three layers are regarded as a combination of three distinct sets of electrical components, namely, A variable AC source, an RLC circuit transitioning to a purely resistive load, and another RLC circuit composed of resistance, capacitance, and inductance.

Employing mathematical models that incorporate nutrient transport, resistance factors, and the cellular response to nutrient availability allows us to simulate cancer cell proliferation dynamics. The simulation provides a quantitative representation of how nutrient availability influences tumor growth and potentially guides therapeutic interventions.

Analyzing the cases in these layers provides insights into the growth rate of cancer cells and assists in optimizing chemotherapy doses.

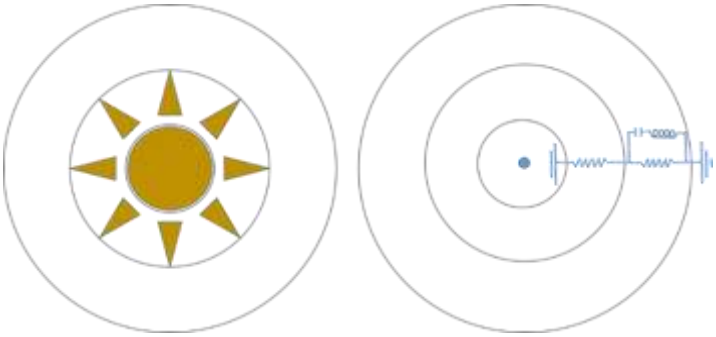

Figure 7. MTS system presentation as a simple electrical circuit (Growth Control in Tumor Dynamics: Bridging Electrical Control Systems and Cancer Intervention Strategies)

This study delves into the utilization of mathematical models to comprehend the mechanisms of infinite growth in tumor development and assess intervention strategies. By incorporating mathematical models that account for nutrient transport, resistance factors, and cellular responses to nutrient availability, we can simulate the dynamics of cancer cell proliferation. This simulation provides a quantitative representation of how nutrient availability influences tumor growth, offering valuable insights into optimizing chemotherapy doses and guiding therapeutic interventions.

In the context of electrical definitions, the treatment of tumor growth aligns with the concept of a closed-loop control system. After delineating the natural conditions of tumor growth within an electrical circuit, configuring it with a control mechanism becomes imperative. This approach allows us to draw analogies between the control of tumor growth and the principles of closed-loop control systems, shedding light on potential strategies for effective intervention and treatment modalities in the pathological condition of uncontrolled proliferation.

The incorporation of this concept not only enhances our understanding of tumor dynamics but also underscores the importance of adopting control strategies to manage and mitigate unregulated proliferation effectively. The analogy drawn between tumor growth and closed-loop control systems provides a conceptual framework that may inform innovative approaches to cancer intervention.

3.1. Model formulation

The following is a typical description of a mass flow of water in the soil-plant concept:

$$J_v(t) = \left(\frac{r^2}{8\eta}\right)\frac{\Delta\Psi(t)}{S} \tag{18}$$

$$J_v(t) = \frac{\Psi_s(t)-\Psi_l(t)}{R_{s-l}(t)} \tag{19}$$

In our examination of the steady-state van den Hornert model, we incorporated the impact of hysteresis by introducing hydraulic capacitance, a concept consistent with prior research. Analogously, in the context of patients undergoing chemotherapy, capacitance is conceptualized as the body's tolerance to the treatment.

$$J_v(t) = \frac{\Psi_s(t)-\Psi_l(t)}{R_{s-l}(t)} - C_h\frac{d\Psi_1(t)}{dt} \tag{20}$$

In the tree-soil concept, the fluctuations in instantaneous water flow rates across various segments of the tree induce an "inductance" effect. This effect has the potential to alter the average driving force of water flow within the plant, a phenomenon analogous to proliferation in the dynamics of cancer cells. As the root water potential declines more rapidly than the soil water potential, the presence of a biological contact potential, functioning akin to a "fuse" in an electrical circuit (Figure 8), is considered susceptible to environmental stress within the tree-soil concept (16) and (17) (Edwards et al., 1986; Ghimire et al., 2016; Jackson et al., 2000; Tuzet et al., 2003; Zweifel et al., 2007).

