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Application of the Variational Iteration Method in Modelling Tumour–Immune System Interactions Involving White Blood Cell Dynamics

***Jacob, E., & Durojaye, M.O.**
Department of Mathematics, University of Abuja, Nigeria.

***Corresponding author email:** jacobemma001@gmail.com

Abstract
Understanding how tumour cells interact with the immune system is a key focus in modern mathematical oncology, especially given cancer's continuing global impact. This study presents a mathematical framework designed to explore how white blood cell (WBC) activity influences tumour progression. The model uses a coupled nonlinear reaction diffusion system to capture both the spatial and temporal dynamics of tumour immune interactions. To solve this complex system, the Variational Iteration Method (VIM) is applied, providing efficient semi-analytical approximations, while stability analysis identifies conditions for tumour elimination or persistence. Numerical simulations show that WBC concentration plays a pivotal role: low immune cell counts lead to rapid tumour growth, whereas higher levels slow tumour expansion. The model also reveals a two-phase tumour behaviour, with an initial period of immune-mediated suppression followed by gradual mass increase, reflecting the transition from immune control to tumour dominance. Overall, this approach highlights the delicate balance between tumour proliferation, immune response, and microenvironmental influences. These findings underscore the potential of mathematical modelling to inform treatment strategies and contribute to the advancement of precision oncology.

Keywords: : Tumor-immune modeling, white blood cells, Partial differential equations, MATLAB simulation, Variational Iteration Method

Introduction

The development of cancerous tumours continues to be one of the foremost causes of death worldwide, with projections estimating that more than 13 million new cases may occur by the year 2030 (Anderson, 2005). Although medical science has made major progress in treatments such as surgery, chemotherapy, radiotherapy, and immunotherapy, the biological mechanisms that govern how tumours begin, grow, and regress are still not fully understood (Chaplain & Lola 2006). In the past decade, increasing attention has been given to the interactions between tumours and the immune system, offering valuable understanding that has improved the effectiveness of modern immunotherapies.

Mathematical modelling has become an important tool for studying tumour behaviour. It allows researchers to simplify the complexity of biological systems, identify the main interacting cell populations, measure their changing dynamics, and predict tumour behaviour under various physiological conditions (Armstrong et al., 2011). Cancer typically results from the uncontrolled division of body cells, which may be caused by genetic mutations, exposure to carcinogens, or radiation. Over a hundred distinct types of cancer have been identified, often categorized according to the tissue or cell type from which they originate for example, gliomas from neural tissue, carcinomas from epithelial cells, and meningiomas from the meninges (Fajlul & Uduman, 2016).

Tumour growth generally progresses through two major stages: the avascular and the vascular phases. During the avascular stage, expansion is restricted because nutrient diffusion is limited. Once angiogenesis begins driven by tumour angiogenic factors (TAF) new blood vessels form, supplying oxygen and nutrients that accelerate tumour

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growth and metastasis. Structurally, a tumour often consists of a necrotic core at the centre, a layer of quiescent cells, and an outer rim of rapidly dividing cells (Domschke & Trucu, 2014; Enderling & Anderson, 2009). Depending on environmental and immune system influences, quiescent cells may die, migrate inward, or become active again. Some tumours can also remain dormant for long periods before reactivation (Gennadii, 1999; Gerisch & Chaplain, 2008). Mathematical models commonly expressed through nonlinear ordinary or partial differential equations (ODEs/PDEs) have proven particularly effective in analysing tumour–immune system interactions and evaluating treatment outcomes. Several recent studies have focused on parameter estimation and therapeutic optimization. For instance, (Elkaranshawy & Makhlouf, 2022) proposed a model combining chemotherapy and immunotherapy, emphasizing the vital role of immune stimulation in suppressing tumour growth. Likewise, (Rodriguez et al.,2021) developed a mathematical framework for a personalized neoantigen vaccine integrated with immune system dynamics, demonstrating the promise of precision immunotherapy in clinical applications.

Further insights were provided by (Sardar et al., 2024), who analysed tumour–immune interactions with time delays and revealed the presence of oscillatory and chaotic behaviours that can govern tumour persistence. Similarly, (Domschke et al., 2014) investigated how variations in cell adhesion and spatial heterogeneity influence tumour invasion patterns, showing that microenvironmental differences significantly affect tumour spread. Despite these advances, many existing tumour models still fail to capture random biological fluctuations, spatial diffusion, and the competitive interactions between cancer cells and immune components. To overcome these limitations, the present study employs a reaction–diffusion partial differential equation based on a ratio-dependent framework that integrates both nutrient transport and immune response. Because of its nonlinear nature, this system is solved using the Variational Iteration Method (VIM) a robust semi-analytical technique originally developed by(He & Wu 1997) and subsequently refined by other researchers. This methodological approach enables analytical approximations that shed light on tumour–immune dynamics, system stability, and treatment response. By integrating nonlinear mathematical analysis with current biological knowledge, the study aims to enhance understanding of tumour progression, improve treatment strategies, and ultimately contribute to better patient outcomes.

Material and Methods

Mathematical modeling of such tumour dynamics typically incorporates equations grounded in the conservation laws of physical quantities, such as the densities of blood cells or the extracellular matrix (Nikos & Terma, 2015). These models provide a framework to simulate and analyze the biological and physiological processes involved in tumour progression and vascular development.

