IIETA International Information and Engineering Technology Association
Advancing the World of Information and Engineering

Mathematical Modelling of Engineering Problems
Vol. 11, No. 12, December, 2024, pp. 3323-3332
Journal homepage: http://iieta.org/journals/mmep

A General Stochastic Model for Tumor Growth: Simulating Cardiac Tumor (Myxoma) Development

Noureddine Ouldkhouia*, Imane Elberrai, Khalid Adnaoui, Anas Benhachem

Laboratory Analysis, Modeling and Simulation LAMS, Department of Mathematics and Computer Science, Faculty of Sciences Ben MSik, Hassan II University of Casablanca, Casablanca B.P 7955, Morocco

Corresponding Author Email: noureddine.ouldk-etu@etu.univh2c.ma

Copyright: ©2024 The authors. This article is published by IIETA and is licensed under the CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0/).

https://doi.org/10.18280/mmep.111212

Received: 3 October 2024
Revised: 3 December 2024
Accepted: 10 December 2024
Available online: 31 December 2024

Keywords:
general tumor growth model, cancer growth model, stochastic tumor growth model, tumor growth volume, tumor size evolution

ABSTRACT

Tumors, whether cancerous or benign, are among the most prominent problems of our time, and creating mathematical models to study, understand, and predict their behavior is extremely important. In this article, we created a general stochastic model to study the development of tumor size and diameter. The significance of our model is that it can study tumor growth in general it takes into consideration the number of capillaries that are inside the tumors and the quantity of blood that enters the tumor as well as the efficiency of the nutrients. We applied this model to simulate the development of a tumor called Myxoma, which is a tumor that grows in the heart. In the simulation of the growth of the Myxoma tumor volume over time in days, we found that tumor volume may reach 7.56 cm^3 which is consistent with experimental studies which confirm that the tumor volume grows between 3.053 and 7.238 cm^3. As for the tumor diameter we have found that the change in diameter of tumor Myxoma ranges between 2 and 2.5 cm in a period of 360 days, and this is almost consistent with the real data where the size of the tumor diameter in the first year ranges between 1.8 and 2.4 cm.

1. INTRODUCTION

Cancer is one of the most deadly diseases in the world, causing the death of millions of people in recent years. The term cancer includes a wide range of diseases that can affect any part of the body, according to the World Health Organization; cancer killed about 10 million people in 2020, which is roughly equivalent to one in six cancer deaths. The most common types of cancer in the world are lung, breast, colon, rectum, and prostate cancer [1].

There is another term that refers to cancer, which is malignant tumors.

In this article, we will use the terms tumors and cancer, the distinctive characteristic of malignant tumors is the rapid growth of abnormal cells, as these cells grow beyond their normal boundaries and can spread and invade surrounding tissues in the body. This process is called Metastasis, which is metastasis that spreads more widely in the body, this process makes cancer more deadly [1]. The main objective of this article is to create a model to study how tumors grow over time.

In order to understand how these tumors grow and develop, many researchers have created mathematical models to predict and study this killer. In 2014, Benzekry et al. [2] discussed several mathematical models to study the development of tumors and how chemotherapy affects the growth of these tumors. These models are often considered simple models, such as the exponential model and the Gompertz model [2]. In the same context, Ledziewicz and Schättler [3] used the Fisher-Kolmogorov and Lotka-Volterra equations to study the development of tumors. There are other articles that study cancer growth using stochastic models, such as the study conducted by Doret and Moseley [4] and Lowengrup et al. [5], who used stochastic and deterministic modeling to model the growth of this disease, namely cancer [5].

In this article, we will follow a different approach from the classical methods of modeling the growth of tumors in general, whether they are malignant or not. The novelty of our model is that it can be useful in studying different types of tumors, and it takes into consideration the number of capillaries inside the tumor, the quantity of blood that enters the tumor, and also nutrient efficiency on the size of the tumor, instead the other models don't take into consideration different variables like the quantity of blood and the efficiency of nutrients.

The specific research questions we are aiming to answer are how can we predict the size of the cancer and what is the relationship between nutrients, the speed of blood entering the tumor, and the size of the tumor? In this article, we will focus on answering these two questions by modeling the growth of cancer volume and finding the relationship between nutrients and their concentration in the blood, the speed of blood entry into tumors, and the size of the tumor, whether it is malignant or not. First, we will review the literature over the past years, where we will focus on the methods used in modeling. After that, we will present some statistics that we have collected about the most common types of cancer and the death rates they cause annually. After that, we will review the stages of development of the normal cell and the difference between it

and the cancer cell. In the next stage, we will model the growth of tumor volume over time. In the penultimate stage, we will simulate the model and compare it with data from reality, where we will find integration between the results of the model and previous studies. Specifically, we will focus on applying the model to a type of non-cancerous tumors that grow in the heart, due to the availability of some data about it, where we will learn about this tumor in the application stage of this article.

