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A Theoretical Analysis of Malignant Tumor Growth Dynamics via the Hahnfeldt Equation Using Maple

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ABSTRACT

This study offers a comprehensive theoretical analysis of malignant tumor growth dynamics through the Hahnfeldt equation, a fundamental mathematical model in the field of mathematical oncology. The Hahnfeldt equation integrates essential biological processes such as angiogenesis, vascular support, and tumor growth inhibition, establishing a comprehensive framework for the analysis of tumor progression and regression. This research utilizes Maple's symbolic computation and numerical simulation capabilities to investigate the equation's behavior across different biological and therapeutic parameters. The study primarily analyzes key parameters, including angiogenic stimulation rates, carrying capacity, and inhibitory factors. We analyze the stability of equilibrium points to determine the impact of parameter variations on tumor growth trajectories. Bifurcation analysis identifies conditions under which small variations in parameters lead to substantial alterations in tumor dynamics, including uncontrolled growth, stable states, or regression. The findings offer significant insights into the non-linear and dynamic characteristics of tumor progression. Using Maple's advanced visualization tools, the study presents graphical representations of tumor size evolution over time, highlighting the impact of different parameter sets. The study also investigates the impact of anti-angiogenic therapies through simulations of their effects on tumor dynamics. This analysis illustrates the efficacy of targeted therapeutic interventions in suppressing tumor growth or stabilizing its progression, providing potential strategies for enhancing cancer treatment. The study examines the limitations of the Hahnfeldt model and suggests potential extensions to improve its applicability in complex biological systems. The extensions involve integrating patient-specific data and linking the model with additional biological processes, including immune responses and drug resistance mechanisms. This research offers a comprehensive mathematical and computational analysis of the Hahnfeldt equation, highlighting its importance in the study of tumor growth and the development of precision medicine strategies. The findings seek to connect theoretical modeling with practical oncology applications, thereby advancing mathematical oncology and optimizing cancer therapy.

Keywords: Tumor growth, Computational oncology, Hahnfeldt equation, Mathematical modeling, Maple.

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Hahnfeldt Denklemi ile Maple Kullanılarak Malign Tümör Büyüme Dinamiklerinin Teorik Analizi

ÖZET

Bu çalışmada, matematiksel onkoloji alanında temel bir matematiksel model olan Hahnfeldt denklemi aracılığıyla kötü huylu tümör büyüme dinamiklerinin kapsamlı bir teorik analizi sunulmuştur. Hahnfeldt denklemi, anjiyogenez, vasküler destek ve tümör büyümesini inhibe etme gibi temel biyolojik süreçleri entegre ederek, tümör ilerlemesi ve regresyonunun analizi için kapsamlı bir çerçeve oluşturur. Bu araştırmada, Maple'in sembolik hesaplama ve sayısal simülasyon yetenekleri kullanılarak denklemin farklı biyolojik ve terapötik parametreler arasındaki davranışı incelenmiştir. Çalışmada, öncelikle anjiyojenik uyarım oranları, taşıma kapasitesi ve inhibe edici faktörler gibi temel parametreler analiz edilmiştir. Denge noktalarının kararlılığı analiz edilmiş, parametre varyasyonlarının tümör büyüme yolları üzerindeki etkisi belirlenmiştir. Bölünme analizi, parametrelerdeki küçük değişimlerin tümör dinamiklerinde önemli değişikliklere yol açtığı koşulları belirler; bu değişiklikler arasında kontrolsüz büyüme, kararlı durumlar veya gerileme bulunur. Bulgular, tümör ilerlemesinin doğrusal olmayan ve dinamik özelliklerine dair önemli bilgiler sunmaktadır. Maple'ın gelişmiş görselleştirme araçlarını kullanarak, çalışmada tümör boyutunun zaman içindeki evrimine dair grafiksel temsiller sunularak farklı parametre setlerinin etkisi vurgulanmıştır. Çalışmada ayrıca, tümör dinamikleri üzerindeki etkiler, simülasyonlar aracılığıyla anti-anjiyojenik tedavilerin etkisi de araştırılmıştır. Bu analiz, tümör büyümesini baskılamak veya ilerlemesini stabilize etmek olarak hedeflenmiş terapötik müdahalelerin etkinliğini gösterir, bu da kanser tedavisini geliştirmek için potansiyel stratejiler sunar. Dolayısıyla, çalışmada Hahnfeldt modelinin sınırlamaları incelenmiş ve karmaşık biyolojik sistemlerdeki uygulanabilirliğini artırmak için potansiyel genişletmeler önerilmiştir. Parametreler, hastanın spesifik verilerinin entegrasyonu ve modeli, bağışıklık tepkileri ve ilaç direnci mekanizmaları gibi ek biyolojik süreçlerle ilişkilendirmeyi içerir. Sonuç olarak, bu araştırmada, tümör büyümesi ve hassas tıp stratejilerinin geliştirilmesi konularındaki önemi vurgulanarak Hahnfeldt denkleminin kapsamlı bir matematiksel ve hesaplamalı analizi sunulmuştur. Bulgular, teorik modellemeyi pratik onkoloji uygulamalarıyla birleştirmeyi amaçlayarak matematiksel onkolojiyi ilerletmekte ve kanser tedavisini optimize etmektedir.

