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Tumour Chemotherapy by Continuous Infusion Drug Using Exponential Growth

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ABSTRACT

We present a theoretical framework combining exponential growth dynamics and Michaelis-Menten kinetics to model the interaction between tumor density and drug concentration delivered via an infusion pump. The model accounts for the saturation of tumor growth inhibition at high drug concentrations, reflecting biological saturation effects. Continuous infusion chemotherapy is highlighted as a superior delivery method, maintaining consistent drug levels at the tumor site while reducing systemic side effects compared to conventional bolus methods. The framework provides a predictive tool for determining the critical drug concentrations and tumor densities required for tumor elimination while minimizing adverse effects. Stability analysis, based on solving nonlinear equations, identifies equilibrium points that represent steady states of tumor density and drug concentration. The stability of these points is examined to assess the long-term effectiveness of chemotherapy regimens. Illustrative numerical simulations demonstrate how variations in drug delivery rates, tumor properties, and kinetic parameters influence therapeutic outcomes. Key factors such as the minimum drug concentration needed to suppress tumor growth and conditions for tumor eradication or regrowth are identified. Sensitivity analysis further reveals how parameter changes affect system stability and outcomes, offering insights for optimizing dosing strategies. This framework bridges theoretical modeling and practical challenges in cancer chemotherapy, providing a versatile tool for understanding and improving treatment strategies. It can be adapted to various tumor types and treatment modalities, supporting advancements in personalized medicine and future cancer therapy research.

Keywords: Chemotherapy, Exponential growth, Infusion drug delivery, Michaelis-Menten kinetics, Stability.

1. INTRODUCTION

Cancer remains a leading cause of mortality worldwide, with an estimated 19.3 million new cases diagnosed annually and 10 million cancer-related deaths **(Berger et al., 2022)**. The

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primary modalities for cancer treatment include surgery, radiation therapy, chemotherapy, and immunotherapy **(Baskar et al., 2012)**. Among these, chemotherapy remains a cornerstone due to its ability to target proliferating cancer cells. However, its efficacy is often limited by systemic toxicity, imprecise drug delivery, and the emergence of drug resistance **(Keefe and Bateman, 2012; Brenner et al., 1967)**. These challenges necessitate the development of advanced therapeutic strategies to optimize drug administration and improve patient outcomes. Chemotherapy involves the administration of pharmacological agents that disrupt the growth and replication of cancer cells. A wide variety of chemotherapeutic agents exist, each targeting specific stages of the cell cycle or molecular pathways involved in tumor progression **(Padmanabhan et al., 2021).** Despite their efficacy, the lack of precise drug delivery mechanisms often leads to systemic side effects and suboptimal therapeutic outcomes. To address these issues, infusion pumps have emerged as a promising technology for controlled and sustained drug delivery. Infusion pumps administer drugs in regulated doses, minimizing toxicity and improving drug targeting **(Mayla et al., 2024; Hassan and Al-Saedi, 2025)**. Several researchers have investigated the potential of infusion pumps in oncology. For instance, **(Jones, 1987; Dibrov et al., 1985)** explored their use for continuous drug delivery in experimental cancer models, highlighting their potential to maintain therapeutic drug levels. **(Blackshear et al., 1979; Aroesty et al., 1973).** Studied the efficacy of implantable pumps, demonstrating reduced complications compared to external devices. More recently, mathematical models have been employed to simulate and optimize chemotherapy delivery systems. **(Ledzewicz and Schättler, 2021).** Developed control strategies for chemotherapy scheduling, while **(Sharpe and Dobrovolny, 2021),** used mathematical models to analyze drug-tumor dynamics. **(Jawad et al., 2023; Anand et al., 2022).** Extended these models by incorporating patient-specific parameters to enhance treatment precision. Despite these advancements, several gaps remain in the literature. Most existing studies focus on the pharmacokinetics of chemotherapy without fully integrating the dynamics of drug delivery systems. Furthermore, few models account for the biological constraints imposed by drug transport kinetics and the interaction of chemotherapeutic agents with tumor cells. This research addresses these gaps by developing a mathematical model that combines Michaelis-Menten kinetics with drug-tumor interactions, specifically tailored for chemotherapy delivery via an implantable infusion pump. Michaelis-Menten kinetics, traditionally used to model enzymatic reactions, provides a robust framework to describe the rate-limiting behavior of drug absorption and metabolism, offering a more realistic representation of the system **(Liu and Yang, 2014).**

The governing problem in this study is to optimize the dosage and timing of chemotherapy to maximize tumor cell eradication while minimizing systemic toxicity. Using a system of coupled differential equations, we model the concentration of the chemotherapeutic drug (C) and the tumor cell population (w). The equations are derived based on fundamental principles of pharmacokinetics and tumor growth, incorporating parameters such as drug efficacy, tumor proliferation rates, and the saturation effects of drug delivery. Additionally, the infusion pump's design is modeled to ensure precise dosing, accounting for the benefits of implantable devices in reducing external complications, such as infection and inflammation.

2. FORMULATING THE MODEL

We begin with a schematic illustration of the application of cancer chemotherapy between tumor density and drug concentration by an infusion pump, as shown in **Fig.1**. F refers to the flow rate of the pump and u to the rate of blood flow away from the tumor site. In many situations, drugs that sustain the health of a patient cannot be administered orally but must be injected directly into the circulation. This can be done with serial injections **(Malinzi et al., 2021)**, or in particular instances, using continuous infusion, which delivers some constant level of medication over an extended time interval.

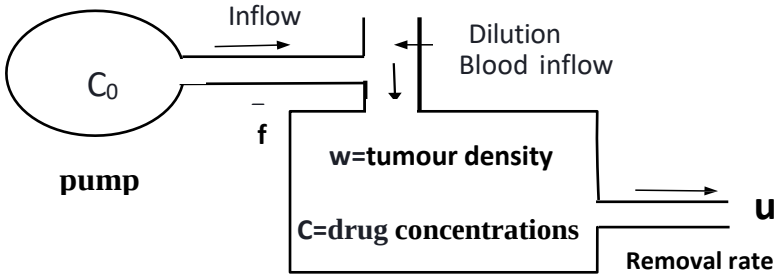

Figure 1. Exponential modeling device for continuous infusion chemotherapy, a tumor (w) is considered to be a group of identical cells, all of which are uniformly exposed to C units of the drug.

The appropriate word equations are, now the system of equations involving the drug C and the tumor cell *w* equation which might contain terms as follows

$$\begin{bmatrix}\text{rate change of}\\ \text{tumor for time}\end{bmatrix} = \begin{bmatrix}\text{growth rate of}\\ \text{cells}\end{bmatrix} - \begin{bmatrix}\text{drug} - \text{induced}\\ \text{death rate}\end{bmatrix}, \tag{1}$$

$$\begin{bmatrix}\text{rate change of}\\ \text{drug for time}\end{bmatrix} = \begin{bmatrix}\text{rate drug}\\ \text{infused}\end{bmatrix} - \begin{bmatrix}\text{rate of}\\ \text{uptake}\\ \text{by cells}\end{bmatrix} - \begin{bmatrix}\text{rate of}\\ \text{removal by}\\ \text{the circulation}\end{bmatrix}, \tag{2}$$

We assume that w is the number of tumor cells per unit of blood volume.
C is the number of drug units in circulation per unit of blood volume.
Now, we will write what each term Eqs. (1)- (2) represents

$$\begin{bmatrix}\text{rate change of}\\ \text{tumor for time}\end{bmatrix} = \frac{dw}{dt} \tag{3}$$

the tumor grows exponentially

$$\begin{bmatrix}\text{growth rate of}\\ \text{cells}\end{bmatrix} = A(C)w, \tag{4}$$

and

$$\begin{bmatrix}\text{drug} - \text{induced}\\ \text{death rate}\end{bmatrix} = Fw. \tag{5}$$

