

Insights on the Application of MATLAB and Chaotic Principles to Determine the Targeted Delivery of a Smart Drug Delivery System against Cancer in the Experimental Phase: A Prospective Approach

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Abstract

The smart drug delivery system (SDDS) is a milestone in cancer therapy and uses nanoparticle drug delivery principles such as surface linking with monoclonal antibodies (MABs). This interaction of SDDS with cancer cells can be ascertained by the MATLAB tool and chaotic dynamic system behavioral evaluation. The successful targeting depends on the interaction between the MAB ligand and the antigenic determinants of tumor antigens. However, the target-specific SDDS is highly influenced by various factors such as spatial orientation around the tumor antigens and specific ligands of the MABs. In this study, we focused on the implications of the MATLAB tool and chaotic principles to determine target-specific treatment with SDDS.

Key words: Cancer, chaotic principles, MATLAB system, monoclonal antibodies, smart drug delivery, targeted drug delivery

INTRODUCTION

The therapeutic implementation of chemotherapy to cure cancer faces a great obstacle due to the development of multiple drug resistance by cancer cells, leading to failure of treatment.^[1,2] This issue might be due to inefficiently/insufficiently delivered drugs at the site of the cancer cell, leading to incomplete treatment, and thus, the cancer cell develops resistance through various cellular and molecular mechanisms.^[3,4] Anticancer drugs have to overcome many hurdles to reach the cancer cell site, called pharmacokinetics (pk) resistance, which affects both conventional cytotoxic drugs and targeted therapies.^[5-7] The pk properties of drug delivery at the site of cancer cells can be enhanced by nanoparticles because their endogenous transport system through the cell membrane becomes very easy due to the nanoscale size of the particles; thus, nanoparticles can improve the therapeutic compatibility at targeted cancer.^[8,9] In this aspect, targeting of anticancer drugs at the cancer

cell level can be further improved by tagging monoclonal antibodies (MABs) with nanoparticles that can easily target molecules such as human epidermal growth factor 2 (HER2) and epithelial growth factor receptor (EGFR) molecules.³ However, these targeted therapies are also highly influenced by pk resistance.

Focusing on new drug development for targeting cancer-associated biomolecules is highly cost-effective. Earlier reports showed that phase II clinical trials of newly developed drug moiety/delivery systems became a great burden for pharmaceutical industries since their investment reached millions of dollars and consumed many years.^[10] Despite these investments, most of

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the time in the later stage of clinical trials, failures in treatment occurred due to the ineffectiveness of the drug and the presence of possible adverse effects. Thus, these investments were a waste. However, the computational tool MATLAB can provide solutions for developing drug delivery models to overcome pk resistance^[10] which can improve patient compliance. In the new area of computational biology, MATLAB can balance a variety of tasks.^[11] MATLAB tools have enabled the organization and distribution of other applications such as Microsoft Excel plug-ins for making graphs to qualify the statistical comparative results.

Besides, an interesting phenomenon of nonlinear system dynamics has been studied, which has theoretical and practical applications in many disciplines, especially in biological function networks. In recent years, several concepts of nonlinear dynamics have been discovered specifically for their utilization in medical science. In this context, cancer reflects a dynamic and multistage process that can be described mathematically by chaos theory, which can be visualized in fractal geometry.^[12] In this review, we focus on the molecular aspects of targeting, the MATLAB tool and chaotic principles in targeted drug delivery systems to improve the pk and pharmacodynamics (pd) profile of drug moieties. This effort will result in important advances against various cancers, as an urgent goal of the scientific world is to improve the health profile of cancer patients.

MOLECULAR ASPECTS OF DRUG TARGETING

The efficacy of conventional anticancer drugs is highly limited because of many barriers in pk and pd action due to poor penetration into the malignant tissue. This issue may also lead to multiple drug resistance, which subsequently leads to poor patient compliance. Moreover, the drugs also induce severe adverse effects on healthy cells. The pharmacological properties of drugs are highly influenced by the interaction between the drug and the receptor non-specifically at the cellular membrane level. However, drug diffusion into the cell is dependent on membrane-bound efflux pump transporters.^[13] Efflux pumps are proteins in the cell membrane that depend on proton motive force to efflux the drugs. Moreover, the efflux pumps are adenosine triphosphate-dependent energy pump transporters that are highly important in the development of multiple drug resistance.^[13,14] A targeted drug delivery system represents the most significant technique used to deliver drugs at cellular levels and is a highly challenging subject in pharmaceutical research. Therefore, the successful therapeutic efficacy of anticancer drugs is highly dependent on targeting one specific cancer cell without interaction with other healthy cells, which will be an important advance in cancer therapy that can be achieved by a nanoparticle drug delivery system