Anahtar Kelimeler: Tümör büyümesi, bilgisayarlı onkoloji, Hahnfeldt denklemi, matematiksel modelleme, Maple.

1 Introduction

Researching the growth of malignant tumors is a crucial field of study in cancer biology, with significant implications for the development of successful treatment techniques. To comprehend the mechanisms of tumor formation, it is necessary to develop strong mathematical models that can precisely depict the intricate interplay among tumor cells, their surroundings, and the driving forces behind their proliferation. Ilea et al. (2013) proposed an original mathematical model with a small parameter for the interactions between two cancer cell sub-populations and the mathematical model of a vascular tumor. Rojas, C. and Belmonte-Beitia J. (2018) applied the tools and methods from optimal control to analyze various minimally parameterized models that describe the dynamics of populations of cancer cells and elements of the tumor microenvironment under different anticancer therapies. Benzekry S. et al. (2015) described a numerical method to estimate these parameters from longitudinal tumor volume measurements.

Mathematical models prove valuable tools to study the proof-of-concept, efficacy and underlying mechanisms of such treatment approaches. The effects of parameter value uncertainties for two models of tumor development under angiogenic signaling and anti-angiogenic treatment are studied by Poleszczuk et al. (2015). The book written by Libeskind-Hadas R. & Bush E. (2014), which assumes no

prior computing experience, provides students with the tools to write their own Python programs and to understand fundamental concepts in computational biology and bioinformatics. Ramirez T. et al. (2017) presented numerical methods for simulation and fitting of ordinary-differential-equation models of malignant tumors implemented in Python.

In 1999, Hahnfeldt et al. proposed a mathematical model for tumor growth as dictated by reciprocal communications between tumor and its associated vasculature, introducing the idea that a tumor is supported by a dynamic, rather than a static, carrying capacity.

Multiple studies have expanded and utilized the Hahnfeldt model to investigate how tumors react to different treatments, such as anti-angiogenic therapy. Utilizing mathematical tools such as Maple (2023) to solve and simulate the Hahnfeldt equation enables researchers to visually represent tumor growth in different settings, offering valuable insights for the development of more efficient treatment options. Researchers can utilize the Hahnfeldt equation to combine experimental data and make predictions about the potential response of tumors to novel medicines. This allows for the optimization of treatment programs that are specifically suited to individual patients.

The equation, formulated by Hahnfeldt and colleagues, considers the interaction between tumor growth and the circulatory system, providing valuable understanding of the elements that impact tumor advancement. The equation has been extensively utilized to model tumor growth under different circumstances, aiding researchers in investigating prospective treatment strategies.

This research explores the proliferation of cancerous tumors using the Hahnfeldt equation, utilizing the Maple software for mathematical analysis and simulations. Maple, renowned for its robust symbolic computation capabilities, enables accurate and efficient investigation of the Hahnfeldt model. The objective of our study is to conduct a comprehensive analysis of the dynamics of tumor growth, utilizing the capabilities of Maple to get a more profound comprehension of the components that contribute to malignancy. Our inquiry seeks to make a valuable contribution to cancer research by providing novel perspectives on the mathematical modeling of tumor progression.

2 Preliminaries

The Hahnfeldt model defines the tumor volume V(t) and vascular carrying capacity K(t) using the following differential equations:

$$\frac{dV}{dt} = \lambda V \ln\left(\frac{K}{V}\right)$$

$$\frac{dK}{dt} = bV - dK^{\left(\frac{2}{3}\right)}$$

where:

λ: tumor growth rate, representing the intrinsic growth capability of the tumor,

b: stimulation rate of angiogenesis, which controls the tumor's ability to increase vascular support,

d: degradation rate of vasculature, indicating the rate at which the blood vessel network supporting the tumor breaks down.