On the other hand, the rate change of drug is defined as

$$\left[\begin{matrix}\text{rate change of}\\ \text{drug for time}\end{matrix}\right] = \frac{\mathrm{dC}}{\mathrm{dt}} \tag{6}$$

where the three terms in Eq. (2) are,

$$\left[\begin{matrix}\text{rate drug}\\ \text{infused}\end{matrix}\right] = \mathrm{FC_0}, \tag{7}$$

$$\left[\begin{matrix}\text{rate of}\\ \text{uptake}\\ \text{by cells}\end{matrix}\right] = -\alpha\, \mathrm{A}(C)\mathrm{w}, \tag{8}$$

and

$$\left[\begin{matrix}\text{rate of}\\ \text{removal by}\\ \text{the circulation}\end{matrix}\right] = -\mathrm{uC}. \tag{9}$$

We are combining the assumptions of a rate change of tumor for time t with a rate change of drug for the time of differential equations.
By substituting an Eqs. (3), (4), and (5) in Eq. (1), we get

$$\frac{dw}{dt} = \mathrm{A}(C)w - F\mathrm{w}. \tag{10}$$

By substituting an Eqs. (6), (7), (8), and (9) in Eq. (2) we get

$$\frac{dC}{dt} = FC_0 - \alpha\, A(C)w - uC. \tag{11}$$

The parameters in the above system and their descriptions are summarised in **Table 1**.

Table 1. Summary of the quantities and model parameters and dimensions of the model Eqs. (10) and (11)

Quantity	Description	Dimensions
A(C)	The tumor growth rate and drug consumption	(1/Unit time)
$\mathbf{A_{max}}$	The maximal tumor reproduction rate	(1/Unit time)
$\mathbf{A_n}$	The amount of medication at which the growth rate is in the middle of the upper limit	(Mass/Volume)
C	The concentration of drug solution in a patient body	(Mass/Volume)
$\boldsymbol{C_0}$	The concentration of drug solution in the infusion pump	(Mass/Volume)
$\boldsymbol{F}$	The pump flow rate	(Volume/Unit time)
$\boldsymbol{u}$	Rate of blood flow away from the tumor site	(Volume/Unit time)
$\boldsymbol{V}$	The volume of the blood in direct contact with the tumor area	Volume
w	The number of tumor cells per unit of blood volume	(Number/Volume)
α	Drug exhaustion rate	(Mass/Number)

2.1 Corrected Version

By writing the exact dimension of Eqs. (10) and (11) we find they are not quite correct, so we now have to discover the mistakes made in writing them.

$$\frac{\text{number}}{\text{volume}*\text{time}} = \frac{1}{\text{time}} * \frac{\text{number}}{\text{volume}} - \frac{\text{volume}}{\text{time}} * \frac{\text{number}}{\text{volume}}. \quad (12)$$

We discovered an inconsistency in the second term for Eq. (10) by looking at the dimensions; one way to correct this problem is to divide Fw by the quantity that holds the size dimensions. Since the only parameter available is V, we can regard $\frac{\text{Fw}}{\text{V}}$, as the appropriate correction. Note that Fw is the number of tumor cells leaving per unit of time, so $\frac{Fw}{V}$, is the effective density of tumour cells leaving per unit of time, thus we find the following corrected version of Eq. (10).

$$\frac{dw}{dt} = \text{A}(C)w - \frac{Fw}{V}. \quad (13)$$

Now, we write a corrected version of Eq. (11).

$$\frac{\text{mass}}{\text{volume}*\text{time}} = \frac{\text{volume}}{\text{time}} * \frac{\text{mass}}{\text{volume}} - \frac{\text{mass}}{\text{number}} * \frac{1}{\text{time}} * \frac{\text{number}}{\text{volume}} - \frac{\text{volume}}{\text{time}} * \frac{\text{mass}}{\text{volume}}. \quad (14)$$

A similar analysis applied to Eq.(11), and reveals that the terms FC_0 and uC should be divided by V after correcting by the same procedure, thus we arrive at the following corrected version of Eq. (11),

$$\frac{dC}{dt} = \frac{FC_0}{V} - \alpha\, A(C)w - \frac{uC}{V}. \quad (15)$$

2.2 Michaelis-Menten Kinetics

The growth rate increases with drug availability only to a certain threshold. The individual tumor cells can only absorb drugs and proliferate at a restricted pace. A mechanism that exemplifies this phenomenon is the Michaelis-Menten kinetics **(Wood and Thakker, 1982).**

$$A(C) = \frac{A_{max}C}{A_n+C}. \quad (16)$$

As shown in **Fig. 2**, the interaction of tumors with drugs is based on the drug catalysis of cell tumors, which is based on a similar model of enzyme catalysis by Michaelis and Menten, developed in **(Michaelis, 1925)**. Kinetics are characterized by a maximal rate of drug growth rate (denoted. A_{max}) and sensitivity to concentration (denoted A_n, referred to as the Michaelis–Menten constant) this latter term is the concentration of the drug that causes the growth rate to function at ½ A_{max} **(Kenakin, 2012)** . The reaction exhibits a slow rise in percentage when the concentrations are low. When concentrations are elevated, the drug's growth rate does not show a percentage change but reaches its maximum rate **(Leskovac, 2003).**

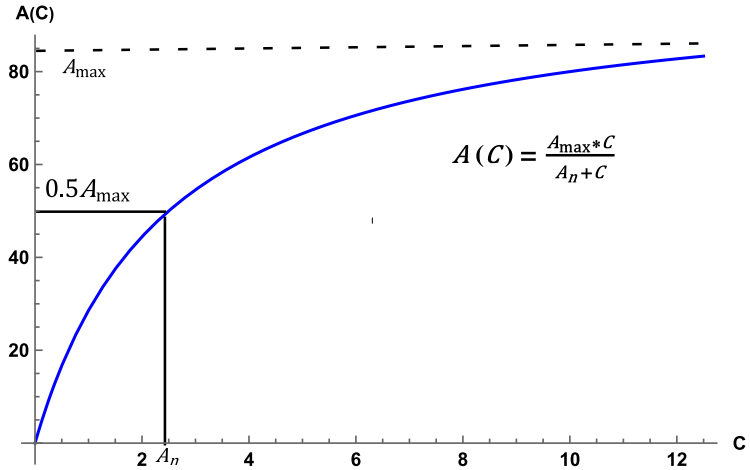

Figure 2. Michaelis-Menten kinetics: tumor growth rate and drug consumption A(C) is assumed to be a saturating function of drug concentration.

Substitute Eq. (16) in Eq. (13) and Eq.(15).

$$\frac{dw}{dt} = \left(\frac{A_{max}C}{A_n+C}\right) w - \frac{Fw}{V}, \tag{17}$$

$$\frac{dC}{dt} = \frac{FC_0}{V} - \alpha \left(\frac{A_{max}C}{A_n+C}\right) w - \frac{uC}{V}. \tag{18}$$

2.3 Non-Dimensionalisation of the Model

Rescaling, or non-dimensionalizing, is the process of transforming a collection of equations (often ordinary differential equations or partial differential equations) into dimensionless forms by modifying the scale of the variables in the model **(Conejo, 2021; Brunetkin et al., 2018)** For the selection of the optimal rescaling technique, we first analyze the situation in which the tumor and medications are uniformly distributed throughout space, thus spatially uniform **(Pérez et al., 2017).**

We make a dimensional analysis of Eqs. (17) and (18). We then substitute $w = w^* \hat{w}$, $C = C^* \hat{C}$, $t = t^* \tau$. into Eq. (17), where w^*, C^* and t^* are those which have no dimensions and $\hat{w}$, $\hat{C}$, τ are those which represent the units of measurement.

$$\frac{dw^* \hat{w}}{dt^* \tau} = \left(\frac{A_{max}C^* \hat{C}}{A_n+C^* \hat{C}}\right) w^* \hat{w} - \frac{Fw^* \hat{w}}{V}. \tag{19}$$

Now we multiply both sides by τ, divided by $\hat{w}$, and the result is

$$\frac{dw^*}{dt^*} = \tau \left(\frac{A_{max}C^* \hat{C}}{A_n+C^* \hat{C}}\right) w^* - \tau \frac{Fw^*}{V}, \tag{20}$$