surface-linked with MABs.^[14-16] During the past two decades, nanoparticle drug delivery systems have been studied as a promising therapeutic approach against cancer. However, the pk profiles of free drugs and the drug-loaded nanoparticles are not the same.^[16] Furthermore, earlier studies suggested that the physicochemical properties of nanoparticles also dictate the pk profile after administration.

The immune response mechanism is based on self and nonself-discrimination. Tumor-associated antigens are a unique class of proteins that are expressed in some normal cells but are overexpressed in cancer cells. Immunologically, these antigens are a target for tumor-reactive T cells originating from the discharge of lymph nodes or in peripheral blood. Besides, tumor antigens can be developed due to point mutations, frameshift insertions, and deletion mutations and produced mutated peptides that are processed inside the cancer cells and presented on the surface of cancer cells, called neoantigens. Neoantigens are ideal targets for cell-mediated cancer immune therapy.^[17-19] Therefore, MAB-based therapies offer many advantages such as specificity, biodistribution, and long half-life; furthermore, these types of therapies are well tolerated and can overcome many aspects of drug-induced toxicity.^[20] The new therapeutic era is focused on targeted drug therapy using macromolecular proteins such as MABs that target specific ligands to enhance the efficacy of cancer cell treatment by not affecting healthy cells, which improves patient compliance.^[21] Besides, the safety profile and targeting efficacy are based on tumor-associated antigens that are expressed homogeneously at constant rates on the surface of the cancer cells. Studies have suggested that the use of antibody anticancer drug conjugates to target malignant cells is a sophisticated option for treatment. There are several categories of MABs targeting tumor antigens.

Hematopoietic differentiation antigens

These are glycoproteins associated with a cluster of differentiation (CD) types that expressed in lymphoid cell development [Table 1]. The following hematopoietic antigens are associated with cancer development.

CD20

CD20 is a nonglycosylated phosphoprotein expressed on the surface of mature naive B cells and is not expressed on stem cells or plasma cells. This protein is involved in the development and differentiation of B cells into effector B cells (plasma cells). Rituximab, tositumomab, and ibritumomab are the currently available anti-CD20 MABs approved for clinical use.^[22-27]

CD30

CD30 is a cell membrane protein of the tumor necrosis factor receptor family and is also known as TNFRSF8. This protein

Table 1: Hematopoietic molecular markers, targeted specific MAB's and their significance

Molecular markers	Expression cells	Specific MAB's	Disease condition	Comments	References
CD20	B cells	Rituximab	Chronic lymphocytic leukemia, thrombotic thrombocytopenic purpura, rheumatoid arthritis, non-Hodgkin's lymphoma	1. Approved by the US FDA for human use 2. Resistance development has been reported 3. SDDS has been screened using mesoporous silica nanoparticles against lymphoma B cells	[25,26]
		Tositumomab with iodine I 131 tositumomab	Certain types of non-Hodgkin's lymphomas	1. Approved by the US FDA for human use 2. Severe adverse effects have been reported	[27]
CD30	T cells	Brentuximab vedotin	Hodgkin lymphoma	1. Approved by the US FDA for human use 2. Resistance development has been reported	[29]
CD33	Myeloid stem cells, myeloblasts and monoblasts, monocytes/macrophages, granulocyte precursors	Lintuzumab	Acute myeloid leukemia	Not approved by the US FDA, it is under clinical trial Phase I studies	[31]
CD52	Lymphoid cells	Alemtuzumab	T and B cell lymphomas, lymphogenous malignancies	1. Approved by the US FDA for human use 2. Resistance development has been reported	[33]

MAB: Monoclonal antibodies

is a tumor marker antigen that is expressed on activated T cells, NK cells, and B cells. CD30 is a marker of Hodgkin lymphoma. Brentuximab is a MAB that targets CD30, which is found on Hodgkin lymphoma and anaplastic large cell lymphoma cells.^[28]

CD33

CD33 is a myeloid surface antigen that is expressed by leukemic blast cells of patients with acute myeloid leukemia (AML). Lintuzumab, an unconjugated, humanized anti-CD33 MAB, has modest single-agent activity against AML.^[29,30]

CD52

CD52 is expressed on the surface of mature lymphocytes, monocytes, and dendritic cells. This protein is associated with some types of lymphoma. Alemtuzumab, a humanized anti-CD52 MAB, is used for the treatment of acute lymphoblastic leukemia.^[32]

Cellular growth factors

Growth factors are polypeptides which are major growth-regulatory molecules that stimulate cell proliferation.