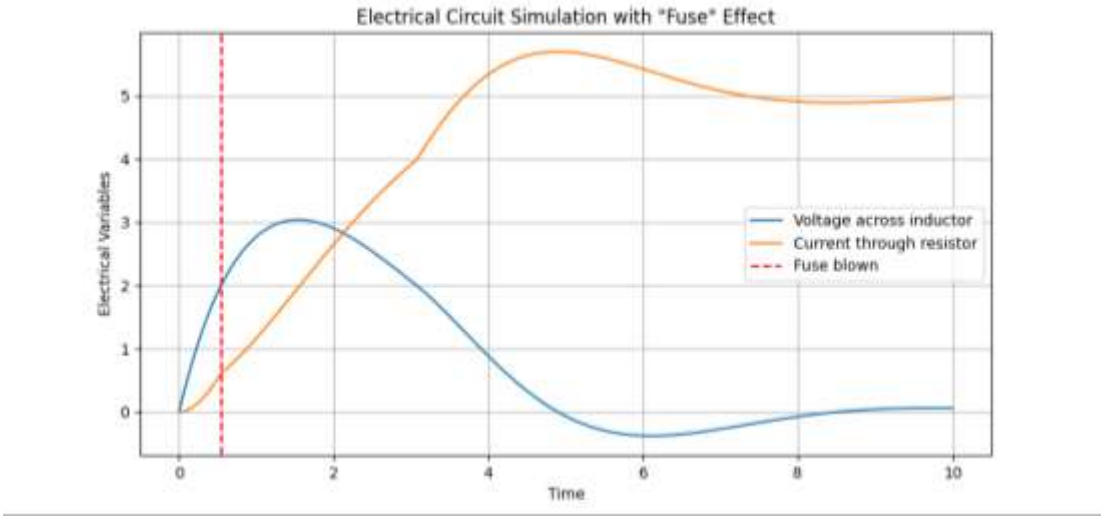

Figure 8. Modeling and Simulation of an Electrical Circuit Analogous to Water Flow in Tree-Soil Systems: Incorporating an Inductance Effect and Environmental Stress Response

$$J_v(t) = \frac{\Psi_s(t)-\Psi_l(t)}{R_{s-l}(t)} - \frac{LdJ_v(t)}{R_{s-l}dt} - C_h\frac{d\Psi_1(t)}{dt} - \frac{A}{R_{s-l}} \tag{21}$$

$$\Delta\Psi_c = -\frac{dJ_v(t)}{dt} \tag{22}$$

The term $\frac{A}{R_{s-l}}$ serves a crucial role in the water flow dynamics between the soil and leaf. Here, A represents a constant related to specific hydraulic properties of the system, reflecting an effective area for water movement. Thee biological contact potential (A in kg/m/s²) acts similarly to a "fuse" in an electrical circuit. This potential is particularly sensitive to environmental stresses, especially when root water potential decreases more rapidly than soil water potential.

To accurately represent these dynamics, we have integrated the principles of "inductance" and "fuse" into (19), resulting in the formulation of a non-steady state model based on the RCL circuit framework. This model facilitates a comprehensive understanding of the complex interactions between water potentials and flow rates, thereby enhancing our insight into the processes governing water movement within the plant system.

The resistance term R_{s-l} denotes the hydraulic resistance to water flow from the soil to the leaf, which can vary based on factors such as soil moisture content and plant physiology. The expression is similar to a fuse, regulating the flow dynamics by limiting the maximum flow rate that can occur under certain conditions.

Here, L represents the inductance arising from the diversity of leaf water potentials at various plant heights. The term dJv(t) acts in opposition to the change in flow rate, signifying the resistance to alterations in flow rate.

$$R_0 = \sqrt{\frac{4L}{C}} \tag{23}$$

$$f = \frac{4L}{2\Pi\sqrt{LC}} \tag{24}$$

$$\Psi_s(t) = \frac{\sum_i \lambda_{r,i}(t)\Psi_{s,i}(t)}{\sum_i \lambda_{r,i}(t)} \tag{25}$$

Cancer cell growth models exhibit notable similarities with the tree-soil paradigm, as both can be elucidated using fundamental principles related to electrically conductive materials and growth rates. The mathematical similarity and electrical analogies prevalent in soil-plant modeling literature are applied in this study to mechanistically represent cancer cell proliferation.