We take a common factor ($\hat{C}$) from the denominator of the first term.

$$\frac{dw^*}{dt^*} = \tau A_{max}\left(\frac{C^*}{\frac{A_n}{\hat{C}}+C^*}\right)w^* - \frac{\tau F}{V}w^*, \tag{21}$$

we choose $\tau = \frac{V}{F}$, and $\hat{C} = A_n$, (22)

substitute Eq. (22) in Eq. (21),

$$\frac{dw^*}{dt^*} = \frac{V}{F}A_{max}\left(\frac{C^*}{1+C^*}\right)\ w^* - \ w^*. \tag{23}$$

Let $\alpha_1 = \frac{V}{F}\ A_{max}$, (24)

$$\frac{dw^*}{dt^*} = \ \alpha_1\left(\frac{C^*}{1+C^*}\right)w^* - w^*. \tag{25}$$

Remove the stars from the equation, so that the final version of Eq.(17) is,

$$\frac{dw}{dt} = \alpha_1\left(\frac{C}{1+C}\right)w - w. \tag{26}$$

Now, in a similar method, we substitute the definitions of the parameters w, C, and t into Eq. (18). We then get

$$\frac{dC^*\hat{C}}{dt^*\tau} = \frac{FC_0}{V} - \alpha\ \left(\frac{A_{max}C^*\hat{C}}{A_n+C^*\hat{C}}\right)w^*\widehat{w} - \frac{uC^*\hat{C}}{V}, \tag{27}$$

If we multiply both sides by τ, divided by $\hat{c}$, the result is,

$$\frac{dC^*}{dt^*} = \frac{\tau}{\hat{C}}\frac{FC_0}{V} - \ \alpha\tau\left(\frac{A_{max}C^*}{\frac{A_n}{\hat{C}}+C^*}\right)\ w^*\ \frac{\widehat{w}}{\hat{C}} - \ \frac{u}{V} * C^*\tau, \tag{28}$$

we substitute Eq. (22) in Eq. (28),

$$\frac{dC^*}{dt^*} = \frac{F}{V}\ .\frac{\frac{V}{F}}{A_n}C_\circ - \alpha\ \frac{V}{F}\left(\frac{A_{max}C^*}{1+C^*}\right)w^*\frac{\widehat{w}}{\hat{c}} - \frac{u}{V}C^*\frac{V}{F}, \tag{29}$$

$$\frac{dC^*}{dt^*} = \frac{C_\circ}{A_n} - \alpha\tau\ \ \left(\frac{A_{max}C^*}{1+C^*}\right)\ w^*\frac{\widehat{w}}{\hat{C}} - \ \frac{u}{F}C^*. \tag{30}$$

$$\frac{dC^*}{dt^*} = \alpha_2 - \ \frac{\alpha\tau A_{max}\widehat{w}}{\hat{c}}\ .\frac{C^*}{1+C^*}\ w^* - \frac{u}{F}C. \tag{31}$$

Let $\hat{w} = \frac{\hat{C}}{\alpha\tau A_{max}}$, $\alpha_2 = \frac{C_o}{A_n}$, and let $\alpha_3 = \frac{u}{F}$. (32)

And substitute Eq. (32) in Eq.(31)

$$\frac{dC^*}{dt^*} = \alpha_2 - \frac{\alpha\tau A_{max}}{\hat{C}} \cdot \frac{\hat{C}}{\alpha A_{max}\tau} \left(\frac{C^*}{1+C^*}\right) w^* - \alpha_3 C. \quad (33)$$

We then remove the stars from the equation,

$$\frac{dC}{dt} = \alpha_2 - \left(\frac{C}{1+C}\right) w - \alpha_3 C. \quad (34)$$

The system of Eq. (17) and (18) with seven parameters is transformed to the dimensionless system with three parameters after the non-dimensionalization process as

$$\dot{w} = \alpha_1 \left(\frac{C}{1+C}\right) w - w. \quad (35)$$

$$\dot{C} = \alpha_2 - \left(\frac{C}{1+C}\right) w - \alpha_3 C, \quad (36)$$

where hypotheses $\alpha_1, \alpha_2, \alpha_3$, in Eqs. (24) and (32) are dimensionless values.

3. LINEAR STABILITY ANALYSIS

In this section, we will discuss steady-state solutions for the model and, linear stability analysis for the continuous infusion model **(Mitlin, 1993).**

3.1 Steady-State Solutions for Model

The equilibrium points $(\bar{w}, \bar{C})$, for the dynamical system can be found by making the right-hand sides of Eqs. (35) and (36) equal to zero as a first step **(Tschoegl, 2000; Zheng et al., 2011)** $\dot{w} = 0, \dot{C} = 0$.

$$\alpha_1 \left(\frac{\bar{C}}{1+\bar{C}}\right) \bar{w} - \bar{w} = 0, \quad (37)$$

$$\alpha_2 - \left(\frac{\bar{C}}{1+\bar{C}}\right) \bar{w} - \alpha_3 \bar{C} = 0. \quad (38)$$

From Eq. (37)

$$\bar{w}\left(\alpha_1 \left(\frac{\bar{C}}{1+\bar{C}}\right) - 1\right) = 0,$$

either, $\hat{w} = 0$, or $\alpha_1 \left(\frac{\bar{C}}{1+\bar{C}}\right) = 1$,

$$\frac{\bar{C}}{1+\bar{C}} = \frac{1}{\alpha_1}. \quad (39)$$

$\alpha_1\bar{C} = 1 + \bar{C}$, which leads to $\alpha_1\bar{C} - \bar{C} = 1$ then $(\alpha_1 - 1)\bar{C} = 1$.

$$\bar{C} = \frac{1}{\alpha_1 - 1}. \quad (40)$$

Substituting, $\bar{w} = 0$ in Eq. (38) $\alpha_2 - 0 - \alpha_3\bar{C} = 0$, $\bar{C} = \frac{\alpha_2}{\alpha_3}$.

The first steady-state point is $S_1 = (\bar{w}_1, \bar{C}_1) = \left(0, \frac{\alpha_2}{\alpha_3}\right)$. (41)

Substituting Eq. (40) in Eq. (38) gives

$\alpha_2 - \left(\frac{\frac{1}{\alpha_1-1}}{1+\frac{1}{\alpha_1-1}}\right)\bar{w} - \alpha_3 \frac{1}{\alpha_1-1} = 0$, leads to $\alpha_2 - \left(\frac{1}{\alpha_1}\right)\bar{w} - \frac{\alpha_3}{\alpha_1-1} = 0$, leads to

$\bar{w} = \alpha_1\left(\alpha_2 - \frac{\alpha_3}{\alpha_1-1}\right)$.

The second steady state point is $S_2 = (\bar{w}_2, \bar{C}_2) = \left(\alpha_1\left(\alpha_2 - \frac{\alpha_3}{\alpha_1-1}\right), \frac{1}{\alpha_1-1}\right)$. (42)

To summarise this section, the steady-state points of the model are

$$S_1 = (\bar{w}_1, \bar{C}_1) = \left(0, \frac{\alpha_2}{\alpha_3}\right). \quad (43)$$

$$S_2 = (\bar{w}_2, \bar{C}_2) = \left(\alpha_1\left(\alpha_2 - \frac{\alpha_3}{\alpha_1-1}\right), \frac{1}{\alpha_1-1}\right). \quad (44)$$

In the next section, we shall now determine whether S_1, S_2, S_3 and S_4 are stable steady states.

3.2 Linear Stability Analysis for Continuous Infusion in Exponential Case

Linearisation is the use of analytical techniques specifically developed for studying linear systems to analyze the properties of a nonlinear function close to a precise point. The linearisation of a function is the identification of the first-order term of its Taylor expansion in the vicinity of the end of interest inside a system defined by the described equation **(Mohsen and Naji, 2022)** The Jacobian matrix eigenvalues calculated at a hyperbolic equilibrium point may be used in the stability analysis of autonomous systems to determine the properties of that equilibrium **(Ghaffari and Lasemi, 2015; Kravaris and Kookos, 2021)** Presented below is a comprehensive explanation of the linearisation theorem. Further clarification is required for linearisation in time-varying systems **(Hartman, 1960; Matthias and Christian, 2014)** where the stability criteria are Tr. (J) < 0 and det(J) > 0.