Signaling pathways regulate the normal physiology of cellular growth and the deregulation process leads to cancer [Table 2].^[33-46]

EGFR

EGFR is an epithelial growth factor receptor, also called ErbB1, a transmembrane protein involved in the growth of malignant cells. Anti-EGFR targets can suppress the growth of malignancy. Cetuximab, a MAB that inhibits the epidermal growth factor, is presently widely used in the treatment of colorectal cancer, head and neck cancer.^[33,34]

HER2/ERbB2

HER2 proteins are expressed on the breast cells from which breast cancer arises. Trastuzumab and pertuzumab are the targeted MABs against HER2.^[38-40]

HER3/ERbB3

Human epidermal growth factor receptor 3 (HER3) is a membrane-bound protein associated with malignant progression and is an important target for targeted therapeutic approaches. HER3 is overexpressed and activated in various cancer types such as breast, colon, ovarian, lung, and prostate.

Table 2: Cellular growth factors, targeted specific MAB's and their significance

Cellular growth factor	Functional aspects	Specific MAB's	Disease conditions	Comments	References
EGFR	1. Transmembrane tyrosine kinase receptor 2. Participates in the proliferation and survival of cancer cells	Cetuximab, panitumumab	Cancer of head and neck, lung, breast, colorectal, kidney, bladder, prostate, ovary, pancreas, brain	1. Cetuximab and panitumumab were approved by the US FDA. Both cetuximab and panitumumab have been reported for the development of resistance. 2. SDDS with cetuximab has been developed using iron oxide nanoparticles for cancer imaging and therapy, poly (γ -glutamic acid)-docetaxel against gastric cancer. SDDS with panitumumab conjugated gold nanoparticles has been against pancreatic carcinoma cell lines.	[34-37]
HER2/ERbB 2	1. Transmembrane receptor tyrosine kinases and plays a role in intracellular signaling 2. Regulate cell growth, survival, and differentiation	Trastuzumab, Pertuzumab	Breast cancer	1. Trastuzumab was approved by the US FDA. Pertuzumab was also approved by the US FDA as adjuvant therapy in combination with trastuzumab against HER2-positive metastatic breast cancers. Resistance to trastuzumab has been reported. The combination of trastuzumab and pertuzumab in permitted doses overcame the resistance development. 2. SDDS with trastuzumab has been developed using mesoporous silica nanoparticles with polymers and linked with trastuzumab antibodies against breast cancer.	[42-46]

MAB: Monoclonal antibodies, HER2: Human epidermal growth factor 2, SDDS: Smart drug delivery system

Seribantumab is a MAB that inhibits ErbB3 signaling and enhances its antitumor activity.^[41]

IGF-1R

The insulin-like growth factor receptor has tyrosine kinase activity and has been recognized to be involved in tumorigenesis and growth. This protein is highly expressed in malignant tissues, where it functions as an antiapoptotic agent by enhancing cell survival. IGF-1R MABs have been developed to target IGF-1R but are still under study.^[47]

Ephrin type A-receptor 3 (EPHA3)

EPHA3 is a tyrosine kinase receptor and has dynamic roles in cell adhesion, migration, and axon guidance during development and homeostasis. EPHA3 is expressed in the tumor vasculature in cancers of the brain, kidney, bladder, and melanoma. EPHA3 is commonly overexpressed

in glioblastoma. Ifabotuzumab is a MAB that has been developed to target glioblastoma multiforme but is still under study.^[48]

Vascular endothelial growth factor (VEGF)/VEGFR

VEGF is a glycoprotein that, along with its receptor VEGFR, is the key mediator of angiogenesis. Bevacizumab is a MAB that blocks the protein VEGF and inhibits cancer.^[49]