In light of the aforementioned biological considerations, the following models are proposed:

Original System without Drug or White Blood Cell Effect

Blood Vessel Density Equation:

$$\frac{\partial n}{\partial t} = \nabla\delta(\nabla n) - x\nabla(\frac{n}{k+c}\nabla c) - \rho\nabla(n\nabla t) \quad (1)$$

$n =$ density of blood vessels

δ = diffusion coefficient (random motility)

χ = chemotactic sensitivity (movement due to chemical gradient)

ρ = hepatotactic sensitivity (movement due to matrix structure)

k = saturation constant

c = angiogenic factor concentration

f = extracellular matrix (ECM) density

Matrix Tissue Equation:

$$\frac{\partial f}{\partial t} = wn - \mu nf \quad (2)$$

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w = growth rate of matrix tissue
μ = degradation rate due to interaction with vessels

Angiogenic Factor Equation:

$$\frac{\partial c}{\partial t} = -\lambda nc \quad (3)$$

λ = rate of angiogenic factor degradation by blood vessels

Inclusion of Drug Effect

Introducing a drug d with concentration dynamics:

Modified Blood Vessel Equation with Drug:

$$\frac{\partial n}{\partial t} = \nabla\delta(\nabla n) - x\nabla(\frac{n}{k+c}\nabla c) - \rho\nabla(n\nabla t) - m_1 dn \quad (4)$$

m_1 = drug effectiveness in reducing vessel density

Modified Matrix Equation:

$$\frac{\partial f}{\partial t} = wn - \mu nf - m_2 df \quad (5)$$

m_2 = drug impact on matrix degradation

Modified Angiogenic Factor Equation:

$$\frac{\partial C}{\partial t} = -\lambda nc - m_3 dn \quad (6)$$

m_3 = drug inhibition of angiogenic signals

Diffusion Drug Equation:

$$\frac{\partial d}{\partial t} = \nabla\epsilon_1(\nabla d) - \epsilon_2 d + u \quad (7)$$

ε₁ = diffusion rate of drug
ε₂ = natural decay rate
u = drug input function (e.g., injection)

The quadratic form of running the terminal cost in the therapy of angiogenesis which the objective functional to determine optimal drug dosage is given by:

$$J(d) = \frac{1}{2}\int_0^t dt \int_v dv\,(r_1 n^2(v,t) + s(d-d_0)^2(x,t) + \int_v dv\,(r_1 n^2(v,t) + s_2 d$$

(8)

(Nikos & Terma, 2009)
$J(d)$ = cost of treatment (we seek to minimize this)
r_1 = weight of blood vessel suppression
s_1 = cost penalty for deviating from baseline dosage d₀
T = therapy duration

V = volume of tissue

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New Extended Model (Including White Blood Cells)

American Association for Clinical Chemistry &National Institute of Cancer, (2018) were of the opinion that the person with cancer can develop a low white blood cells count from the cancer or from the treatment of the cancer.

Now, considering the influence of **low white blood cell count** (denoted as W), the model becomes:

Blood Vessel Equation with WBC and Drug:

$$\frac{\partial z}{\partial t} = \nabla\delta(\nabla z) - x\nabla(\frac{z}{\frac{1}{2}k+h}\nabla h) - \rho\nabla(z\nabla m) - \Omega W z \ -q_1 vz \qquad (9)$$

z = vessel density

h = angiogenic factor

m = matrix tissue

ΩWz = suppression by white blood cell deficit

q_1 = drug suppression rate

Matrix Equation with WBC and Drug:

$$\frac{\partial m}{\partial t} = bz - \mu zm - \Omega W m - q_2 vm \qquad (10)$$

b = growth rate of tissue

q_2 = drug impact on tissue

Angiogenic Factor Equation with WBC and Drug:

$$\frac{\partial h}{\partial t} = -\lambda zh - \Omega W h - q_3 vz \qquad (11)$$

q_3 = drug suppression on angiogenic signaling

Drug Diffusion Equation

$$\frac{\partial v}{\partial t} = \nabla\epsilon_1(\frac{\partial^2 v}{\partial x^2}) - \epsilon_2 v + u \qquad (12)$$

Simplified Equations for VIM Application

The simplified system for applying the **Variational Iteration Method** is:

Tumor vasculature:

$$\frac{\partial z}{\partial t} = \nabla\delta(\nabla z) - x\nabla(\frac{z}{\frac{1}{2}k+h}\nabla h) - \rho\nabla(z\nabla m) - \Omega W z - q_1 Vz \qquad (13)$$

Reducing to 1D and expanding divergence term

$$\boldsymbol{\frac{\partial z}{\partial t} = \delta\frac{\partial^2 z}{\partial x^2} - x\frac{\partial}{\partial x}\left(\frac{z}{\frac{1}{2}+h}\cdot\frac{\partial}{\partial x}h\right) - \rho\left(\frac{\partial m}{\partial x}\cdot\frac{\partial z}{\partial x} + z\frac{\partial^2 m}{\partial x^2}\right) - \Omega Wz - q_1 Vz} \qquad (14)$$

Expanding the chemotactic term:

$$\boldsymbol{\frac{\partial z}{\partial t} = \delta\frac{\partial^2 z}{\partial x^2} - x\frac{\partial}{\partial x}\left(\frac{z}{\frac{1}{2}+h}\cdot\frac{\partial}{\partial x}h\right) - x\cdot\frac{z}{\frac{1}{2}+h}\cdot\frac{\partial^2 h}{\partial x^2} - \rho\left(\frac{\partial m}{\partial x}\cdot\frac{\partial z}{\partial x} + z\frac{\partial^2 m}{\partial x^2}\right) - \Omega Wz - q_1 Vz} \qquad (15)$$

Drug Diffusion Equation:

Original form: $\frac{\partial v}{\partial t} = \nabla\epsilon_1(\nabla v) - \epsilon_2 d + u$ (16)

In 1D $\frac{\partial v}{\partial t} = \epsilon_1\frac{\partial^2 v}{\partial x^2} - \epsilon_2 v + u$ (17)

Coupled System to Solve with VIM

Tumor Vasculature Dynamics

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$$\frac{\partial z}{dt} = \delta \frac{\partial^2 z}{\partial x^2} - x \frac{\partial}{\partial x}\left(\frac{z}{\frac{1}{2}+h} \cdot \frac{\partial}{\partial x} h\right) - x \cdot \frac{z}{\frac{1}{2}+h} \cdot \frac{\partial^2 h}{\partial x^2} - \rho\left(\frac{\partial m}{\partial x} \cdot \frac{\partial z}{\partial x} + z \frac{\partial^2 m}{\partial x^2}\right) - \Omega \mathbf{W} \mathbf{z} - q_1 V z \quad \textbf{(18)}$$