2. LITERATURE REVIEW

For a long time, researchers from all over the world have been interested in finding ways to study tumors, whether benign or malignant, in order to understand how they grow and develop, and also to find ways to treat them. In this review of the literature, we will review the most important methods used during the past few years.

Trobia et al. [6] used dynamic logistic modeling to study the growth of brain cancer, specifically studying the interaction of gliomas and neurons. They used this model to study the effect of chemotherapy and how it can be used in a way that kills glioma cells with a minimum of neurons. This study concludes that adopting appropriate strategies can theoretically allow us to use chemotherapy to kill gliomas with minimal damage to neurons.

Later research was done by Khaliq et al. [7], who used fuzzy modeling to model cancer growth in the article, aiming to model tumor growth in a fuzzy environment using differential equations in order to model tumor growth more accurately by taking into account that despite the presence of data, there is still a certain percentage of error. This is why Rubeena Khaliq and others chose fuzzy modeling. The study concludes that the fuzzy model will reduce uncertainty by finding parameters using real data coming from clinical trials [7].

Ghaffari Laleh, et al. [8] looked at how well six classical mathematical models can predict tumor growth in patients receiving chemotherapy and immunotherapy. The study used data from 1472 patients with solid tumors and applied these common mathematical models: Exponential, Logistic, Classic Bertalanffy, General Bertalanffy, Classic Gompertz, and General Gompertz models. The goal was to see how well these models fit the tumor growth patterns and predict treatment results. Ghaffari Laleh et al. [8] conducted two experiments: the first used all available patient data, and the second focused on using early data to predict how tumors would grow later on. To find the best model parameters, they used optimization methods like differential evolution. Their findings showed that the Gompertz model performed the best, offering a good balance between accuracy and simplicity. The General Bertalanffy model also did good but was more complex. Interestingly, early treatment responses did not strongly predict the final outcomes, which shows the need for more detailed models to forecast tumor progression. Overall, the research provides a useful tool for evaluating cancer treatments using standard clinical data [8].

In the same context, Wei [9] used a dynamic model for triple-negative breast cancer, where the model focused on studying the interaction of immune cells and cancer cells. One of the most prominent findings of this study is that in the case of a model immune system, the immune system can eliminate a relatively small tumor by simulating the model using certain parameters. This article also concluded that natural killer cells can effectively eliminate cancer cells.

In the same year, Alinei-Poiana et al. [10] presented that fractional calculus can improve tumor growth modeling. They took four well-known models used for measuring tumor volume and modified them to include fractional calculus. The models they focused on were the Exponential, Logistic, Gompertz, General Bertalanffy-Pütter, and Classical Bertalanffy-Pütter models, and they applied these to data from both treated and untreated tumors. In their work, Tudor Alinei-Poiana et al. [10] compared the fractional models with the traditional integer-order models. To do that, they looked at the Mean Squared Error (MSE) to measure how accurate each model was. The results showed that the fractional models performed much better, with their MSE being at least 50% lower than the traditional models. Alinei-Poiana et al. [10] have shown that fractional calculus, which has a memory feature, is well-suited for describing biological processes like tumor growth. The fractional models provided a better way to predict how tumors evolve, making fractional calculus a promising tool for improving cancer modeling and treatment in the future.

Flandoli et al. [11] presented a model that explains how solid tumors grow by focusing on the interaction between cancer cells, oxygen levels, and the formation of new blood vessels, known as angiogenesis. The model uses a stochastic approach, treating cancer cells as individual units that multiply based on how much oxygen is available around them. Meanwhile, oxygen and VEGF are described using partial differential equations.

The model shows how the tumor evolves over time, both before and after new blood vessels start to form. It highlights how cells divide into different regions of the tumor, with proliferating cells near the outer layers where there's more oxygen and hypoxic cells deeper inside.

Through numerical simulations, Flandoli et al. [11]'s model proves to be accurate in reflecting how tumors grow and change. The detailed, microscopic perspective also makes it possible to adjust the model to specific patients, potentially leading to personalized cancer treatments.

Returning to the dynamic models, Azizi [12] studied the importance of mathematical models in studying the growth and understanding the development of tumors by presenting a three-part dynamic model, explaining that it is important to combine mathematical and physical models to predict tumor behavior and also the effect of some physical factors such as the pressure applied to the tumor and others on its growth and the formation of capillaries that feed the tumor. In order not to forget, the article presented a common physical model in the field of tumor modeling called the reaction-diffusion-advection equation. The article concludes that mathematical oncology, in conjunction with experiments, will lead to finding effective strategies to understand the hidden aspects of the development and growth of tumors in general and cancers in particular, and will also enable the creation of new approaches to accelerate the process of finding appropriate treatments [12].

There are other studies that use different types of mathematical models such as modeling by artificial intelligence to detect cancer and others, but in this review of the literature, we focused on the most prominent models and studies that were conducted in the past few years, which we were exposed to in the research phase to create the stochastic model, which is the focus of this article. However, through all these articles that we discuss, we conclude that mathematical

models play a vital role in understanding and predicting the growth of tumors, both cancerous and benign, and this will accelerate the process of finding treatments and medications for these tumors.