Cell surface differentiation antigens

Cell surface differentiation antigens are usually found on the surface of normal and cancer cells. These antigens are either glycoproteins or carbohydrate in nature. The present therapeutic approach has spurred research into new molecular targets, and specifically targeting tumor antigens by MABs has great potential to save patients. However, specifically

targeting cancer cells by MABs involve a deep understanding of cancer biology, immune clearance mechanisms, and *in vivo* pk/pd profiles. Knowledge of these aspects is essential for the characterization of the physicochemical properties of antibodies, analysis of the biodistribution and localization at the site of the malignant cell, and understanding of the spatial orientation of the cancer cells and MABs to determine the maximum possible attachment. However, targeting cancer cells only by MABs have limitations because the elimination of cancer cells is dependent on the immune clearance mechanism, where resistant factors are also an important component to nullify the effect of cancer. Thus, cancer therapy can be improved by a targeted drug delivery system using nanoparticles surface-linked with MABs.^[50]

A targeted drug delivery system in principle should block the growth and spread of cancer by interacting with specific molecules. However, targeting also varies based on the nature of the targeted molecule. In general, drug targeting can be grouped into passive targeting and active targeting. Passive targeting is highly influenced by enhanced permeability retention (EPR), which determines the diffusion of the nano-drug delivery system into malignant tissues through leaky tumor vasculature.^[51]

However, active targeting is focused on molecular ligand-receptor interactions. The interaction between molecular ligands on specific receptor molecules is highly dependent on the distance between the drug ligand and the receptor molecule and is a key factor for successful targeting. The delivered drug reaches the target site through blood circulation and extravasation. pk drug resistance is influenced by various physiological barriers imposed by cancer cells, the tumor vasculature, the microenvironment, and the spatial

orientation around the cancer cells, which all contribute to the pk resistance of cancer cells.^[52]

Nano-drug delivery systems with improved targeted efficacy to deliver the cytotoxic drug at the cancer site can overcome primary and secondary resistance in a reduced dosage form and thus overcome pk drug resistance. However, the interaction of nanoparticles with cancer cells is restricted due to the spatial orientation, the free space between the TAs on the cancer cells, and the spatial orientation available around a cytotoxic drug-loaded nanoparticle surface-linked with a MAB [Figure 1].

The distance between the MAB ligand and cancer targets is highly important to achieve target-specific treatment. Earlier reports showed that the distance between the ligand and receptor molecule should be <0.5 nm for successful targeting.^[53]

This can be expressed by the modified equation of Groh *et al.*, 2014^[52] as follows:

$$V1 \frac{dc1}{dt} = ak1.\sigma^2$$

where V1 is the extracellular space; c1 is the concentration of the nanoparticle; a is the area around the targeted molecule; k1 is the rate constant; and σ^2 is the distance between the targeted TA molecule and the MAB ligand with the nanoparticle.

Therefore, a successful targeted drug delivery system should meet certain criteria such as the following:

1. The system must bind to a specific molecule on the cell membrane.
2. The drug should be delivered at the site of tumor cells either by receptor-mediated interactions or through an EPR effect.