The tumor growth mechanism is depicted through the utilization of an RLC circuit. An elevation in the value of dh, attributed to cancer cell activity, indicates a rise in potential energy within the necrotic core. The duration required for treating cancer over a specified period is perceived as an inductive load on the system, depicted in a sample in Figure 9.

A pivotal aspect of the modeling process involves defining an appropriate model structure. This structure captures tumor dynamics by incorporating considerations of initial tumor volume, chemotherapy doses and frequencies, and tumor proliferation.

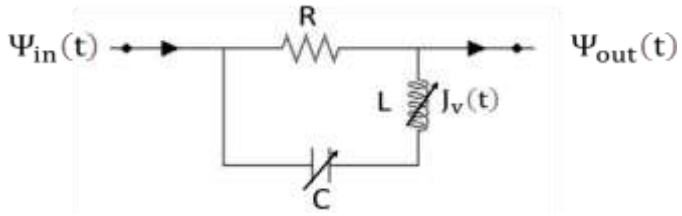

Figure 9. A simple electrical circuit for tumor proliferation modeling

The electrical analogy derived from the soil-tree concept is seamlessly applied to represent tumor growth in (21), and the simulator is depicted in Figure 10. (Zhuang et al., 2014)

$$J_v(t) = \frac{\Psi_{in}(t) - \Psi_{out}(t)}{R_{out-in}(t)} - \frac{L dJ_v(t)}{R_{out-in} dt} - C\frac{d\Psi_{in}(t)}{dt} - \frac{A}{R_{out-in}} \tag{26}$$

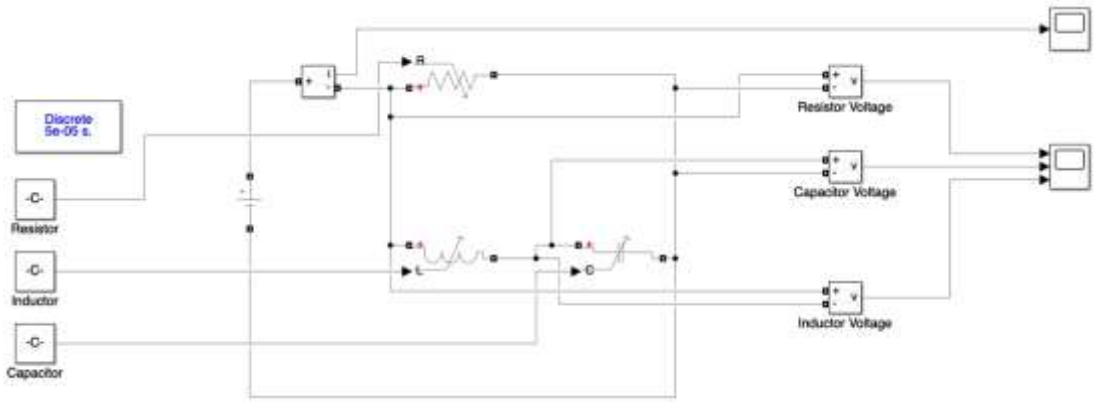

Figure 10. A tumor growth model computer simulator based on electrical analogy

A living cell can be analogized to a piece of machinery, although its intricacy sets it apart from artificially manufactured machines. Despite recent studies utilizing advanced experimental techniques capable of real-time tracking of individual molecules within cells, challenging the conventional engineering perspective of the cell, the machine conception of the cell continues to derive much of its success from the traditional methods employed in molecular biology (Nicholson, 2019).

The dynamics of the tumor system are inherently nonlinear, playing a pivotal role in determining the optimal chemotherapy dose and frequency crucial for effective treatment. Advanced optimal control algorithms have been introduced to investigate tumor treatment under random perturbation conditions. This involves formulating a model-based optimal control problem and integrating it with updated parameters to devise an optimal treatment strategy.

Frequent comparisons of simulation results with actual values allow for the assessment of accuracy, facilitating adjustments to the model to approach the optimal solution. Both system optimization and parameter estimation rely on this iterative approach. Despite variations in the model's reality, the iterative method effectively approximates the optimal solution to the initial optimal control problem.