If we assume the right-hand sides of Eqs. (35) and (36) as the functions f and g.

$$f(w, C) = \alpha_1\left(\frac{C}{1+C}\right)w - w. \quad (45)$$

$$g(w,C) = \alpha_2 - \left(\frac{C}{1+C}\right) w - \alpha_3 C. \quad (46)$$

Then the nonlinear functions f and g are assumed to have steady-state solutions, denoted by $\bar{w}$ and $\bar{C}$, the Jacobin matrix for the nonlinear system of Eqs. (46) and (48).

$$J(w,g) = \begin{bmatrix} \frac{\partial f}{\partial w} & \frac{\partial f}{\partial C} \\ \frac{\partial g}{\partial w} & \frac{\partial g}{\partial C} \end{bmatrix}, \quad (47)$$

where

$$\frac{\partial f}{\partial w} = \alpha_1 \left(\frac{C}{1+C}\right) - 1, \ \frac{\partial f}{\partial c} = \alpha_1 w \left(\frac{1}{(1+C)^2}\right), \quad (48)$$

$$\frac{\partial g}{\partial w} = -\left(\frac{C}{1+C}\right), \ \frac{\partial g}{\partial c} = -\left(\frac{1}{(1+C)^2}\right) w - \alpha_3. \quad (49)$$

We then substitute Eqs (48) and (49) in Eq (47).

$$J(w,c) = \begin{bmatrix} \alpha_1 \left(\frac{C}{1+C}\right) - 1 & \alpha_1 w \left(\frac{1}{(1+C)^2}\right) \\ -\left(\frac{C}{1+C}\right) & -\left(\frac{1}{(1+C)^2}\right) w - \alpha_3 \end{bmatrix}, \quad (50)$$

For the first equilibrium point $s_1 = \left(0, \frac{\alpha_2}{\alpha_3}\right)$

$$J_{S_1} = J\left(0, \frac{\alpha_2}{\alpha_3}\right) = \begin{bmatrix} \frac{\alpha_1 \alpha_2}{\alpha_3 + \alpha_2} - 1 & 0 \\ \frac{-\alpha_2}{\alpha_3 + \alpha_2} & -\alpha_3 \end{bmatrix}. \quad (51)$$

$$Tr\left(0, \frac{\alpha_2}{\alpha_3}\right) = \frac{\alpha_1 \alpha_2}{\alpha_3 + \alpha_2} - \alpha_3 - 1, \quad (52)$$

$$det\left(0, \frac{\alpha_2}{\alpha_3}\right) = -\alpha_3 \left(\frac{\alpha_1 \alpha_2}{\alpha_3 + \alpha_2} - 1\right), \quad (53)$$

since $\alpha_1 > 1$ This led to $\frac{\alpha_1 \alpha_2}{\alpha_3 + \alpha_2} > 1$, leads to det(J) < 0.

Then ($\bar{w}_1$, $\bar{C}_1$), is a saddle point.

For the second equilibrium point $s_2 = \left(\alpha_1 \left(\alpha_2 - \frac{\alpha_3}{\alpha_1 - 1}\right), \frac{1}{\alpha_1 - 1}\right)$,

$$J\left(\alpha_1\left(\alpha_2+\frac{\alpha_3}{1-\alpha_1}\right),\frac{1}{\alpha_1-1}\right)=\begin{bmatrix}0 & (\alpha_1-1)^2\left(\alpha_2-\frac{\alpha_3}{\alpha_1-1}\right)\\ -\frac{1}{\alpha_1} & -\frac{(-1+\alpha_1)^2\alpha_2+\alpha_3}{\alpha_1}\end{bmatrix}, \quad (54)$$

$$Tr(J)=-\frac{(-1+\alpha_1)^2\alpha_2+\alpha_3}{\alpha_1} \text{ leads to } \alpha_2>\frac{\alpha_3}{\alpha_1-1} \text{ then } Tr(J)<0, \quad (55)$$

$$det(J)=\frac{(-1+\alpha_1)((-1+\alpha_1)\alpha_2-\alpha_3)}{\alpha_1}>0. \quad (56)$$

Then $(\bar{w}_2,\bar{C}_2)$, is stable.

3.3 Analysis for Stability of Steady States for Continuous Infusion in Exponential Case

In conclusion to the delivery of drugs by continuous infusion system, we will interpret the various results to extract helpful information from the mathematical analysis. To summarize our findings, we have determined that a sensibly operating delivery of drugs will always have a stable steady-state solution with the tumor populating the growth cell. Recall that this equilibrium can be biologically meaningful provided that, $\alpha_1$and α_2 , satisfy the inequalities.

From Eq. (44), $\alpha_1-1>0$, leads to $\alpha_1>1$, (57)

This constraint must be satisfied to prevent negative values of the drug concentration, $\hat{c}_2$.

From the same Equation, the first term which represents the tumour density

$\alpha_1\left(\alpha_2-\frac{\alpha_3}{\alpha_1-1}\right)$, which is also non-negative and leads to $\alpha_2>\frac{\alpha_3}{\alpha_1-1}$, (58)

This constraint must be satisfied to prevent negative values of the tumor population, $\bar{w}_1$.

From Eq. (24), $\alpha_1=\frac{V}{F}A_{max}$, (59)

$\alpha_2=\frac{c_\circ}{A_n}$, (60)

The first condition (57) is thus equivalent to

$A_{max}>\frac{F}{V}$,

We notice that both sides of this inequality have dimensions $1/time$. It is more revealing to rewrite this as

$\frac{1}{A_{max}}<\frac{V}{F}$. (61)

To interpret this, observe that. A_{max} , is the maximal tumor reproduction rate (in the presence of unlimited drugs. $\frac{dw}{dt} = \mathrm{A_{max}}w$). Thus $\frac{1}{\mathrm{A_{max}}}$, is proportional to the doubling time of the tumor population. $\frac{\mathrm{v}}{\mathrm{F}}$ is the time it takes to replace the whole fluid volume in the medicine pump with a fresh drug medium. Eq. (61) reveals that if the tumor doubles the time. τ_2, is smaller than the emptying time of the chamber (×1/ ln 2), the tumor will not be washed out in the efflux faster than it $\bar{C}_2 = \frac{1}{\alpha_1 - 1}$, and from Eq.(32). $\alpha_2 = \frac{C_\circ}{A_n}$, by substituting these equations into Eq.(58).

$\alpha_2 > \frac{\alpha_3}{\alpha_1 - 1}$, leads to $\frac{C_\circ}{A_n} > \bar{C}_2\alpha_3$, this means $C_\circ > A_n\bar{C}_2\alpha_3$
Substituting the value of $\bar{C}_2$

$C_\circ > \frac{A_n\alpha_3}{\alpha_1 - 1}$, by substituting the value of α_1,

$C_\circ > \frac{A_n\alpha_3}{\frac{V}{F}A_{max} - 1}$ leads to

$$C_\circ > \frac{A_n\alpha_3 / A_{max}}{\frac{V}{F} - \frac{1}{A_{max}}}, \text{ Or } \frac{C_\circ}{A_n} > C_2, \quad (62)$$

Since $\hat{C} = A_n$, is the reference concentration used in endearing Eq.(35) and (36) dimensionless, we see that

$\bar{C} = \bar{C}_2\hat{C} = A_n\bar{C}_2$,

The original dimension-carrying steady state (whose units are mass per unit volume) thus, Eq. (62), is equivalent to

$C_\circ > \bar{C}_2$.

This summarizes an intuitively obvious: the initial drug is larger than the drug in the medicine pump, and its concentration in the tank does not exceed its concentration. The time required for the tumor to multiply must be less than the time needed for complete drug replacement within the tumor site.
The values we choose must satisfy the condition we have deduced.