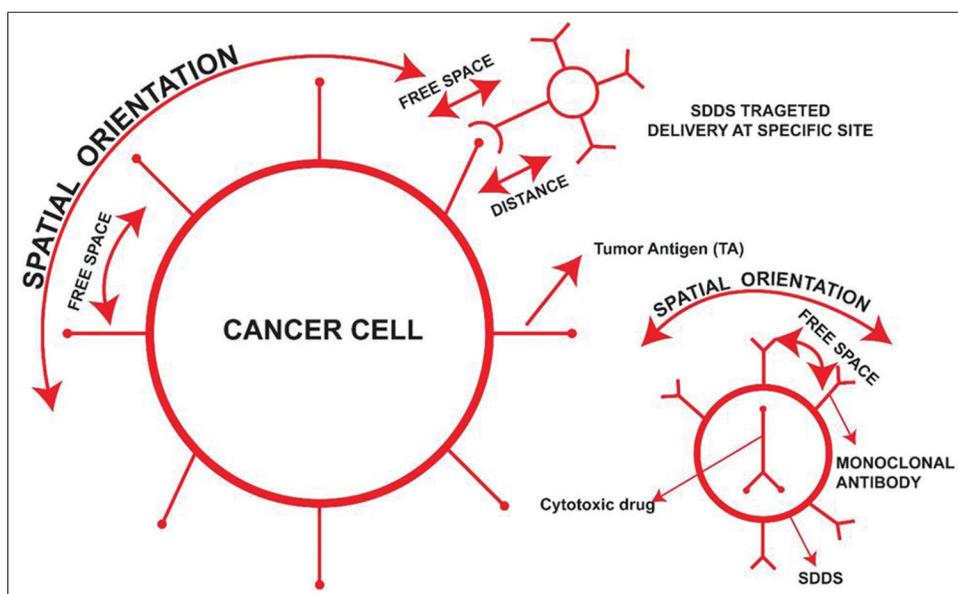


Figure 1: Impact of spatial orientation on the efficacy of a smart drug delivery system (SDDS). The targeted efficacy of SDDS to deliver the cytotoxic drug at the cancer site. The interaction of SDDS with cancer cells is restricted due to the spatial orientation, the free space between the tumor antigens on the cancer cells and the available spatial orientation

- The achieved pk profile must elicit the desired pd effect so that unwanted complications such as nonspecific action on other healthy cells can be avoided.

Overall, with the present therapeutic era of MABs, these drugs are playing more significant roles in cancer care, specifically rituximab and trastuzumab. Accordingly, the biopharmaceutical industry has focused on developing many MABs against various cancer drugs over the past 15 years.^[54,55] Research findings have proven that antibody-based therapies have many advantages such as biodistribution in the extracellular fluid space, good tolerance, and a long half-life.^[56] However, the immune response to TAs is derived from the interplay between the host immune response and the malignant cells. The anticancer immune response is directly linked to the concurrent inhibitory mechanisms. Therefore, a smart drug delivery system (SDDS) will be a better therapeutic approach to cure cancer. When developing an SDDS, it is mandatory to ascertain the successful target TAs on the cancer cells, which can be achieved by predicting the chaotic behavior of both cancer cells and SDDSs. These behaviors can be explained by 3-dimensional (3D) plots expressing the cancer growth and determining the efficacy of the target treatment [Figure 2].

MATLAB tool and chaotic principles for cancer targets

MATLAB, which is an abbreviation for Matrix Laboratory, is a high-performing language for computing technical aspects to build a more interactive environment for programming, visualization, and solutions expressed in numerical computation. The applications of MATLAB are highly focused on computational biology, bioinformatics, and biological sciences. Recently, Pfizer pharmaceuticals developed an integrated Systems for Pharmacology approach using MATLAB and SimBiology to model receptor-based drug targets and to identify the exact concentration of a drug molecule that is needed to elicit the required inhibition, as well as to simulate and analyze biological systems in the earliest stages of drug discovery.^[57] On the other hand, Chaos is an interesting complex phenomenon for understanding nonlinear systems and has theoretical and practical applications.^[58] The primary characterization of a chaotic system as nonlinear differential equations can be applied to both temporal and spatial aspects such as

- High sensitivity to initial conditions^[59]
- Pattern structure of a strange analyte.^[60]