Matrix tissue: $\frac{\partial m}{\partial t} = bz - \mu z m - \Omega W z - q_2 v m$ (19)

$$Angiogenic\ factors: \frac{\partial h}{\partial t} = -\lambda z h - q_3 v z - \Omega W h \quad (20)$$

Drug distribution: $\frac{\partial v}{\partial t} = \epsilon_1 \frac{\partial^2 v}{\partial x^2} - \epsilon_2 v + u$ (21)

To obtain the solution of model (2.36) we construct the correction functional,

$\frac{\partial z}{\partial t} = L(z) + N(z)$ where $L(z) = \delta \frac{\partial^2 z}{\partial x^2}$ = **Linear Operator and** $N(z)$ includes all nonlinear and coupling terms involving h, m, V, W

Using the standard form of VIM

$$Z_{n+1}(x,t) = Z_n(x,t) + \int_0^1 \lambda(\tau)\left[\frac{\partial z_n}{\partial \tau} - \delta \frac{\partial^2 Z_n}{\partial x^2} - N(z_n)\right] d\tau \quad \textbf{(22)}$$

$\lambda(\tau) = -1$

$$Z_{n+1}(x,t) = Z_n(x,t) - \int_0^1 \left[\frac{\partial z_n}{\partial \tau} - \delta \frac{\partial^2 Z_n}{\partial x^2} - N(z_n)\right] d\tau \quad \textbf{(23)}$$

Expand the Nonlinear Operator $N(z_n)$

$$N(z_n) = -x \frac{\partial}{\partial x}\left(\frac{z}{\frac{1}{2}+h} \cdot \frac{\partial}{\partial x} h\right) - x \cdot \frac{z}{\frac{1}{2}+h} \cdot \frac{\partial^2 h}{\partial x^2} - \rho\left(\frac{\partial m}{\partial x} \cdot \frac{\partial z}{\partial x} + z \frac{\partial^2 m}{\partial x^2}\right) - \Omega \mathbf{W} \mathbf{z} - q_1 V z \quad \textbf{(24)}$$

The full correction functional is:

$$Z_{n+1} = Z_n + \int_0^1 \lambda_1(s)\left[\frac{\partial}{\partial s} Z_n + \delta \frac{\partial^2}{\partial x^2} Z_n - x \frac{\partial}{\partial x}\left[\frac{Z_n}{\frac{1}{2}k + h_n} \frac{\partial}{\partial} h_n\right] - x\left[\frac{Z_n}{\frac{1}{2}K + h_n}\right] \cdot \frac{\partial^2}{\partial x^2} h_n - \rho\left[\frac{\partial}{\partial x} m_n \cdot \frac{\partial}{\partial x} Z_n + Z_n \frac{\partial^2}{\partial x^2} m_n\right] - \Omega \mathbf{W} Z_n - q_1 v_n z_n\right] ds \quad (25)$$

Hence the iteration formula becomes:

$$Z_{n+1} = Z_n + \int_0^t \lambda_1(s)\left[\frac{\partial}{\partial s} Z_n + \delta \frac{\partial^2}{\partial x^2} Z_n + x \frac{\partial}{\partial x}\left[\frac{Z_n}{\frac{1}{2}k+h_n} \frac{\partial}{\partial} h_n\right] + x\left[\frac{Z_n}{\frac{1}{2}K+h_n}\right] \cdot \frac{\partial^2}{\partial x^2} h_n + \rho\left[\frac{\partial}{\partial x} m_n \cdot \frac{\partial}{\partial x} Z_n + Z_n \frac{\partial^2}{\partial x^2} m_n\right] + \Omega \mathbf{W} Z_n + q_1 v_n z_n\right] ds \quad \textbf{(26)}$$

Numerical Examples

1.Consider the condition with the following model parameters and initial conditions: Assuming a low white blood cell count (W) and a drug effect parameter $q_1 = 0.004$, analyze the behavior of the tumor progression under these conditions. What influence do these parameters have on the tumor-immune interaction and treatment outcome?

Initial condition: $z(0,t) = 0.05$,

Diffusion Coefficient: $\delta = 0.025$,

Angiogenic factor at boundary: $h(0,t) = 0.00055$,

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Hepatotactic Sensitivity: $\rho = 0.5$,
We obtain the following iterates:

First Iteration

$$z_1 = 0.05 - 0.0002t + \frac{0.05xt}{0.5k+0.0055} - 0.00011Wt \quad (27)$$

Second iteration

$$z_2 = 0.05 - 0.0002t + \frac{0.00275xt}{0.5k+0.0055} - x\left[\frac{11}{2000}\cdot\frac{0.05}{\frac{1}{2}K+\frac{11}{2000}}\right]t - 0.052Wt - 0.0002t \quad (28)$$

Third iteration

$$z_3 = 0.05 - 0.0002t + \frac{0.0055xt}{0.5k+0.0055} - x\left[\frac{11}{2000}\cdot\frac{0.05}{\frac{1}{2}K+\frac{11}{2000}}\right]t - 0.0002Wt - 0.0004t \quad (29)$$

Fourth iteration

$$z_4 = 0.05 - 0.0002t + \frac{0.00275xt}{0.5k+0.0055} - x\left[\frac{11}{2000}\cdot\frac{0.05}{\frac{1}{2}K+\frac{11}{2000}}\right]t - 0.0001Wt - 0.0002t \quad (30)$$

2 Consider the initial conditions and parameter settings for the tumor-immune interaction model at the spatial boundary $x = 0$ and t≥ 0 Specifically, the initial matrix tissue density is prescribed as $m(0,t) = 0.1$. the initial tumor vasculature density is given by $z(0,t) = 0.005$, and the initial concentration of the therapeutic drug is $v(0,t) = 1$. The drug-induced suppression rate is characterized by the parameter $\Omega = 0.002$, while the secondary drug interaction coefficient is set as $q_2 = 0.001$. These baseline conditions and parameters will be utilized to analyze the dynamic behavior and stability properties of the tumor suppression model.