4. Simulations and Test Results

An indispensable tool for initial design studies, a graphical simulator facilitates the enhancement of treatment strategies by illustrating treatment methodologies in relation to physical performance. At each stage, the evaluation of process block performance is contingent upon patient-specific characteristics. The capability to observe tumor growth simulations across diverse pathologies contributes to the formulation of innovative treatment approaches. The graphical simulator proves instrumental in crafting the most effective and optimized scenarios, guiding preliminary design research.

Moreover, the simulator serves the purposes of forecasting and long-term planning. During the Research and Development stages, therapeutic interventions are simulated through a user-friendly interface. The outcomes of a series of simulations can be extrapolated to similar patients, providing insights into tumor and patient characteristics. Graphs derived from these simulations play a pivotal role in assessing patient performance under therapeutic conditions.

4.1. Benchmark of existing mathematical models with an electrical analogy

The simulator undergoes monthly and annual operations for short-term and long-term tests, respectively. Monthly simulations facilitate the observation of various tumor growth scenarios and the assessment of system dynamics accuracy, while annual simulations offer insights into long-term conditions. The outcomes are then juxtaposed with data obtained from one year of observations based on existing mathematical models.

Current research findings from actual measurements can be treated as system output data based on a nonlinear model. These nonlinear measurements are compared to validate the process model employed in the simulation.

Figure 7 illustrates the Electrical Analogy (EA) method alongside a comparison with the existing exponential growth model, with the results scaled over an annual period. The EA method provides an accurate and observable modeling approach for different tumor growth parameters. However, it is crucial to acknowledge that this model is suitable for demonstrating tumor growth in an infinite space without considering treatment methods and natural conditions.

The notion of unbridled tumor growth proves impractical; the assumption of exponential tumor growth is encumbered by various constraints. Consequently, multiple models have been devised to incorporate saturation limits. Notable examples include the Gompertz and generalized logistic models, which have demonstrated satisfactory outcomes in the scientific literature. The nonlinear model based on the electrical analogy of tumor growth is simulated to achieve an efficient and adaptable treatment approach. This simulator elucidates the optimal configuration of a cancer cell growth model, taking into consideration treatment effects and natural conditions within the human body. The equivalent circuits for tumor growth are dynamically specified.

Within the simulator, the dynamic behavior of the tumor in the analogous electrical model is observed, allowing for the classification of tumor sizes and characteristics. The simulation results of the proposed alternative electrical analogies model are scrutinized and interpreted within the context of existing studies.

Different tumor types may require the utilization of varied models in various studies focused on simulating tumor growth. In Figure 11, the interface of the simulator developed within the scope of this study is presented, enabling a comparative evaluation of the system's exponential growth with the electrical analogy model.