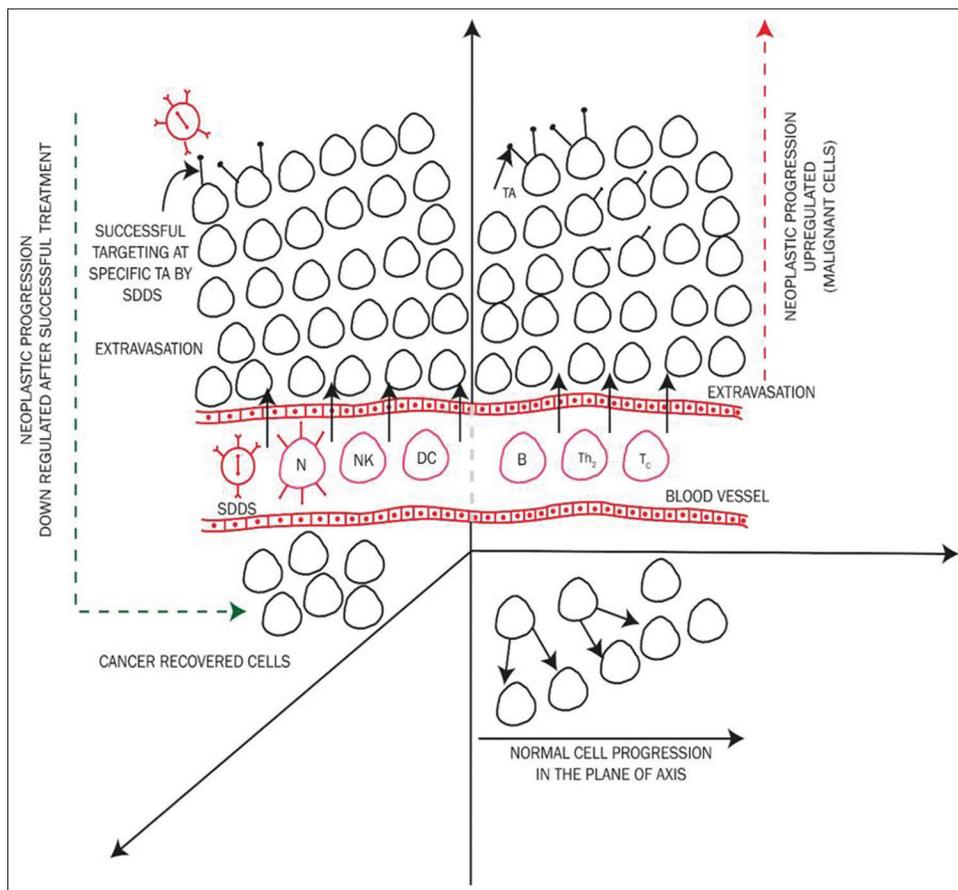


Figure 2: The chaotic behavior of cancer cells and smart drug delivery system (SDDS) and their successful target on the tumor antigens of cancer cells expressed as chaotic behavior model which is 3-dimensional plot expressing the normal cell progression, cancer development and determining the efficacy of the targeted treatment with SDDS

The first chaotic model was discovered by Lorenz in 1963^[61] and explained a 3D chaotic system; this was followed by many researchers who developed 3D smooth autonomous chaotic systems. Recently, researchers developed 3D smooth autonomous chaotic systems that can analyze various dynamic behaviors.^[62] The concept of the cellular dynamics of cancer and carcinogenesis has evolved with the development of multiple hypotheses where the chaotic process is the prominent dynamic process to determine the nonlinear fashion of cancer cell growth.^[63] Therefore, chaotic systems can be involved in genetics, extracellular and intracellular processes, and the development of tumors.^[64,65]

The successful targeting of a drug to a cancer cell in a microenvironment consisting of a group of cells is highly invasive, and there is a need to understand cancer progression. The understanding of and progress toward the present goal of targeting the cancer growth population by a clinical intervention can be achieved through various aspects of mathematical, physical, and computational techniques that have been developed for evaluating cancer growth. Unfortunately, interactions between healthy host cells, exponential cancer cell growth, and efficient drug targeting for cancer and tumor cells cannot be assumed, and the key parameters remain to be identified. Due to the interactions of cancer cell populations, problems arise, such as the genetic uncertainty of cancer cells and the unpredictability of cancer cell growth.^[66] Carcinogenesis population-based models, strange-attractor models, and four-dimensional spatiotemporal cancer models have all been investigated to understand the dynamics of cancer cells for treatment responses, metastasis, tumor growth, and strong nonlinear couplings.^[67] Cancer cell growth is different for every patient concerning their age, health, etc. These parameters must be clarified to understand the dynamic system characteristics such as sensitivity to initial conditions. Furthermore, if dynamic nonlinear system chaos is established, strategies could be used to adjust to fighting cancer using chaos control or chaos anticontrol. Regarding chaos in the brain, cardiac rhythm, and cell population dynamics have a better value than statistical linear methods. However, the earlier discussion is continued to be in the form of a dynamic analysis of healthy host cells, and a drug targeting growth model can provide insights through the application of MATLAB and Simulink tools. This model approach followed by data fitting is useful in analysis and scenarios regarding the efficacy of a therapeutic process; the investigation is motivated by a need to understand the behavior of cancer cell growth in a dynamic manner, specifically their chaotic features, if any. From a technical viewpoint, the Lorenz system is nonlinear, 3D, and deterministic.^[68]

A drug targeting growth model that exhibits chaos in the parameter range of interest is described below. Three new parameters α , β , and γ are introduced, and the variables are considered as a transformation of x_1 , x_2 , x_3 , and x_4 for Simulink computations and better clarity.