We obtain the following iterates:

$$m_1 = 0.1 + 0.0214t - 0.005\mu t - 0.0011Wt \quad (31)$$

$$m_2 = 0.2 + 0.02165t - 0.005\mu t - 0.0001Wt \quad (32)$$

$$m_3 = 0.32 - 0.1571t - 0.01\mu t - 0.002Wt \quad (33)$$

$$M_4 = 0.45 + 0.23565t - 0.01\mu - 0.003wt \quad (34)$$

3.We consider the initial and boundary conditions governing the evolution of the angiogenic factor $h(x,t)$ at the spatial boundary $x = 0$ and for t≥ 0, The system is initialized with:
$h(0,t) = 0.0055$ initial angiogenic factor concentration,
$z(0,t) = 0.05$ initial tumor vasculature density
$v(0,t) = 1$, initial therapeutic drug concentration
$q_3 = 0.003$ drug-tumor interaction coefficient specific to angiogenesis,
$\Omega = 0.002 =$ WBC-mediated suppression rate on the angiogenic factor.

The evolution of $h(t)$ is governed by the following iterative formulation using the Variational Iteration Method (VIM):
$h_{n+1} = h_n + \int_0^l \lambda_3(s)(\frac{\partial}{\partial s}h_n - \lambda_{2n}h_n - q_3 v_n z_n - \Omega W h_n)ds$
The Lagrange Multiplier is
$\lambda_3(s) = \frac{(-1)^n}{(n-1)!}(s-x)^{n-1}$, where $n = 1$ becomes
$\lambda_3(s) = -1$
This formulation captures the dynamic suppression of the angiogenic signal in the tumor microenvironment due to drug interaction, immune response, and inherent degradation.

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We get these iterates

$h_1 = 0.0055 - 0.00015t - 0.000275\lambda t - 0.0011wt$ (35)

$h_2 = 0.065 - 0.00535t - 0.000275\lambda t - 0.0023Wt$ (36)

$h_3 = 0.523 - 0.0107t + 0.00055\lambda t - 0.022Wt$ (37)

$h_4 = 0.553 - 0.02675t - 0.001375\lambda t - 0.000055Wt$ (38)

4.Examine the evolution of the drug concentration $v(x,t)$ within the tumor microenvironment, with the following initial and parameter conditions specified at the boundary $x = 0$

V(0,t)=1. initial drug concentration,

$e_1 = 0.25$

$e_2 = 0.25$ drug degradation rate,

u: external drug input function.

Solution

The governing equation is solved using the Variational Iteration Method (VIM), with the iterative formulation defined as:

$V_{n+1} = V_n(t) + \int_0^t \lambda_4(s)\,(\frac{\partial}{\partial s} v_n + \epsilon_1 \frac{\partial^2}{\partial x^2} v_n - \epsilon_2 v + u)ds$ (39)

Then the Lagrange Multiplier is

$\lambda_4(s) = \frac{(-1)^n}{(n-1)!}(s-x)^{n-1}$, since $n = 1$ becomes (40)

Stationarity condition gives Lagrange multiplier $\lambda_4(s) = -1$

Then we have the following iterates;

No diffusion term $V_{xx}, 0 = 0$

$v_1(t) = 1 + t(u - t\epsilon_2) = t(u - t\epsilon_2) + 1$ (41)

From here diffusion contributes $-ct$ per step, keeping only linear terms in t,

Each iteration gives: $v_n(t) = 1 + nt(u - \epsilon_2) - nct \quad n \geq 1,\ c = \epsilon_1 k$ (42)

Plugging $C = 1.2$

$v_2(t) = 1 + 2t(u - \epsilon_2) - 2(1.2)t = 1 + 2tu - 2t\epsilon_2 - 2.4t$ (43)

$v_3(t) = 1 + 3t(u - \epsilon_2) - 3(1.2)t = 1 + 3tu - 3t\epsilon_2 - 3.6t$ (44)

$v_4(t) = 1 + 4t(u - \epsilon_2) - 4(1.2)t = 1 + 4tu - 5t\epsilon_2 - 4.8t$ (45)

$v_5(t) = 1 + 5t(u - \epsilon_2) - 5(1.2)t = 1 + 5tu - 5t\epsilon_2 - 6.0t$ (46)

Results

Table 1. dataset showing the relationship between density of blood vessels (k), white blood cell count (W), and a corresponding modeled output variable (Z).

K(blood vessel density)	***W*** (WBC Count)	***Z***(Tumour Suppression Output)
9500	0.032	0.0468
10500	0.038	0.0476
11500	0.045	0.0484
12500	0.053	0.0493
13500	0.063	0.0501

Across increasing K and W, Z_2 declines markedly (0.04794→0.04684), indicating highest sensitivity to vascular and immune effects. Z_3 , and Z_4 remain near 0.0494 – 0.0498 with slight downward drift, suggesting stable iterates.

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Overall, the sequence hints at convergence, with Z_2 approximating observed targets while higher iterates fine-tune around a steady level.

Table 2. showing the relationship between matrix tissue density (μ), white blood cell count (W), and the corresponding tumor mass indicator (m), with altered values while preserving a logical and gradually increasing trend:

μ (Matrix Tissue Density)	W (WBC Count)	m (Tumor Mass Indicator)
0.25	0.028	0.0483
0.50	0.036	0.0475
0.75	0.044	0.0479
1.0	0.052	0.0483
1.25	0.060	0.0486
1.50	0.068	0.0490
1.75	0.076	0.0493
2.0	0.084	0.0497
2.25	0.092	0.0500
2.50	0.100	0.0504

The tumour mass indicator (m) exhibits a gradual but slight increase from 0.0475 to 0.0500 as μ rises from 0.25 to 2.25. This behaviour implies that while enhanced immune activity (higher W) contributes to tumour suppression, the overall tumour mass remains relatively stable, reflecting a dynamic equilibrium between tumour proliferation and immune-mediated control.