The first condition $\alpha_1 > 1$, or the second condition $\alpha_2 > \frac{\alpha_3}{\alpha_1 - 1}$. (63)

4. NUMERICAL RESULTS AND DISCUSSION

In this section, the interaction between tumor volume and drug concentration by the infusion pump is studied. We apply three numerical cases for the values in **Table 2** and **Table 3**. Using MATHEMATICA code to solve the model in Eqs. (45) and (46), MATLAB R2023a is used to find out the numerical solution of the system of Eqs. (45) and (46) via the Runge-Kutta method, where the blue curve indicates the tumor density and the red curve

indicates the drug concentration. Exponential model programming is used to use Eqs. (45) and (46). phase-plane diagrams; can depict each of these situations graphically.

4.1 Standard Parameters Set

To implement numerical examples in the aforementioned system, we need to choose numbers that meet the criteria in **Table 2** and simulate several scenarios to demonstrate the outcomes in each scenario. Hence, we choose the predetermined parameters shown in the table. The parameter V, as stated in a 2020 article **(Sharma and Sharma, 2024)**, comprises around 10.5 pints (5 liters) on average (V=5000 ml) of blood in the typical human adult body, with potential variations influenced by many variables. Theoretical knowledge of the parameter F is derived from its calibration by the pump manufacturer. The standard value of F falls within the range of 1-6 ml/day **(Edelstein-Keshet, 2005)**. The highest tumor reproduction rate, denoted as A_{max}, is equivalent to the intensity of the administered dosage. Assuming the values of the coefficients provided in the exponential model **(Hassan and Al-Saedi, 2024)**, r $= 0.0331$ and $A_{max} = 0.0331$. Adjusted dosage (A_n) is the dosage at which the growth rate falls between the upper and lower limits. Let A_n be equal to 0.015545.

Table 2. Model parameters and their units.

Symbol	Description	Typical value	Unit	Source
A_{max}	The maximal tumor reproduction rate	0.0331	(1/day)	**(Hassan and Al-Saedi, 2024)**
A_n	The amount of medication at which the growth rate is in the middle of the upper limit	0.015545, 0.001,0.005,0.01,0.02, 0.06	(Mass/ *ml*)	estimated
$C_\circ$	The concentration of the drug in the infusion pump	0.0331	(Mass/*ml)*	**(Hassan and Al-Saedi, 2024)**
F	The pump flow rate	6, 6, 6, 6, 6, 5	(Ml/day)	**(Edelstein-Keshet, 2005)**
u	The rate of blood flows away from the tumor site.	3, 3, 3, 3, 3, 8	(Ml/day)	estimated
V	The volume of the blood in direct contact with the tumor area	5000, 5000, 5000, 5000, 5000, 226.586	*Ml*	**(Sharma and Sharma, 2024)**
α	The drug exhaustion rate	0.0005	*(Mass/number)*	estimated

We will substitute the values in **Table 2**. into Eqs. (24) and (32) we will get the values of α_1, α_2, and α_3 as in the following Error! Not a valid bookmark self-reference.

Table 3. Dimensionless parameter values of the model.

Nondimensional parameter	Dimension form	value	Unit
α_1	$\frac{V}{F} A_{max}$	26	dimensionless
α_2	$\frac{C_\circ}{A_n}$	0.20753, 33.1, 6.62, 3.31, 1.665	dimensionless
α_3	$\frac{u}{F}$	0.5	dimensionless

Finally, we apply a numerical case. Substitute the values in **Table 2** and **Table 3.** The interpretation of these equilibrium points is as follows: Using several examples as shown in **Table 2** we solve the equations, find the points, and identify the stable and unstable points. We take different cases of α as in **Table 3** and observe how the solution behaves. A numerical simulation of the system of Eqs. (45) and (46) are performed to illustrate the analytical behavior to provide a picture of the level. As a result, the model can be predicted in terms of how it will behave under a variety of initial conditions, but for a pre-defined set of parameter values. The curve (path) of the initial values is shown in **Fig. 3.** Using MATHEMATICA(13.2) and seeing the agreement of the analytical solution with the numerical solution later, we take the stable points to denote the tumor volume and the drug dose.

4.2 Case Study One

We will take the first case when $\alpha_1 > 1$ and $\alpha_2 > \frac{\alpha_3}{\alpha_1 - 1}$, where $\alpha_1 = 26$, $\alpha_2 = 0.20753$ and $\alpha_3 = 0.5$, it is seen from the numerical results $\alpha_1 > 1$, $\alpha_2 < 1$ and $\alpha_3 < 1$, that it has two points, one is stable (4.87578,0.04), and the other is unstable (0,0.41506). In **Fig. 4(a)**, and **(b)** the tumor goes to the point where the tumor is stable when the point is stable (4.87578,0.04). We took different initial conditions greater than the stable point when the initial condition was w_0=6, C=0.009, and noticed that the curve was heading towards the stable value as in **Fig. 4(a)** and we took different initial conditions smaller than the stable point when the initial condition was w_0=4, C=0.1, and notice that the curve was heading towards the stable value as in **Fig.4(b)** this is consistent with the analytical aspect of the problem, which is the linear stability analysis in **Fig. 3.** We notice that there is one stable point (4.87578,0.04), so to find the real values with dimension units of tumors and drugs, we use

$$w = w^* \hat{w} = 4.87578 * \frac{0.015545 * 6}{0.0005 * 5000 * 0.0331} = 5.49563 \text{ (Number/Volume)}, \quad (64)$$

$$C = C^* \hat{C} = 0.04 * 0.015545 = 0.0006218 \text{ (Mass/Volume)}. \quad (65)$$

This means the size of the tumor is 5.49563, it needs a concentration of drug 0.0006218, and in the same way for other cases.

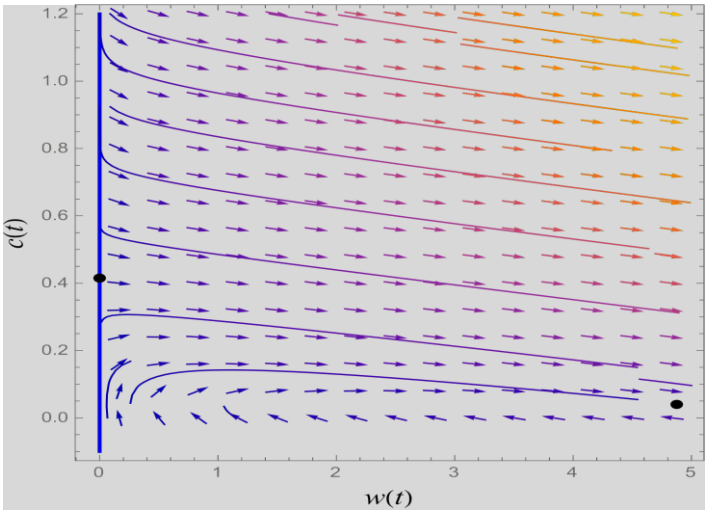

Figure 3. MATHEMATICA generated a phase-plane diagram (the delivery of drugs by continuous infusion of a two-species system with $\alpha_1 = 26$, $\alpha_2 = 0.20753$ and $\alpha_3 = 0.5$).