The resulting model is the following:

$$x_1 = 0$$

$$x_2 = \alpha (y-x)$$

$$x_3 = x (\beta-z) - y + \gamma$$

$$x_4 = \delta x y - z$$

Where $\alpha = 3.0$; $\beta = 26.5$; $\gamma = 0.74$; $\delta = 0.5$ (1)

where x_1 is the cancer cell density, x_2 is the number of healthy host cells before cancer appeared at time t , x_3 is the number of malignant cells at time t , and x_4 is the number of cells suppressed after drug targeting at time t . In the above equations, we can easily assume that α , β , and γ are the positive system parameters; x_1 , x_2 , x_3 , and x_4 represent the system state; and this time. The model consists of three cell populations. All of the parameters α , ρ , and β are motivated by the fact that the cancer cell represents a visual manifestation of a fundamental balance of forces. More precisely, the parameters signify the following measures: α is the healthy cancer cell volume (propagation/non-propagation fraction), β is the exponential cancer cell volume, and γ is the volume of cancer cells after drug targeting concerning efficient targeting/inefficient targeting.

The set of equations in (1) defines a drug targeting growth model, showing the competition in the flow of graph, as seen in Figure 3. Dashed lines represent the nonlinear interactions, and the sign describes the cancer growth (+) and suppression (-) by the drug targeting model. Dissimilar to what is frequently observed in this drug target model, the target is

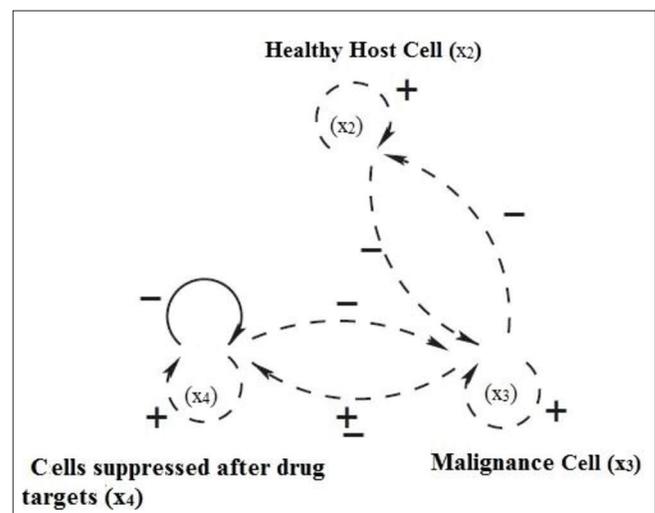


Figure 3: Graphical reorientation of the flow for the drug target cancer model. Dashed lines represent the nonlinear interactions, (+) the sign describes the cancer progression, whereas suppression of cancer progression by the drug targeting model is expressed as (-). Considering x_1 as an initial point of cancer development, $x_1 = 0$