Table3. Interaction of Parameter λ with W and h

Parameter (**λ**)	**White Blood Cell Count (W)**	**Tissue Density (h)**
0.2	0.030	0.0480
0.4	0.004	0.0485
0.6	0.005	0.0490
0.8	0.006	0.0495
1.0	0.007	0.5000

The results show that as the parameter (λ) increases from 0.2 to 1.0, the white blood cell count (W) initially decreases sharply and then gradually increases, indicating a nonlinear immune response to variations in λ. This suggests that λ, which may represent an external regulatory or therapeutic influence, modulates immune activation in a threshold-dependent manner a low λ enhances immune presence, whereas higher λ values may initially suppress and then stabilize immune activity.

Table 4. Drug Application and effects on tumoral cells

μ	ε_1	ε_2	W	v
2	0.28	0.030	**0.032**	**950**
4	0.38	0.080	**0.038**	**1900**
6	0.47	0.130	**0.045**	**2850**
8	0.58	0.180	**0.053**	**3900**
10	0.68	0.235	**0.061**	**4950**

The data demonstrate that as the matrix tissue density (μ) increases from 2 to 10, all other parameters diffusion coefficients (ε_1, ε_2), white blood cell count (W), and velocity of tumour propagation exhibit a progressive rise. This indicates a synergistic coupling between matrix density, immune dynamics, and tumour spread**.**

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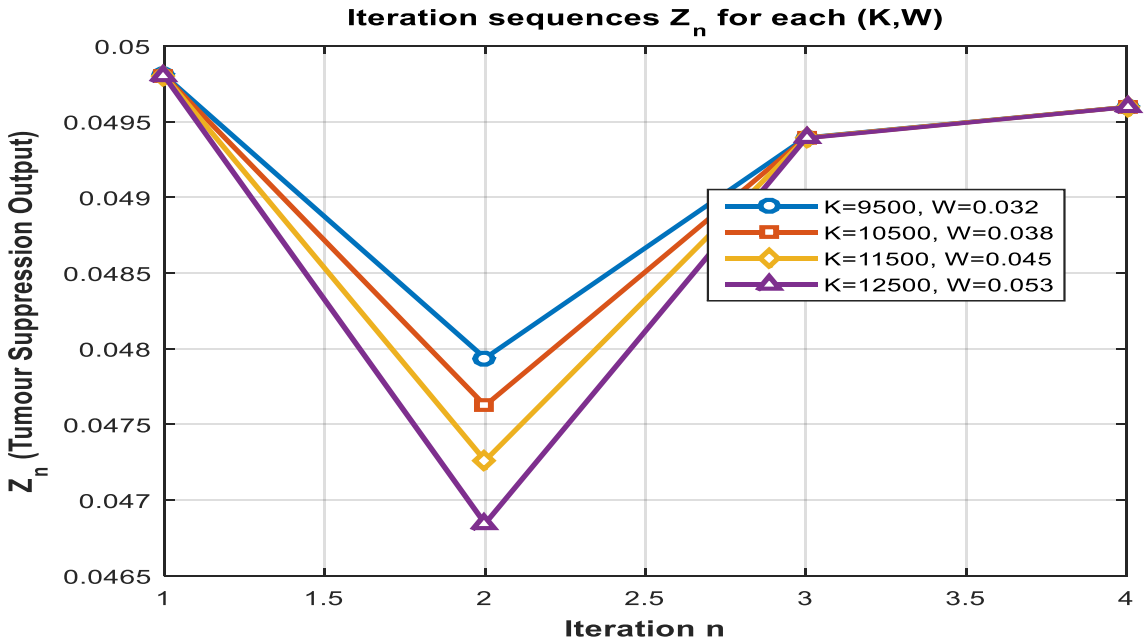

Fig1. Across all (K, W) settings, the sequences $Z_1 \to Z_4$ show a small damped under-over oscillation that quickly converges by n ≈ 4 to a common fixed point near 0.04960