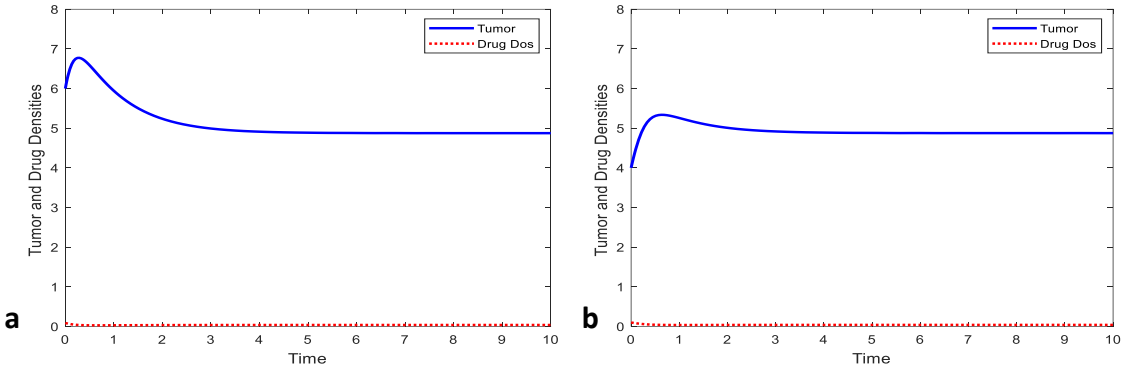

Figure 4. MATLAB numerical results of the Delivery of Drugs by Continuous Infusion of a two-species system with $\alpha_1 = 26$, $\alpha_2 = 0.20753$ and $\alpha_3 = 0.5$. **a)** When the initial condition w_0=6, C=0.09. **b)** When the initial condition w_0=4, C=0.1.

4.3 Case Study Two

We will take the second case when $\alpha_1 > 1$ and $\alpha_2 > \frac{\alpha_3}{\alpha_1 - 1}$, where the value of $\alpha_1 = 26$, $\alpha_2 = 33.1$, and $\alpha_3 = 0.5$. We take different values of A_n are found in Michelis-Menten the lower the value of A_n , the faster it is to reach half A_{max}. We will take four cases for A_n, for example, $A_n = 0.001$, $A_n = 0.005$, $A_n = 0.01$, $A_n = 0.02$ as in **Fig.5**.

From the numerical results of the second case that meets the condition $\alpha_1 > 1, \alpha_2 < 1, \alpha_3 < 1$, in **Fig.(7)(a)** and **(b)**, it is seen that it has two points, one is stable (860.08,0.04), and the other is unstable (0,33.1) that the tumor goes to the point where the tumor is stable when the point is stable (860.08,0.04). We took different initial conditions greater than the stable point when the initial condition was w_0=900, C=0.09, and noticed that the curve is heading towards the stable value as in **Fig.7(a)**.

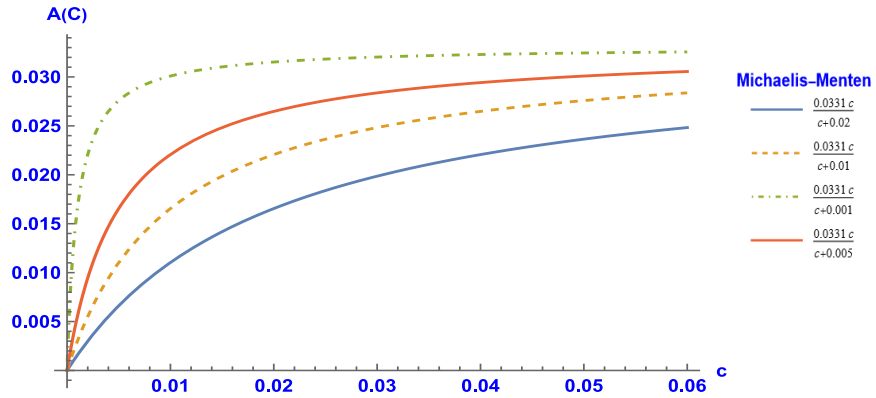

Figure 5. Michaelis-Menten kinetics with different values for A_n.

We took different initial conditions smaller than the stable point when the initial condition was w_0=800, C=0.01, and noticed that the curve is heading towards the stable value as in **Fig.7(b)** this is consistent with the analytical aspect of the problem, which is the linear stability analysis in **Fig. 6(a).** and we noticed that there is one stable point (860.08,0.04), to find the real values with dimension units of tumors and drugs, we use

$$w = w^*\hat{w} = 860.08 * \frac{0.001*6}{0.0005*5000*0.0331} = 62.36229 \ \textit{(Number/Volume)}, \tag{66}$$

$$C = C^*\hat{C} = 0.04 * 0.001 = 0.00004 \ \textit{(Mass/Volume)}. \tag{67}$$

This means the size of the tumor is 62.36229 it needs a concentration of drug 0.00004, and in the same way for other cases.

In **Fig.(7)(c)** and **(d)** the value of $\alpha_1 = 26$, $\alpha_2 = 6.62$, and $\alpha_3 = 0.5$. It has two points, one is stable (171.6,0.04), and the other is unstable (0,13.24) that the tumor goes to the point where the tumor is stable when the point is stable (171.6,0.04). We took different initial conditions greater than the stable point when the initial condition was w_0=200, C=0.09, and noticed that the curve is heading towards the stable value as in **Fig.7(c)** and we took different initial conditions smaller than the stable point when the initial condition was w_0=100, C=0.01, and noticed that the curve is heading towards the stable value as in **Fig.7(d)** this is consistent with the analytical aspect of the problem, which is the linear stability analysis in **Fig. 6(b).** We notice that there is one stable point (171.6,0.04), to find the real values with dimension units of tumors and drugs, we use

$$w = w^*\hat{w} = 171.6 * \frac{0.005*6}{0.0005*5000*0.0331} = 62.21148 \ \textit{(Number/Volume)}, \tag{68}$$

$$C = C^*\hat{C} = 0.04 * 0.005 = 0.0002 \ \textit{(Mass/Volume)}. \tag{69}$$

This means the size of the tumor is 62.21148 it needs a concentration of drug 0.0002, and in the same way for other cases.

In **Fig.(7)(e)** and **(f)** the value of $\alpha_1 = 26$, $\alpha_2 = 3.31$, and $\alpha_3 = 0.5$. It has two points, one is stable (85.54,0.04), and the other is unstable (0,6.62) the tumor goes to the point where the tumor is stable when the point is stable (85.54,0.04). We took different initial conditions greater than the stable point when the initial condition was w_0=90, C=0.09, and noticed that

the curve is heading towards the stable value as in **Fig. 7(e)** and we took different initial conditions smaller than the stable point when the initial condition was w_0=80, C=0.01, and noticed that the curve is heading towards the stable value as in **Fig.7(f)** this is consistent with the analytical aspect of the problem, which is the linear stability analysis in **Fig. 6 (c).** we notice that there is one stable point (85.54,0.04), to find the real values with dimension units of tumors and drugs, we use

$$w = w^*\hat{w} = 85.54 * \frac{0.01*6}{0.0005*5000*0.0331} = 62.02296 \ \textit{(Number/Volume)}, \quad (70)$$

$$C = C^*\hat{C} = 0.04 * 0.01 = 0.0004 \ \textit{(Mass/Volume).} \quad (71)$$

This means the size of the tumor is 62.02296 it needs a concentration of drug 0.0004, and in the same way for other cases.

In **Fig. 7 (g)** and **(h)** the value of $\alpha_1 = 26$, $\alpha_2 = 1.655$, and $\alpha_3 = 0.5$. It has two points, one is stable (42.51,0.04), and the other is unstable (0,3.31) the tumor goes to the point where the tumor is stable when the point is stable (42.51,0.04). We took different initial conditions greater than the stable point when the initial condition was w_0=45, C=0.09, and noticed that the curve is heading towards the stable value as in **Fig. 7(g)** and we took different initial conditions smaller than the stable point when the initial condition was w_0=40, C=0.01, and we noticed that the curve is heading towards the stable value as in **Fig. 7(h)** this is consistent with the analytical aspe ct of the problem, which is the linear stability analysis in **Fig. 6(d).**