These equations predict tumor growth based on vascular support limitations, enabling researchers to explore how therapies that impact K(t) (vascular capacity) might alter tumor progression.

2.1 Implementation in Maple

Maple was used for solving the Hahnfeldt equations, including defining parameters, solving the differential equations, and visualizing results.

The following parameters were used based on values from the literature $\lambda = 0.192$, $b = 0.1$, $d = 0.03$ with the initial conditions $V(0) = 1.0$, $K(0) = 2.0$.

Using these parameters, we simulated tumor growth over 100 days to examine how vascular capacity and tumor size evolve under normal angiogenesis. The Maple code for implementing the model as follows:

We define the parameters

```
> lambda := 0.192:     # Tumor growth rate constant
> b := 0.1:            # Angiogenesis stimulation parameter
> d := 0.03:           # Vascular degradation rate
```

with following initial conditions,

```
> V0 := 1.0:           # Initial tumor volume
> K0 := 2.0:           # Initial vascular capacity
```

define and solve the Hahnfeldt equation system

```
> Hahnfeldt := { diff(V(t),t) = lambda*V(t)*ln(K(t)/V(t)),
>               diff(K(t),t) = b*V(t) - d*K(t)^(2/3) }:
> initial_conditions := { V(0) = V0, K(0) = K0 }:
> sol := dsolve(Hahnfeldt union initial_conditions, {V(t), K(t)}, numeric):
```

and finally demonstrate tumor volume and vascular capacity:

```
> plots:-odeplot(sol, [[t, V(t)], [t, K(t)]], t=0..100,
>       legend=["Tumor Volume V(t)", "Carrying Capacity K(t)"],
>       title="Tumor Growth Model with Hahnfeldt Equations",
>       color=[red, blue],
>       thickness=2);
```

3 Results and Analysis

3.1 Tumor Growth Dynamics

The simulation results, shown in Figure 1, display the dynamics of tumor volume V(t) and vascular carrying capacity K(t) over time. Initially, tumor volume grows rapidly, but as K(t) reaches its threshold,

growth plateaus due to limited vascular support. This behavior matches expected biological patterns, with early exponential growth slowing as vascular resources become constrained.

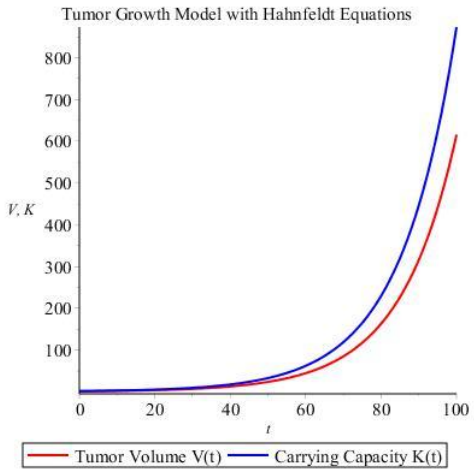
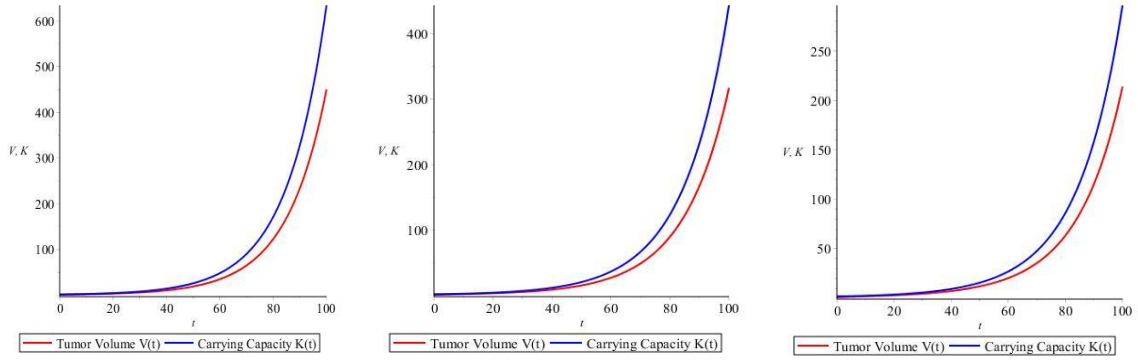


Figure 1: Tumor volume and vascular carrying capacity plotted over 100 days with baseline parameters.