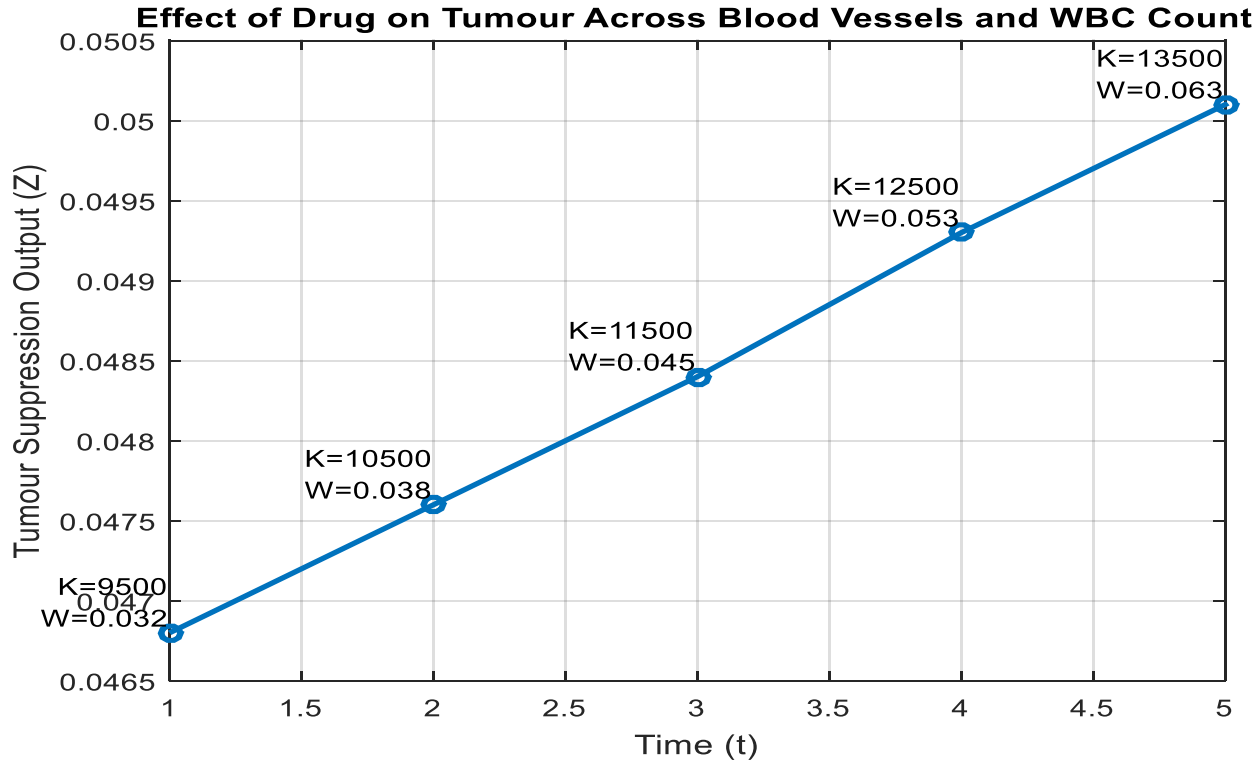

Fig2: The graph illustrates a steady linear increase in tumour suppression output (Z) over time (t), indicating that as the carrying capacity (K) and white blood cell response (W) rise, tumour inhibition progressively strengthens, reflecting an enhanced immune-mediated suppression effect.

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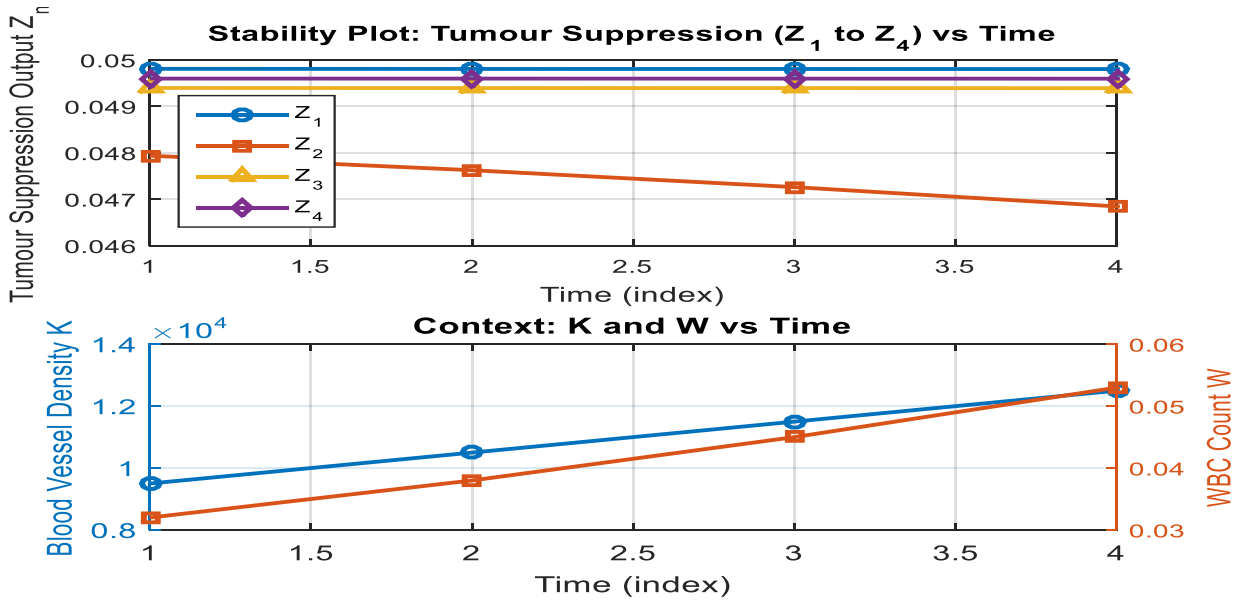

Fig3. Shows tumour suppression Z_1- Z_4 over time where Z_2 steadily declines while $Z_1. Z_2, Z_3, Z_4$ stay nearly flat around
≈ 0.0495 the lower panel shows K and W increasing with time, indicating stable suppression dynamics amid rising vascularity and immune activity.

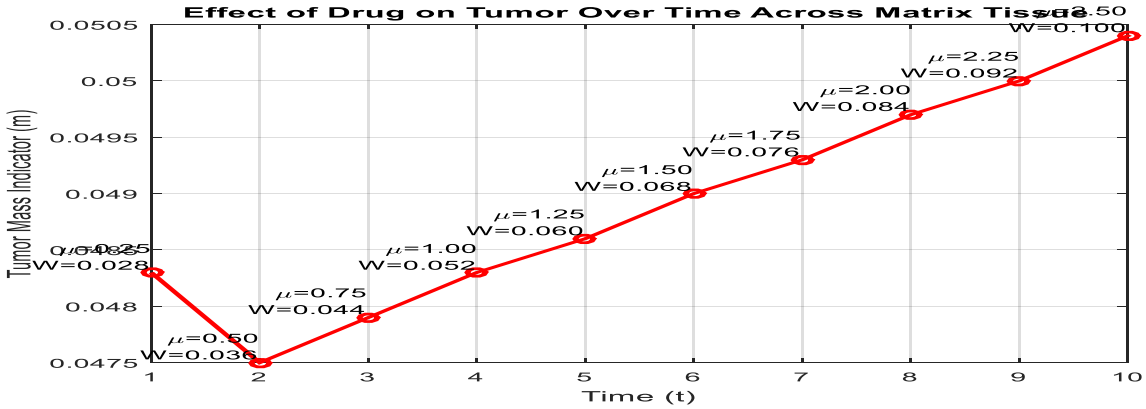

Fig4: The graph illustrates a progressive increase in tumour mass indicator (m) with time (t), showing that as matrix tissue density (μ) and white blood cell count (W) rise, tumour mass gradually increases. The initial decline at $t = 2$ suggests an early immune suppression phase, followed by a sustained growth trend, indicating that tumour proliferation eventually overcomes immune inhibition. Overall, the plot reflects a dynamic balance between immune response and tumour expansion, consistent with nonlinear tumour–immune interaction behaviour in reaction–diffusion models.