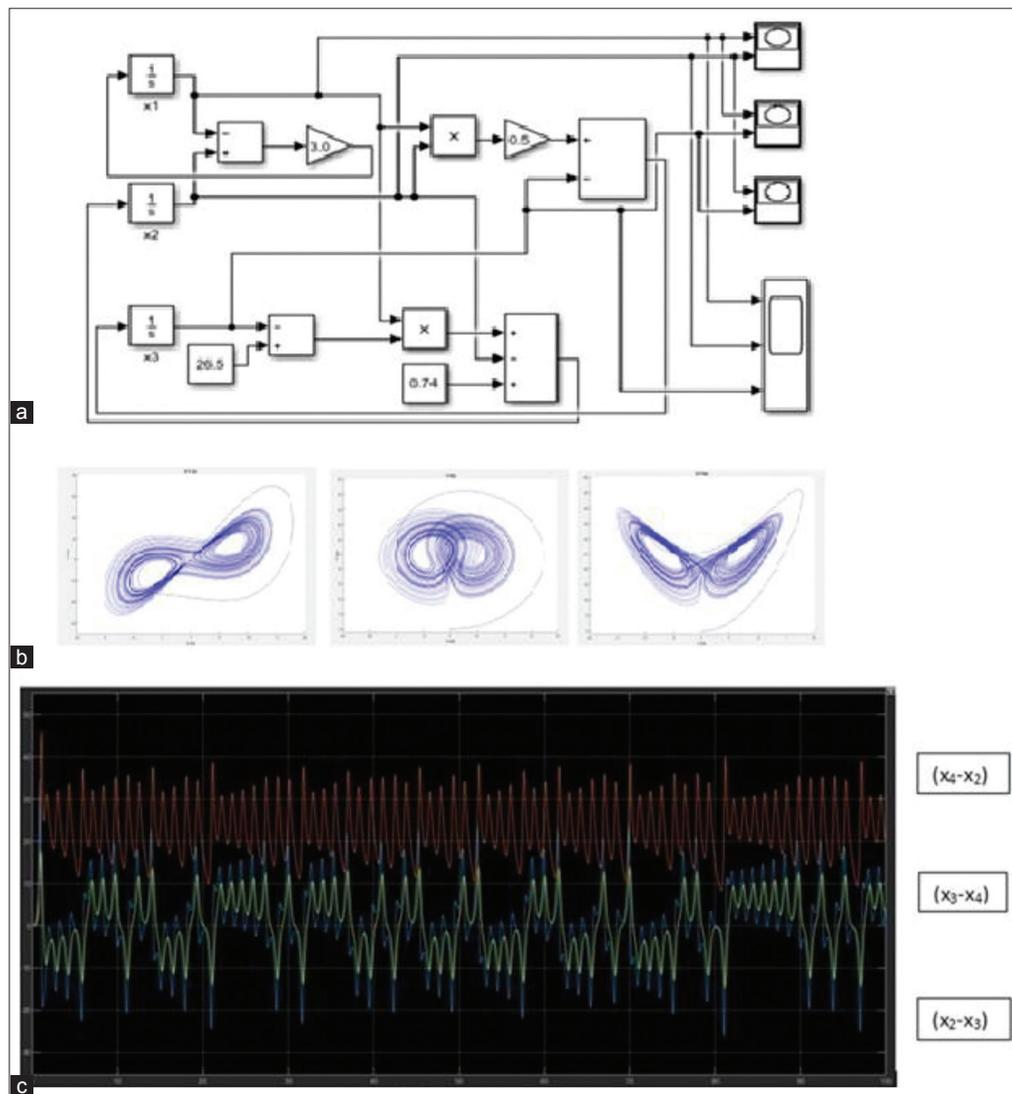


Figure 4: The chaotic pattern and Simulink of cancer targets: (a) Insight the analog circuit of the drug targeting cancer cell model; (b) Numerical simulation of phase portrait in the (x_2-x_3) , (x_3-x_4) , (x_4-x_2) ; (c) Time response of the system states in the (x_2-x_3) , (x_3-x_4) , (x_4-x_2)

not defined in a particular way. Nothing is stimulating the growth of a new cell, and all of the interactions between the dissimilar populations are suppressing this growth. There is no interaction between healthy host cells and cells suppressed after drug targeting.

The phase portraits and the corresponding power spectra of (x_2-x_3) , (x_3-x_4) , and (x_4-x_2) are shown in Figure 4a and b. The corresponding power spectra between the growth rate of healthy host cells, healthy host cells into an exponential cancer cell volume, and exponential cancer cell volume in the volume of cancer cells after drug targeting are shown. The time response of the system states in (x_2-x_3) , (x_3-x_4) , and (x_4-x_2) are shown in Figure 4c. The corresponding time evolution between the growth rate of healthy host cells, healthy host cells into an exponential cancer cell volume, and exponential cancer cell volume in the volume of cancer cells after drug targeting are shown.

CONCLUSION

The development of an SDDS against cancer will be an important advance in curing cancer since conventional drug therapy acts not only on cancer cells but also on adjacent normal cells. In the present modern therapeutic era, targeted specific MABs have been discovered against various cancers. Although many reports have addressed the successful treatment of MABs against various cancers, their efficacy is highly dependent on an immune clearance mechanistic approach and that may lead to drug resistance, which ends in the failure of treatment. During the past two decades, pharmaceutical researchers have focused on nanoparticle drug delivery systems for the treatment of cancer to limit the drug dosage and increase the pharmacokinetic and pharmacokinetic profiles. SDDSs are more target-specific and cytotoxic to only cancer cells; thus, harm to normal cells can be prevented. Although there are many

advantages to SDDSs, their action is highly challenging due to pharmacokinetic profiles of the specifically targeted cells, attachment of tumor antigens, and spatial orientation of the cancer cells/SDDS during targeting; these systems are still at the preclinical experimentation level today. Model-based drug development is an effective approach for success in preclinical experimentation work and the development of effective treatment strategies. To overcome the lacunae of SDDSs, the present goal of understanding and predicting targeted cancer therapy can be accomplished through the application of MATLAB tools and deterministic chaotic principles, which represent an important advance in the development of novel drug delivery approaches against cancer.

DECLARATION OF INTEREST

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