3.2 Effects of Increased Vascular Degradation Rate (d)

We simulated anti-angiogenic therapy by increasing the vascular degradation rate d from 0.03 to 0.06. Figure 2 illustrates that the increased d value significantly decreases K(t), thereby restricting tumor growth and resulting in eventual regression. This outcome is consistent with the therapeutic objectives of anti-angiogenic agents, which diminish blood supply to limit tumor growth.



a) b) c)

Figure 2: Tumor volume and vascular capacity with increased degradation rates for *a)* d = 0.04, b) d = 0.05 and *c)* d = 0.06 respectively, simulating anti-angiogenic therapy effects.

3.3 Influence of Reduced Angiogenesis Stimulation Rate (b)

We also explored the effect of lowering the angiogenesis stimulation rate b from 0.1 to 0.05, reflecting the impact of limiting pro-angiogenic factors. Figure 3 shows that with a reduced b, the vascular capacity K(t) does not increase sufficiently to sustain the tumor, resulting in a slower growth rate and reduced final tumor size.

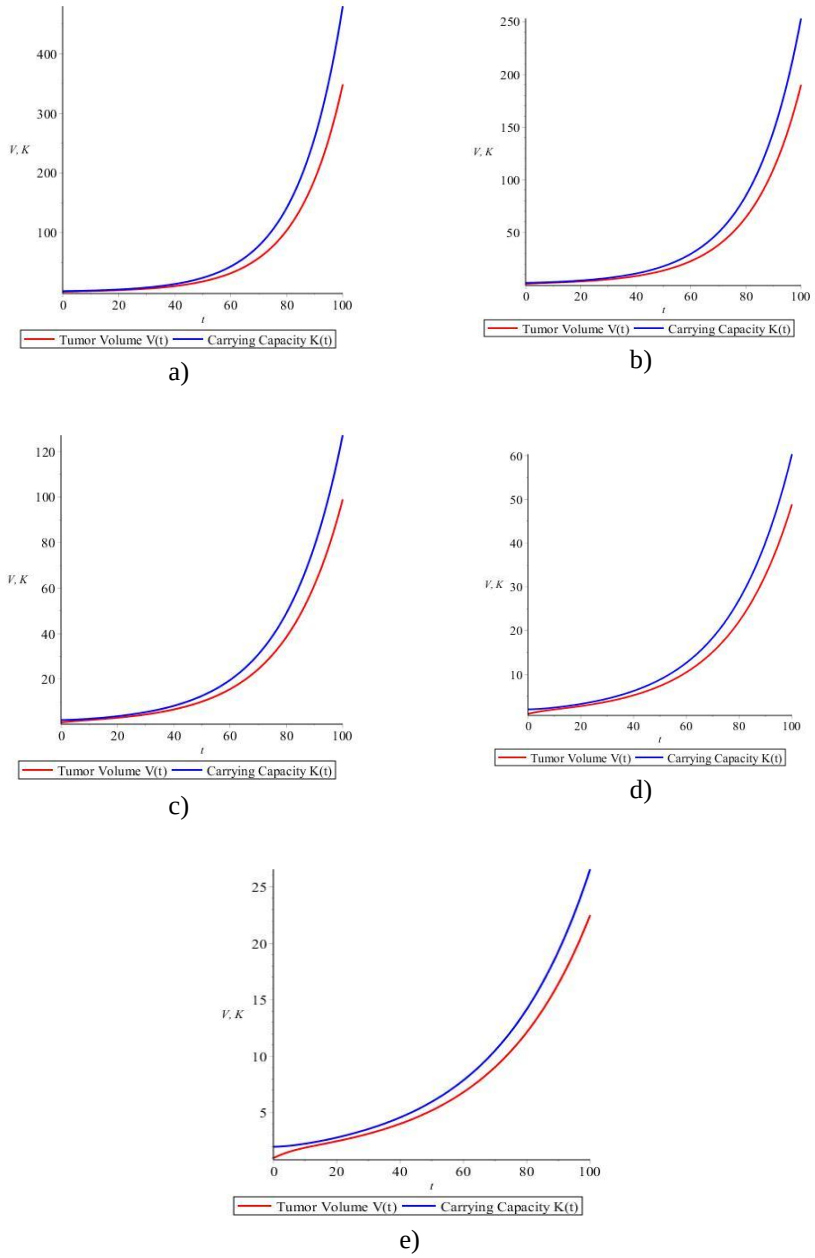


Figure 3: Tumor volume and vascular capacity with decreased angiogenesis stimulation rates a) b = 0.09, b) b = 0.08, c) b = 0.07, d) b = 0.06 and e) b = 0.05 respectively.