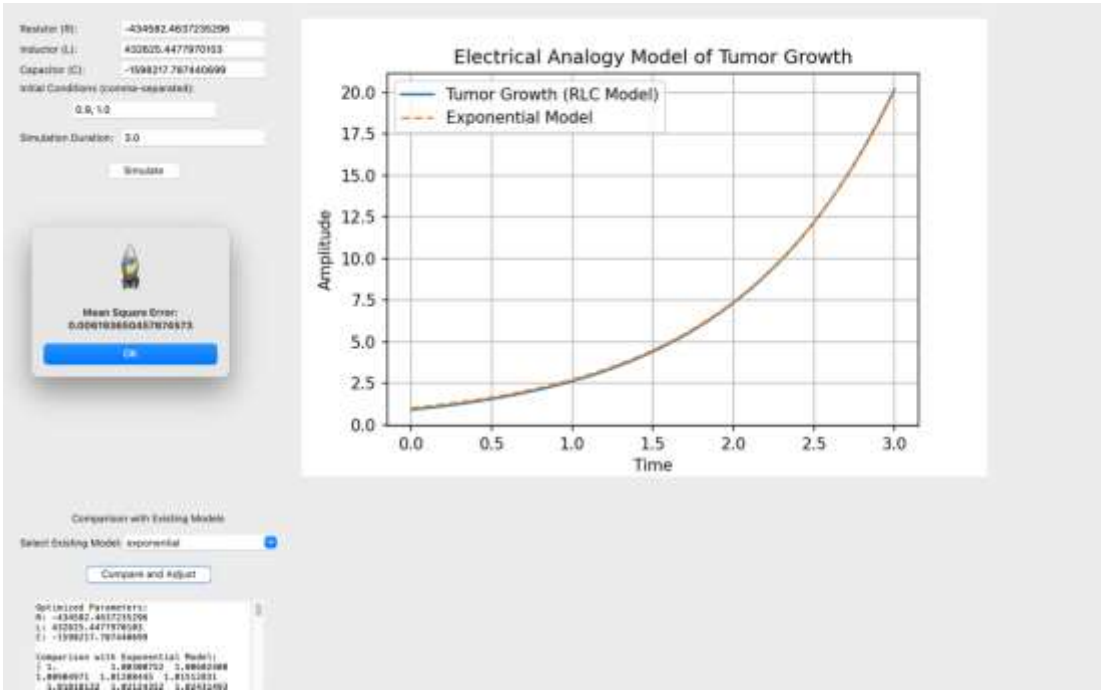

Figure 11. Exponential growth and EA growth performance

Figures 12-17 illustrate power-law and Gompertz models for comparative analysis, respectively. This approach allows for the examination of model effectiveness across different tumor types, contributing to a more comprehensive understanding of tumor growth dynamics in simulation studies.