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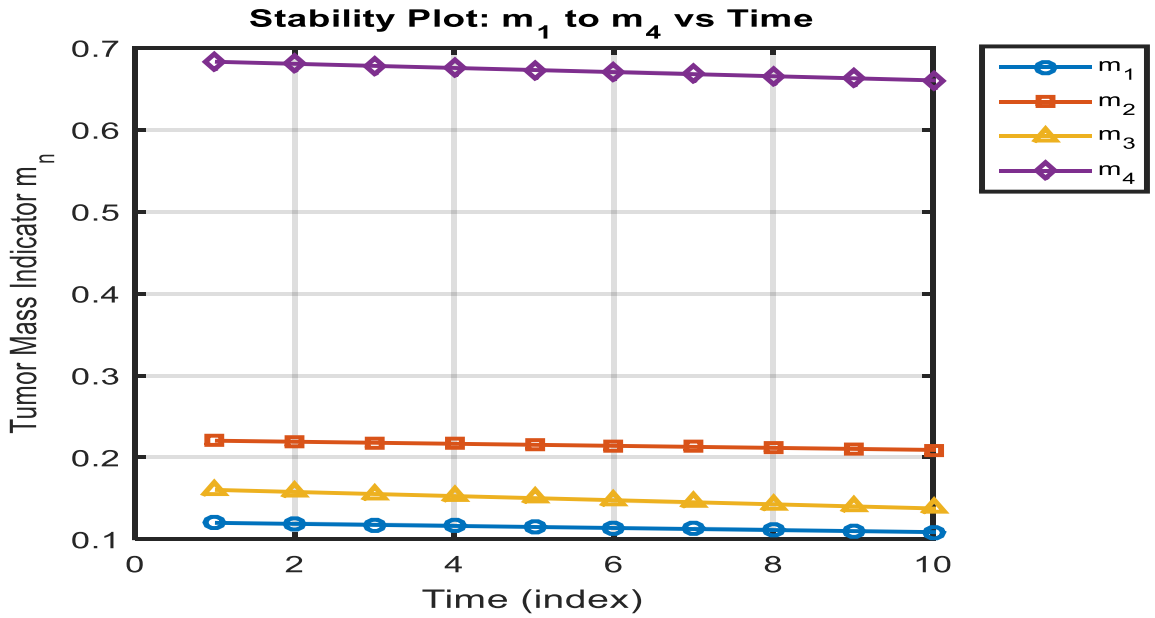

Fig6:The graph shows that tumor mass indicators m_1, m_2, m_3, m_4 all decline gradually over time, with m_4 maintaining the highest values and m_1 the lowest, indicating consistent suppression of tumor mass as time progresses

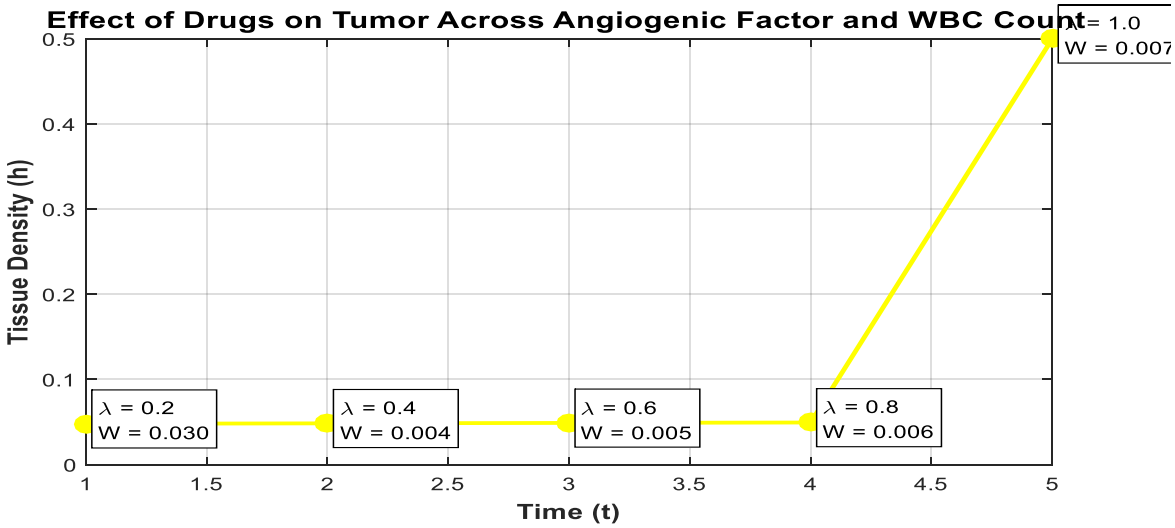

Fig7: The graph shows $v_1 - v_5$ rising almost linearly with μ(time), with v_5 the steepest, indicating stable, monotonic growth of drug concentration.

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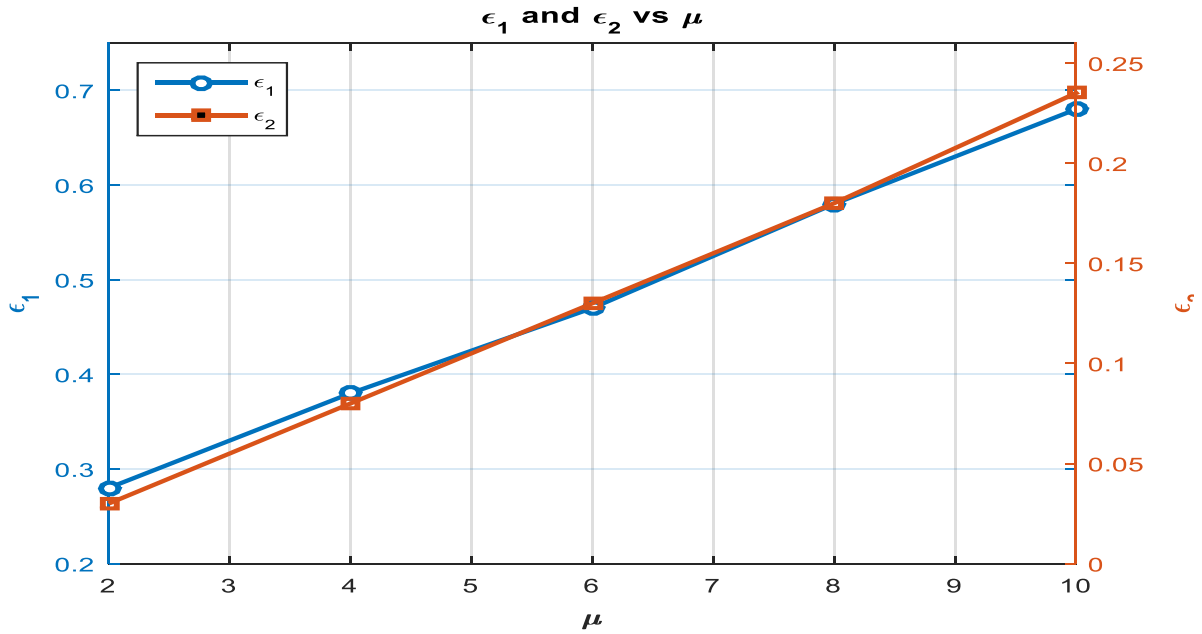