3.4 Sensitivity Analysis

The tumor growth rate λ determines the tumor's intrinsic proliferative capacity. Higher λ values lead to a faster initial growth rate of V(t), resulting in a steep increase in tumor size in the early stages. As the tumor grows more rapidly, the demand for vascular support increases, leading to a higher K(t). However, if λ is too high, vascular support K(t) may lag behind, eventually causing a constraint on growth as the tumor outpaces its blood supply.

In contrast, decreasing λ slows tumor growth, allowing vascular capacity to keep pace with tumor volume. This slower growth reduces the stress on angiogenic processes and may lead to a more sustainable balance between tumor size and vascular support.

The angiogenesis rate b controls how quickly the tumor can recruit new blood vessels to support its growth. Higher b values lead to an increase in K(t), providing the tumor with ample vascular support for expansion. Enhanced vascular support allows the tumor to grow more consistently without reaching a plateau prematurely. This sustained growth is critical for large tumors that rely on continuous vascularization.

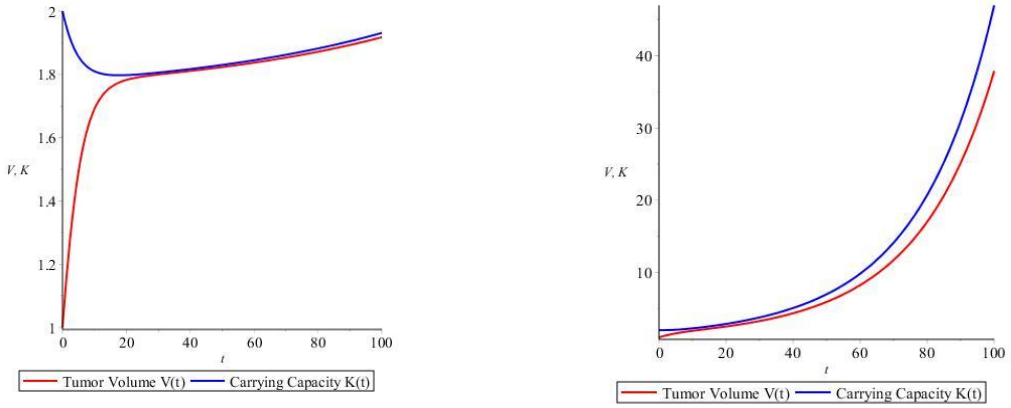
Conversely, reducing b limits the tumor's ability to increase K(t), leading to a reduction in tumor volume over time as the vascular network fails to keep up with demand. Low angiogenesis rates are thus beneficial in anti-angiogenic therapy, as they limit the tumor's growth potential by cutting off its blood supply.

The degradation rate d represents the breakdown of the vascular network that sustains the tumor. Higher d values accelerate vascular degradation, leading to a marked decrease in K(t), depriving the tumor of necessary resources as illustrated in Figure 4. As K(t) declines, tumor growth stagnates, and regression may occur due to insufficient blood supply. This is reflected in a reduction of V(t), showing the efficacy of increased d in limiting tumor expansion.

A lower d allows for more stable vascular capacity, resulting in gradual tumor growth, as K(t) can sustain the tumor volume. Modulating d is therefore an effective strategy for anti-angiogenic therapies aiming to induce vascular degradation.

3.5 Combined Effects and Interplay

If λ and b are high but d is low, the model predicts rapid tumor growth toward the carrying capacity K(t). High d with moderate λ and b may keep the tumor in check, stabilizing growth or leading to regression. The ratio b / d is crucial for angiogenesis versus degradation effects. When b > d, angiogenesis overpowers degradation, potentially allowing growth; when d > b, degradation becomes more significant, possibly resulting in a stable or declining tumor size.



a) b)

Figure 4: Sensitivity of tumor growth and vascular carrying capacity to different values of *a)* λ = 0.194, b = 0.05, *and* d = 0.06 *and b)* λ = 0.194, b = 0.07, *and* d = 0.05

Table 1 illustrates the effects of various combinations of λ, b, and d on tumor growth and vascular support, facilitating a comprehensive sensitivity analysis over a period of 100 days.