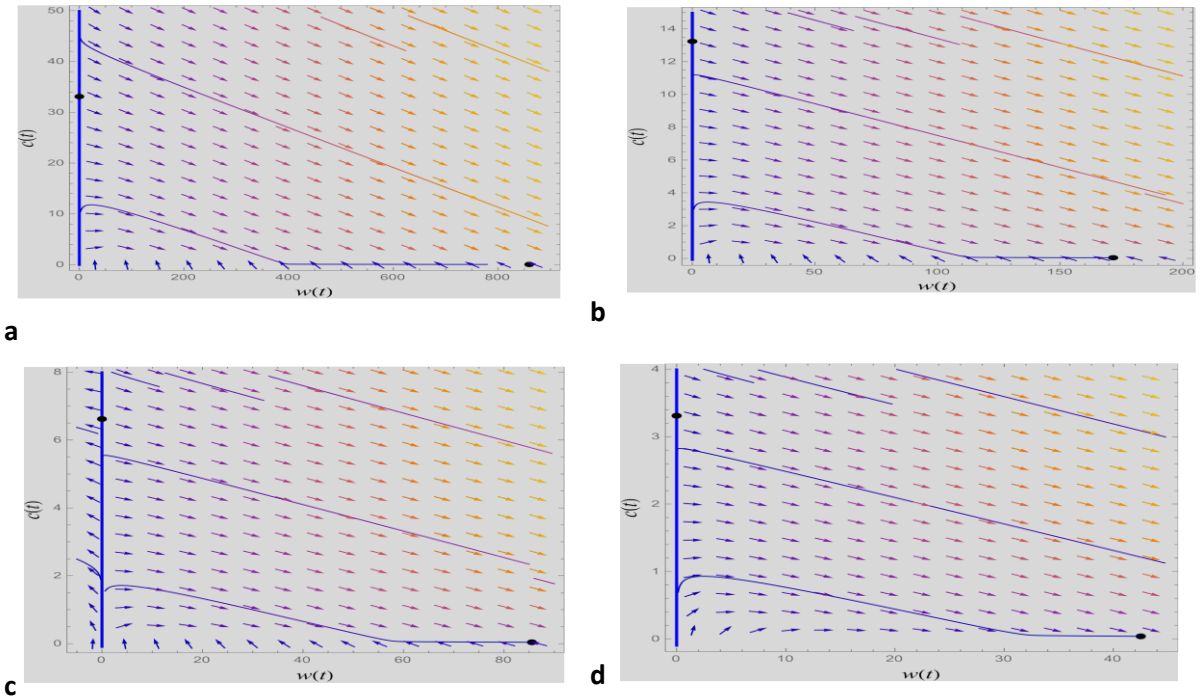

Figure 6. MATH EMATICA generated a phase-plane diagram (the Delivery of Drugs by Continuous Infusion of a two-species s yst em) with **a)** $\alpha_1 = 26, \alpha_2 = 33.1, \alpha_3 = 0.5$. **b)** $\alpha_1 = 26, \alpha_2 = 6.62, \alpha_3 = 0.5$, **C)** $\alpha_1 = 26, \alpha_2 = 3.31, \alpha_3 = 0.5$. **d)** $\alpha_1 = 26, \alpha_2 = 1.655, \alpha_3 = 0.5$.

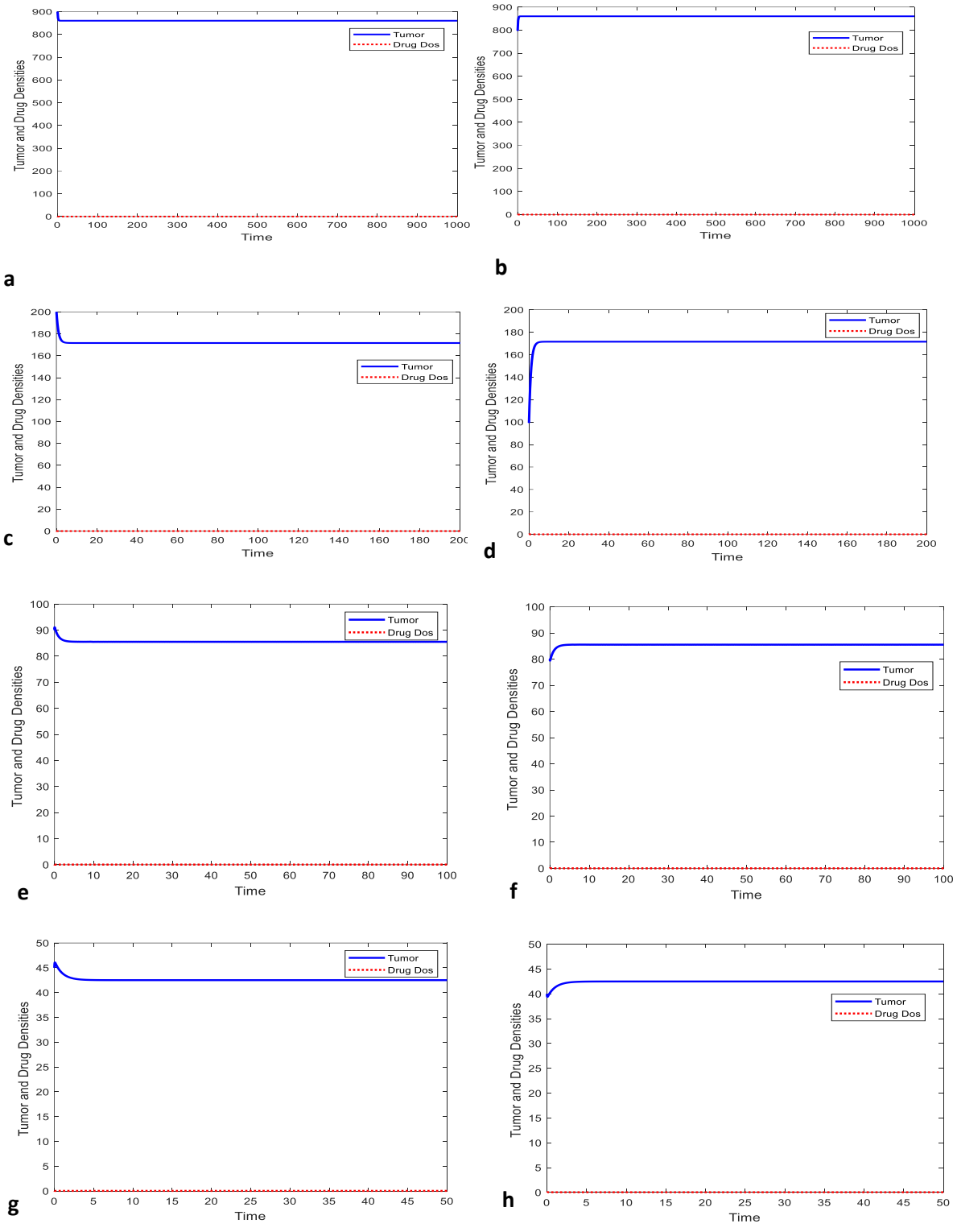

Figure 7. MATLAB numerical results of the Delivery of Drugs by Continuous Infusion of a two-species system with different values for A_n.

a)When the initial condition w_0=900, C=0.09. **b)** When the initial condition w_0=800,C=0.01.
c) When the initial condition w_0=200, C=0.09. **d)** When the initial condition w_0=100, C=0.01.
e) When the initial condition w_0=90, C=0.09. **f)** When the initial condition w_0=80, C=0.01.
g) When the initial condition w_0=45, C=0.09. **h)** When the initial condition w_0=40,C=0.01.

We notice that there is one stable point (42.51,0.04), to find the real values with dimension units of tumors and drugs, we use

$$w = w^*\hat{w} = 42.51 * \frac{0.02*6}{0.0005*5000*0.0331} = 6264592 \quad \text{(Number/Volume)}, \tag{72}$$

$$C = C^*\hat{C} = 0.04 * 0.02 = 0.0008 \text{ (Mass/Volume)}. \tag{73}$$

This means the size of the tumor is 6264592 it needs a concentration of drug 0.0008, and in the same way for other cases

4.4 Case Study Three

We will take the third case when $\alpha_1 > 1$ and $\alpha_2 < \frac{\alpha_3}{\alpha_1 - 1}$.