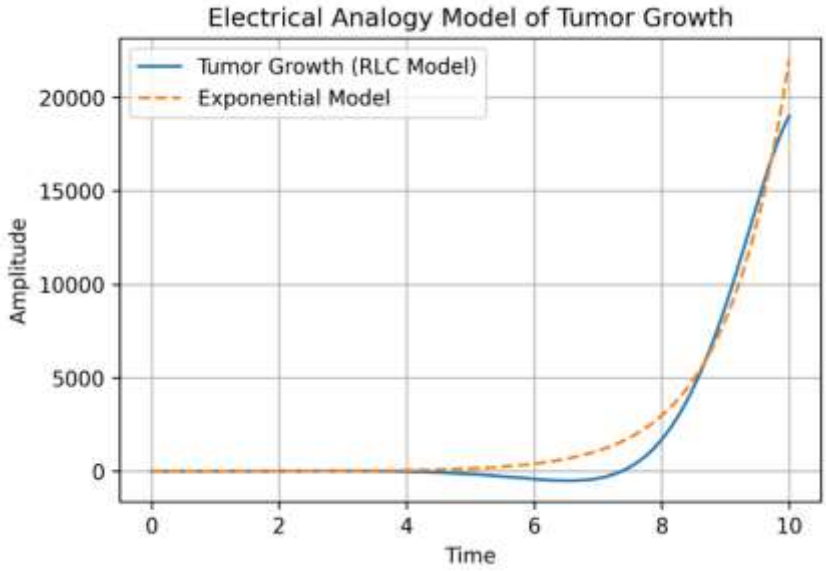

Figure 12. Exponential growth and EA growth performance

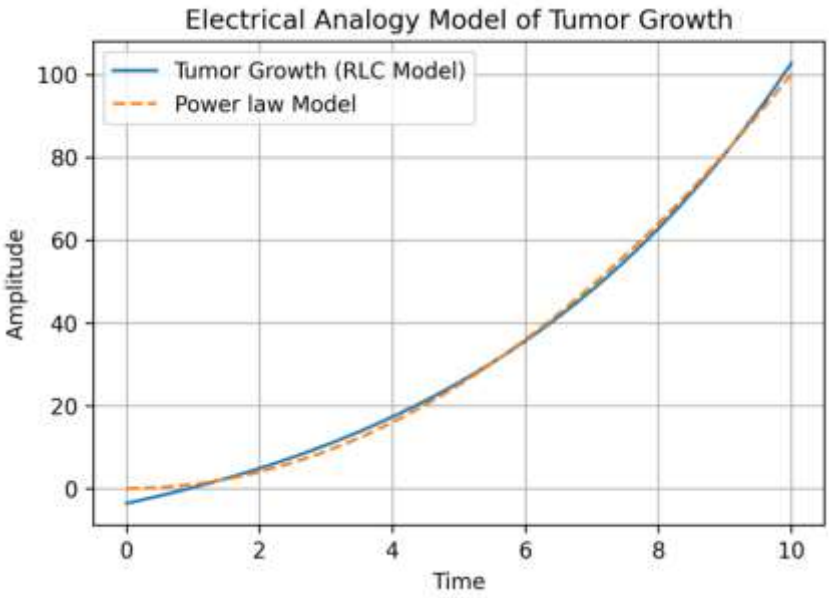

Figure 13. Power Law growth and EA growth performance

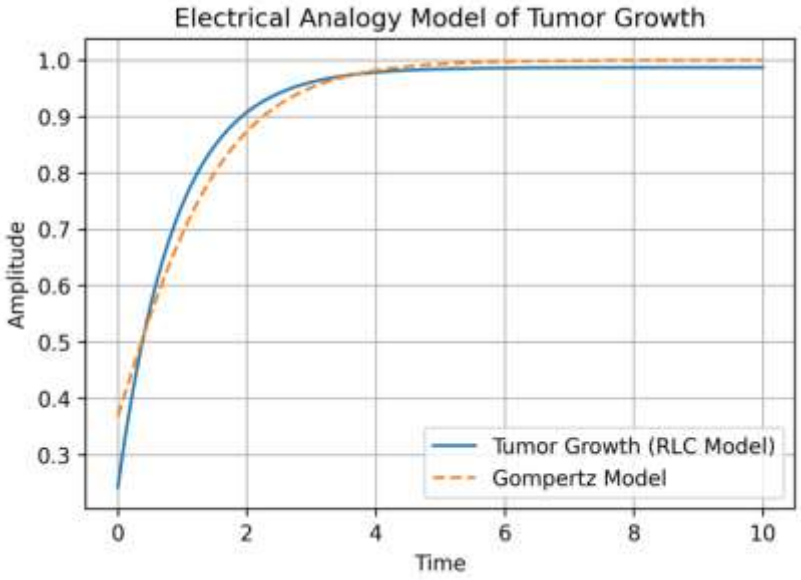

Figure 14. Gompertz growth and EA growth performance

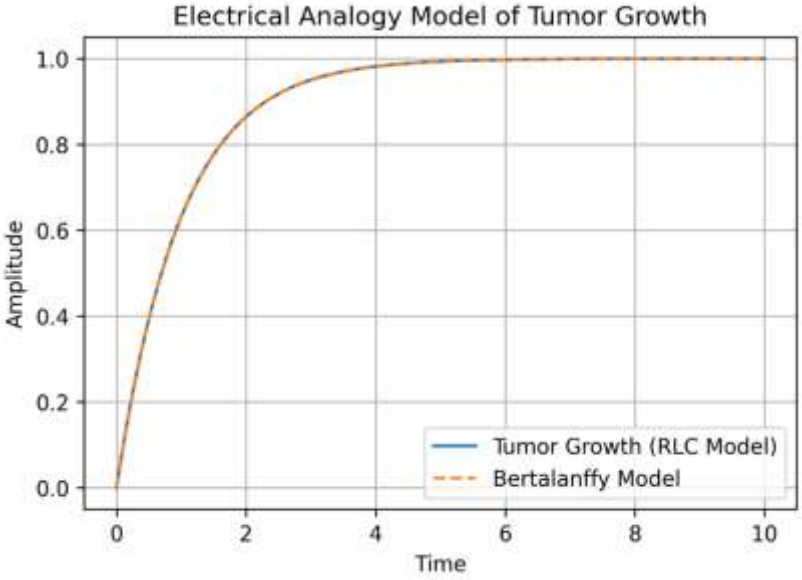

Figure 15. Bertalanffy growth and EA growth performance

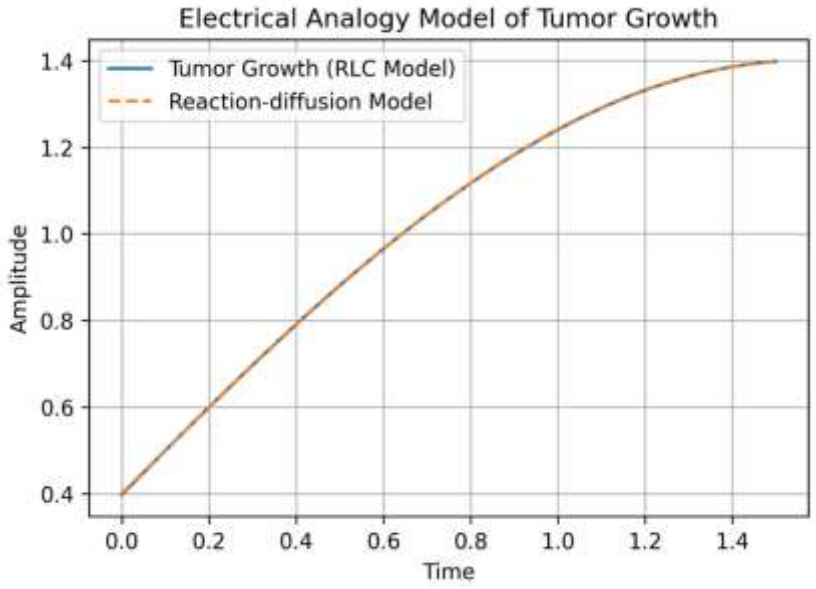

Figure 16. Reaction-diffusion growth and EA growth performance

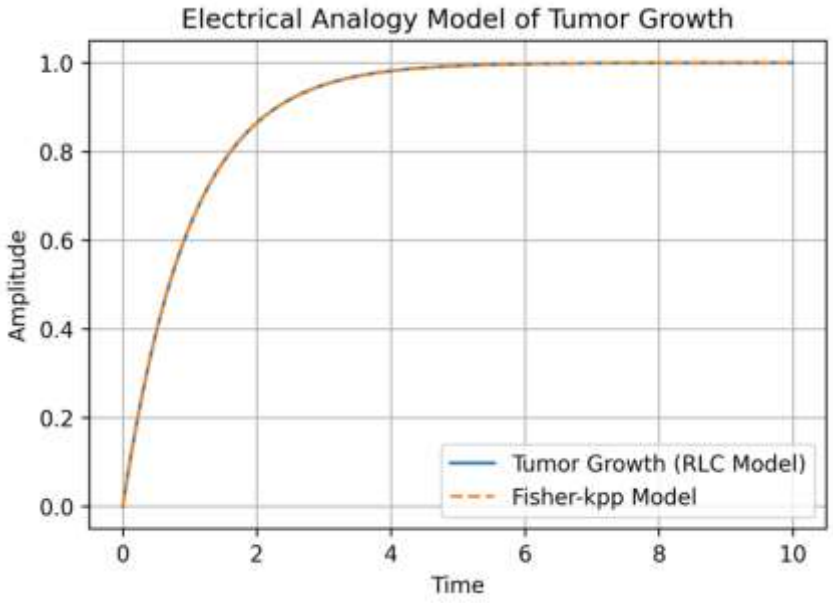

Figure 17. Fisher-KPP growth and EA growth performance

Consequently, Electrical Analogy (EA) emerges as a versatile alternative to create personalized models by incorporating pertinent control parameters into the control structure. Within this control framework, factors like cancer cell types and cell growth rates can be effectively modeled, especially in the presence of therapeutic or external disturbances. This approach is pivotal for formulating precise and dynamic treatment strategies within the framework of control engineering.

$$\mathrm{MSE} = \frac{1}{\mathrm{n}}\sum_{\mathrm{i}=1}^{\mathrm{n}}(\mathrm{y_i} - \widehat{y_i})^2 \tag{27}$$

where n is the total number of observations, y_i is the observed value (actual data), $\hat{y}_i$ is the predicted value (model output).

Table 1. Comparison of Tumor Growth Models: Mean Square Error Analysis

Existing Tumor Growth Models	Mean Square Error
Exponential	0.0061
Power Law	0.0059
Gompertz	0.048
Bertalanffy	0.0093
Reaction-Diffusion Models	0.0057
Fisher-KPP Equation	0.0034

5. Conclusion and Future Works

The comprehensive integration of principles from the plant-soil analogy and control engineering into mathematical modeling for cancer research presents a novel and dynamic framework for understanding tumor growth. This interdisciplinary approach not only contributes to the theoretical foundation but also holds significant promise in guiding the development of targeted therapeutic strategies in the ongoing battle against cancer.