Table 1: *Various growth dynamics scenarios with all possible permutations with λ = [0.1, 0.15, 0.2], b = [0.05, 0.1, 0.15], and d = [0.01, 0.03, 0.05] range of values.*

λ	***b***	***d***	***Final Tumor Volume V (100)***	***Final Vascular Capacity K (100)***
0.1	0.05	0.01	**30**	**42**
0.1	0.05	0.03	**12.5**	**16.2**
0.1	0.05	0.05	**3.6**	**4.1**
0.1	0.1	0.01	**249**	**450**
0.1	0.1	0.03	**78**	**129**
0.1	0.1	0.05	**145**	**250**
0.1	0.15	0.01	**1150**	**2400**
0.1	0.15	0.03	**800**	**1610**
0.1	0.15	0.05	**510**	**1050**
0.15	0.05	0.01	**46**	**59**
0.15	0.05	0.03	**18**	**22**
0.15	0.05	0.05	**4.7**	**5.3**
0.15	0.1	0.01	**615**	**951**
0.15	0.1	0.03	**360**	**550**
0.15	0.1	0.05	**188**	**279**
0.15	0.15	0.01	**4500**	**8001**
0.15	0.15	0.03	**3050**	**4480**
0.15	0.15	0.05	**1999**	**2495**
0.2	0.05	0.01	**61**	**74**
0.2	0.05	0.03	**23**	**27**
0.2	0.05	0.05	**5.6**	**6.2**
0.2	0.1	0.01	**1175**	**1615**
0.2	0.1	0.03	**661**	**944**
0.2	0.1	0.05	**346**	**477**
0.2	0.15	0.01	**11770**	**18315**
0.2	0.15	0.03	**7960**	**10930**
0.2	0.15	0.05	**5130**	**8190**

By adjusting λ, b, and d, researchers can simulate different tumor growth scenarios, analyze treatment impacts, and optimize approaches that may inhibit growth.

4 Discussion and Conclusions

The Hahnfeldt equation model utilized in Maple offers insights into the tumor-vascular dynamics that regulate malignant progression.

The model forecasts an initial rapid expansion of the tumor, followed by a deceleration in growth as vascular capacity approaches its limit, indicating biological constraints imposed by angiogenesis. Increasing d or reducing b mimics the effects of anti-angiogenic therapies, demonstrating that regulating vascular degradation can restrict tumor growth. The model demonstrates that tumor response is significantly influenced by variations in d and b, which are essential for vascular support. Modifying these parameters may be essential for the advancement of targeted cancer therapies.

In this paper, we explored the growth dynamics of malignant tumors using the Hahnfeldt equation, supported by computational analysis in Maple. The Hahnfeldt model provided a robust framework for understanding the complex interactions between tumor cells and their vascular environment, particularly in relation to angiogenesis and its influence on tumor growth.

By leveraging Maple's powerful symbolic and numerical computation capabilities, we were able to simulate various scenarios and examine the effects of different parameters on tumor development. This approach not only allowed us to validate the theoretical aspects of the Hahnfeldt equation but also facilitated a deeper understanding of how these dynamics can be manipulated for therapeutic purposes.

The findings underscore the importance of mathematical modeling in cancer research, particularly in optimizing treatment strategies and predicting outcomes. The use of Maple in this context proved to be invaluable, offering precise and efficient tools for both analysis and visualization.

Overall, this investigation highlights the potential of combining mathematical models with computational tools to advance our understanding of tumor growth, ultimately contributing to more effective and personalized cancer treatment approaches. Further research could expand on this work by integrating more complex biological factors and exploring the model's application in different types of cancers.

5 Declarations

5.1 Study Limitations

The author(s) declared none of the limitations faced in this study that might significantly affect the research outcome.

5.2 Acknowledgements

The author(s) present his/their thanks to the anonymous reviewers for constructive suggestions, which improve the quality of the paper.

5.3 Funding source

The author(s) declared no funding source.

5.4 Competing Interests

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

6 Human and Animal Related Study

For this type of study, formal consent is not required.

6.1 Ethical Approval

Since this study involved a desk review, the author(s) assert that all procedures contributing to this study comply with the ethical standards of the relevant institutional committees. For this type of study, formal consent is not required.

6.2 Informed Consent

Informed consent was obtained from all individual participants included in the study.

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