$\alpha_1 = \frac{V}{F} A_{max} = \frac{226.5861*0.0331}{5} = 1.5$, $\alpha_2 = \frac{C_\circ}{A_n} = \frac{0.0331}{0.06} = 0.55166$, $\alpha_3 = \frac{u}{F} = \frac{8}{5} = 1.3$, the values we have chosen do not meet conditions in Eq. (63). From the numerical results in **Fig.9(a)** and **(b)** the value of $\alpha_1 = 26$, $\alpha_2 = 1.655$, and $\alpha_3 = 0.5$. it has two points, one is stable (0,0.42435), and the other is unstable $(-3.07251,2)$ the tumor goes to the point where the tumor is stable when the point is stable (0,0.42435). We took different initial conditions greater than the stable point when the initial condition was w_0=5, C=0.9, and noticed that the curve is heading towards the stable value as in **Fig. 9(a)** and we took different initial conditions smaller than the stable point when the initial condition was w_0=0.5, C=0.2, and we noticed that the curve is heading towards the stable value as in **Fig.9(b)** this is consistent with the analytical aspect of the problem, which is the linear stability analysis in **Fig. 8**, we notice that there is one stable point (0,0.42435), to find the real values with dimension units of tumors and drugs, we use

$$w = w^*\hat{w} = 0 * \frac{0.06*6}{0.0005*226.586*0.0331} = 0 \ \textit{(Number/Volume)}, \tag{74}$$

$$C = C^*\hat{C} = 0.04 * 0.06 = 0.025461 \ \textit{(Mass/Volume)}. \tag{75}$$

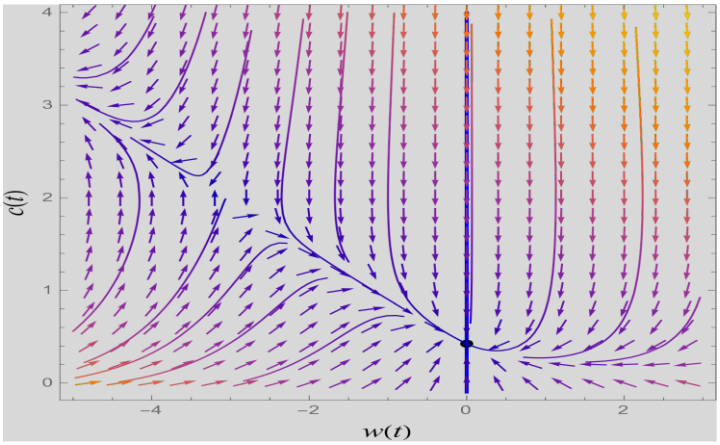

Figure 8. MATHEMATICA generated a phase-plane diagram (the Delivery of Drugs by Continuous Infusion of a two-species system with :$\alpha_1 = 1.5$, $\alpha_2 = 0.55166$, $\alpha_3 = 1.3$.

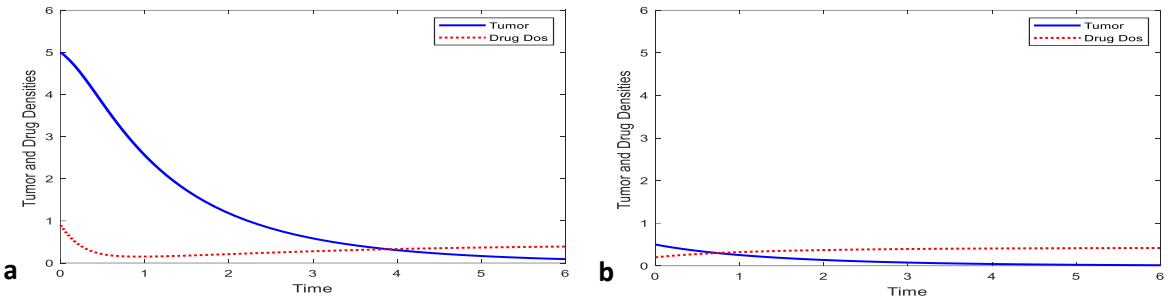

Figure 9. MATLAB numerical results of the delivery of drugs by continuous infusion of a two-species system, $\alpha_1 = 1.5$, $\alpha_2 = 0.55166$, $\alpha_3 = 1.3$. a) When the initial condition w_0=5, C=0.9. b) When the initial condition w_0=0.5, C=0.2.

5. CONCLUSIONS

This study presents a mathematical model integrating exponential growth and Michaelis-Menten kinetics to explore the dynamic interaction between tumor growth and chemotherapy drug infusion. Through dimensional analysis and model refinement, we derived a non-dimensionalized system of equations, which enabled detailed stability analysis and parameter optimization. The findings demonstrate that continuous drug infusion can stabilize tumor growth within a specific range of parameters, shedding light on effective treatment strategies and highlighting the critical role of precise dosing and timing in chemotherapy. The theoretical insights are further validated by numerical simulations, which illustrate the robustness of the model and its potential to guide practical decision-making in cancer treatment. Importantly, the model underscores the value of mathematical frameworks in unraveling the complexities of tumor-therapy interactions, paving the way for more personalized and effective treatment approaches. Future research could expand this model to include additional biological complexities, such as the role of the immune response, tumor heterogeneity, and the effects of angiogenesis. Furthermore, the incorporation of multi-drug therapies and combination treatments could enhance the model's relevance to clinical oncology, providing a foundation for optimizing combination regimens. These extensions could also allow for the integration of patient-specific data, advancing the potential for precision medicine in cancer care. Overall, this work highlights the transformative potential of mathematical modeling in advancing our understanding and management of cancer chemotherapy.

Credit Authorship Contribution Statement

Sokaina Sabah Hassan: Writing – review & editing, Writing – original draft, Software, Methodology. Hayder M. Al-Saedi: Writing – review & editing, Writing – original draft, Validation, Software, Methodology.

Declaration of Competing 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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علاج الكيميائي للأورام عن طريق الحقن المستمر للدواء باستخدام النمو الأسي

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الخلاصة

نقدم إطارًا نظريًا يجمع بين ديناميكيات النمو الأسي وحركية مايكلز–مينتن لنمذجة التفاعل بين كثافة الورم وتركيز الدواء المقدم عبر مضخة التسريب. يأخذ النموذج في الاعتبار تشبع تثبيط نمو الورم عند تركيزات عالية من الدواء، مما يعكس تأثيرات التشبع البيولوجي. يتم تسليط الضوء على العلاج الكيميائي بالتسريب المستمر كطريقة توصيل متفوقة، حيث يحافظ على مستويات ثابتة من الدواء في موقع الورم مع تقليل الآثار الجانبية الجهازية مقارنة بأساليب الحقن التقليدية. يوفر الإطار أداة تنبؤية لتحديد تركيزات الدواء الحرجة وكثافات الورم المطلوبة للقضاء على الورم مع تقليل الآثار الضارة. يحدد تحليل الاستقرار، بناءً على حل المعادلات غير الخطية، نقاط التوازن التي تمثل حالات ثابتة لكثافة الورم وتركيز الدواء. يتم فحص استقرار هذه النقاط لتقييم فعالية أنظمة العلاج الكيميائي على المدى الطويل. توضح المحاكاة الرقمية التوضيحية كيف تؤثر الاختلافات في معدلات توصيل الدواء وخصائص الورم والمعلمات الحركية على النتائج العلاجية. يتم تحديد العوامل الرئيسية مثل الحد الأدنى لتركيز الدواء اللازم لقمع نمو الورم والظروف اللازمة لاستئصال الورم أو إعادة نموه. يكشف تحليل الحساسية أيضًا عن كيفية تأثير تغييرات المعلمات على استقرار النظام والنتائج، مما يوفر رؤى لتحسين استراتيجيات الجرعات. يربط هذا الإطار بين النمذجة النظرية والتحديات العملية في العلاج الكيميائي للسرطان، مما يوفر أداة متعددة الاستخدامات لفهم وتحسين استراتيجيات العلاج. يمكن تكييفه مع أنواع مختلفة من الأورام وطرق العلاج، مما يدعم التقدم في الطب الشخصي وأبحاث علاج السرطان في المستقبل.

الكلمات المفتاحية: العلاج الكيميائي، النمو الأسّي، توصيل الدواء عن طريق الحقن، حركية ميكايليس مينتين، الاستقرارية.