The research adopts an electrical analogy of water flow through the soil-plant system to construct a cancer cell growth model, providing a quantitative and dynamic representation of tumor development under various treatment methods. In contrast to traditional dynamic mathematical models, this model simulates tumor growth specifically under therapeutic conditions. The simulations consider a range of treatments and patient scenarios, offering insights into the advantages of different treatment strategies and optimal designs for the efficient eradication of cancer cells. The simulator operates annually, incorporating diverse patient characteristics and treatment approaches.

Utilizing nonlinear simulation models allows for a comparative analysis of results in terms of trajectory and precision, providing a valuable alternative to conventional time-dependent dynamic mathematical models. The introduction of a novel elastic cancer modeling mechanism further contributes to the identification of optimal drug dosages and frequencies for cancer treatment. Through computer simulations, the model demonstrates substantial improvements in operational flexibility, showcasing its effectiveness in cancer treatment.

The proposed elastic modeling mechanism is suggested as a case study, demonstrating the practical value of the approach within ethical boundaries. The empirical results highlight that the optimally designed tumor growth system outperforms existing models, emphasizing the pragmatic significance of the study. Consequently, the proposed approach offers a promising avenue for modeling and formulating therapeutic strategies in cancer tumor growth, with potential implications for advancing cancer treatment methodologies.

The current study presents a robust framework for comprehending tumor growth and optimizing therapeutic strategies. However, several promising pathways for future research and exploration warrant attention:

Integration of Multi-Omics Data: The incorporation of multi-omics data, encompassing genomics, transcriptomics, and proteomics, into the existing modeling framework can significantly enhance predictive precision. Future investigations may delve into methodologies to effectively integrate these complex datasets, providing a more nuanced portrayal of the molecular intricacies governing tumor behavior.

Personalized Treatment Approaches: Subsequent research efforts could focus on refining the model to facilitate personalized treatment approaches. This entails tailoring therapeutic strategies based on individual patient characteristics, including genetic profiles, with the objective of optimizing treatment efficacy while minimizing adverse effects.

Incorporation of Immunotherapy: Given the rising prominence of immunotherapy in cancer treatment, future models could benefit from incorporating immune system dynamics. Such an inclusion would allow for an assessment of the synergistic effects between traditional treatments and immunotherapies.

Validation and Clinical Trials: Rigorous validation of the proposed model through both retrospective analyses and prospective clinical trials is imperative. Collaborative efforts with clinical researchers and oncologists will be instrumental in translating theoretical insights into pragmatic applications, ensuring the model's relevance and reliability in real-world clinical scenarios.

Exploration of Drug Resistance Mechanisms: A deeper understanding of drug resistance mechanisms is pivotal for developing effective long-term treatment strategies. Future research could delve into the molecular intricacies underlying resistance and integrate this knowledge into the model for predicting and counteracting emerging resistance patterns.

Continuous Model Refinement: Embracing a dynamic approach, the model should undergo continual refinement to align with advancements in cancer research. This may involve the incorporation of real-time patient data, fine-tuning simulation parameters, and adapting the model to evolving therapeutic paradigms.

Ethical and Social Implications: The ethical dimensions of model development and implementation are paramount. Subsequent research endeavors should address ethical concerns related to patient privacy, consent, and the responsible utilization of predictive models in clinical decision-making.

Global Collaboration: Encouraging collaboration among researchers, clinicians, and institutions on a global scale holds promise for the amalgamation of diverse datasets and perspectives. Such collaborative efforts can lead to more comprehensive models that account for population-specific variations and global trends in cancer biology and treatment.

In summation, prospective research endeavors should strive to augment the precision, applicability, and ethical considerations of cancer growth models. By addressing these areas, researchers can make significant contributions to the evolving landscape of cancer research and facilitate the development of more effective and personalized cancer treatments.

Ethics Permissions

This paper does not require ethics committee approval.

Author Contribution

Bayram Arda Kuş conceptualized the study by identifying the research gap, designed and developed the cancer growth modeling framework, performed simulations, analyzed the outcomes, and drafted the manuscript. Mustafa Gürbüz critically reviewed the manuscript, provided scientific validation, and ensured the methodological rigor and accuracy of the findings. AI-based tools were employed for text revisions and editing.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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