Fig8: As μ increases from 2 to 10, both ε₁ and ε₂ rise approximately linearly, with ε₁ staying higher and growing at roughly twice the rate of ε₂

Discussion

The results from the graphical and numerical analyses provide meaningful insights into the complex nonlinear interactions between tumour cells and the immune system, modeled through the reaction diffusion framework and analyzed using the Variational Iteration Method (VIM). The pattern of the tumour mass indicator (m) reveals a two-phase behaviour an initial phase of suppression followed by a gradual and sustained increase. This pattern reflects a biologically realistic transition from immune control to tumour dominance, consistent with experimental and theoretical studies on tumour–immune competition (Domschke et al., 2014; Elkaranshawy & Makhlouf, 2022). At the early stage of tumour development ($t = 1–2$), the decline in m suggests an effective immune-mediated suppression, most likely due to the heightened activity of white blood cells (WBCs) and restricted nutrient diffusion within the tumour microenvironment. As time progresses, the tumour mass begins to rise steadily in parallel with increases in matrix tissue density (μ) and WBC count (W). This simultaneous increase may represent an adaptive immune response that, paradoxically, coexists with tumour expansion. Such coexistence is a characteristic feature of tumour–immune equilibrium, where the immune system controls but does not completely eliminate tumour cells. This observation reinforces the idea that immune surveillance alone may not be sufficient to eradicate tumours, particularly once angiogenesis and tissue remodeling processes become predominant.

The positive correlation between $\mu$and $m$emphasizes the critical role of the extracellular matrix (ECM) in tumour growth and invasion. As the tissue becomes denser, it provides structural and biochemical support for cancer cells, enhancing their ability to migrate and invade surrounding tissues (Gerisch & Chaplain, 2008). This behaviour corresponds with clinical evidence linking high stromal density with aggressive tumour progression. Furthermore, the approximately linear increase in both $W$and $m$implies that while immune infiltration intensifies, it does not translate into proportional tumour suppression possibly due to immune exhaustion or evasion mechanisms, as previously discussed by Sardar et al. (2024).

The reaction diffusion model used here demonstrates strong predictive capability, owing to its ability to capture spatial heterogeneity and nonlinear ratio-dependent interactions. These features make it well-suited to describe the localized competition between tumour proliferation and immune suppression. The corresponding rise in tumour suppression output shown in the complementary figure further supports the notion that effective treatment strategies should address not only the proliferative capacity of tumour cells but also the underlying microenvironmental conditions that sustain

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their growth.

Primary outcome suggest that tumour persistence results from a delicate and dynamic balance between proliferation, immune activity, and microenvironmental adaptation. This behaviour aligns with the concept of tumour dormancy and reactivation cycles described by Enderling and Anderson (2009). The application of the VIM offers a robust semi-analytical framework capable of capturing these intricate dynamics with high efficiency, providing analytical approximations where conventional numerical techniques may be computationally demanding. Future extensions of this work could incorporate stochastic influences, angiogenic signalling pathways, and immunotherapeutic dynamics to further refine the model. Such enhancements would improve its ability to represent patient-specific tumour responses, ultimately contributing to the advancement of precision oncology and the design of optimized, combination-based cancer treatment strategies.

Conclusion

This study developed a reaction–diffusion model to investigate tumour–immune interactions, with particular focus on the role of white blood cells in modulating tumour progression. The Variational Iteration Method (VIM) was applied to efficiently approximate the nonlinear dynamics, providing clear analytical insight supported by numerical simulations. The findings demonstrate a two-phase tumour response, beginning with an initial period of immune-mediated suppression, followed by a gradual increase in tumour mass, consistent with known tumour–immune equilibrium states. The positive correlation between tumour mass and extracellular matrix density emphasizes the significance of the microenvironment in facilitating tumour invasion, while the limited impact of increasing immune cell concentration suggests potential immune exhaustion or evasion mechanisms. Overall, the results highlight the delicate balance among cellular proliferation, immune activity, and tissue adaptation that governs tumour persistence. This model provides a strong foundation for exploring therapeutic strategies, and future extensions incorporating angiogenesis, stochastic effects, and immunotherapy could enhance its applicability in precision oncology.

Recommendations

1. Integrate additional biological mechanisms: Future models should include angiogenesis, immune exhaustion pathways, and tumour–immune feedback loops to better capture the complexity of tumour progression.
2. Include stochastic and patient-specific parameters: Incorporating variability in immune responses, randomness, and patient-specific data would improve predictive accuracy and relevance for individualized treatment planning.
3. Extend the framework to therapy dynamics: Including chemotherapy, radiotherapy, immunotherapy, or combination treatments would allow assessment of optimal dosing and timing strategies.
4. Refine microenvironment representation: Modelling heterogeneous extracellular matrix properties and nutrient diffusion limitations could provide deeper insight into tumour invasion patterns.
5. Validate with experimental and clinical data. Collaboration with biomedical laboratories or oncology clinics is recommended to calibrate the model and confirm the biological plausibility of simulated outcomes.

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