In this literature review, we have seen different researches on the topic of tumor growth. In our model, we will cover an important gap because we will take into account to create our model the quantity of blood inside the tumors and also nutrient efficiency to model and predict the tumor size, and this method of modeling tumor growth is a new approach. The researches that were done before us and that we have mentioned in the literature review did not include these variables in their model which we will consider into account in our article.

3. METHODOLOGY

Before going into the details of the model, let's review some statistics we have collected.

3.1 Some statistics about cancer

3.1.1 Cancer prevalence by continent

There are continents that are characterized by a higher number of cancer cases than others, and this is according to the statistics presented by the World Health Organization on its official website [1], where Figure 1 shows that Asia is sweeping the first place in terms of the number of cancer cases.

This may give an idea that cancer infection can be affected by geographical factors, although we will not include geographical factors in our model, but we present statistics to enrich this work and contribute to understanding this disease.

To make this data clearer, we have represented it on a world map. In Figure 2, we clearly see that Latin America, the Caribbean region, and the African continent are the places with the fewest cancer cases. This is due to several reasons.

Through these statistics, we find that cancer not only invades and destroys the human body, but also invades the world day after day and claims millions of lives around the world.

3.1.2 The most common types of cancer in the world

There are many types of cancer that affect the human body, and there are more common types than others. According to statistics from the World Health Organization published on its website, breast cancer comes in the first stage in terms of the number of infections in the world, with about 418,677 infections in the year 2022, followed by prostate cancer, which affected about 329,035 people in the year 2022 as shown in Figure 3.

In most cases, these cancers lead to death in the absence of an effective treatment for these cancers. Below, we will gradually understand how cancer cells multiply and tumors grow to finally reach a model for studying the growth of tumors in general, whether cancerous or otherwise.

3.2 Tumor growth volume modeling

3.2.1 Stages of cell development

In order to model the growth of cancer cells, we need to understand how they work, which is a very complex process. Therefore, in this section, we will discuss some of the basics of how a normal cell divides and the most prominent differences between a cancer cell and a normal cell.

A cell, whether cancerous or normal, goes through four basic stages as shown in Figure 4.

1) In stage G1 or the initial growth stage, the cell increases in size and prepares the components necessary for DNA replication, this stage is considered important.

2) In stage S or synthesis stage, the cell replicates its DNA in order to divide.

3) In stage G2, it is the stage of preparation for cell division, where the cell completes the preparation of the necessary components for cell division.

4) In stage M, which is the final stage, the cell divides into two daughter cells.

Cancer cells, like normal cells, go through the same stages as mentioned, but there are some differences that we will discuss [13].

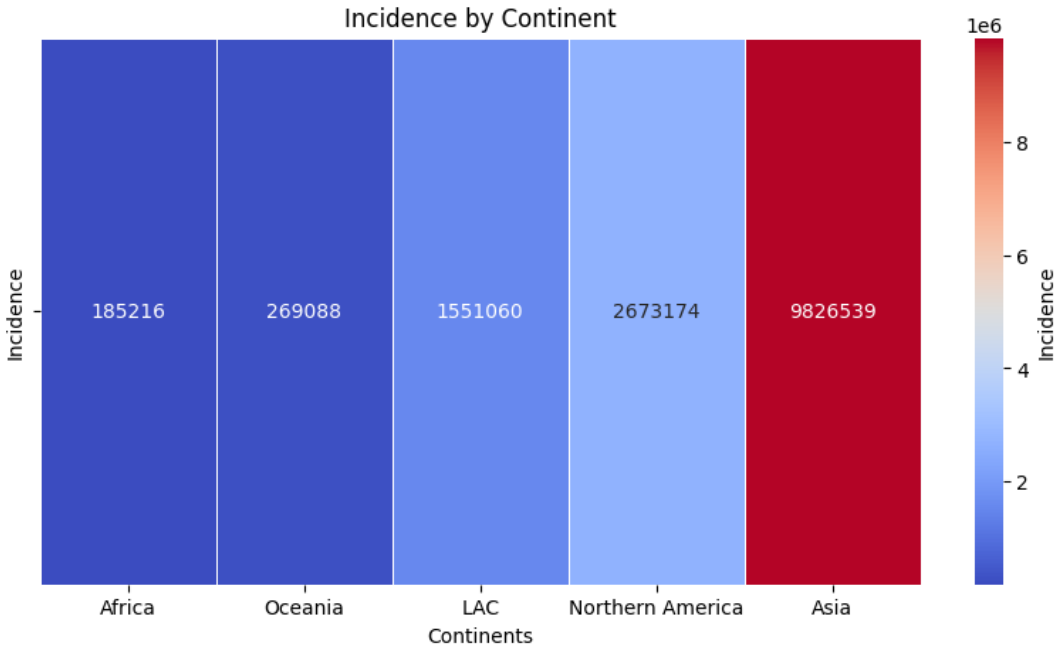

Figure 1. Number of cancer cases by continent

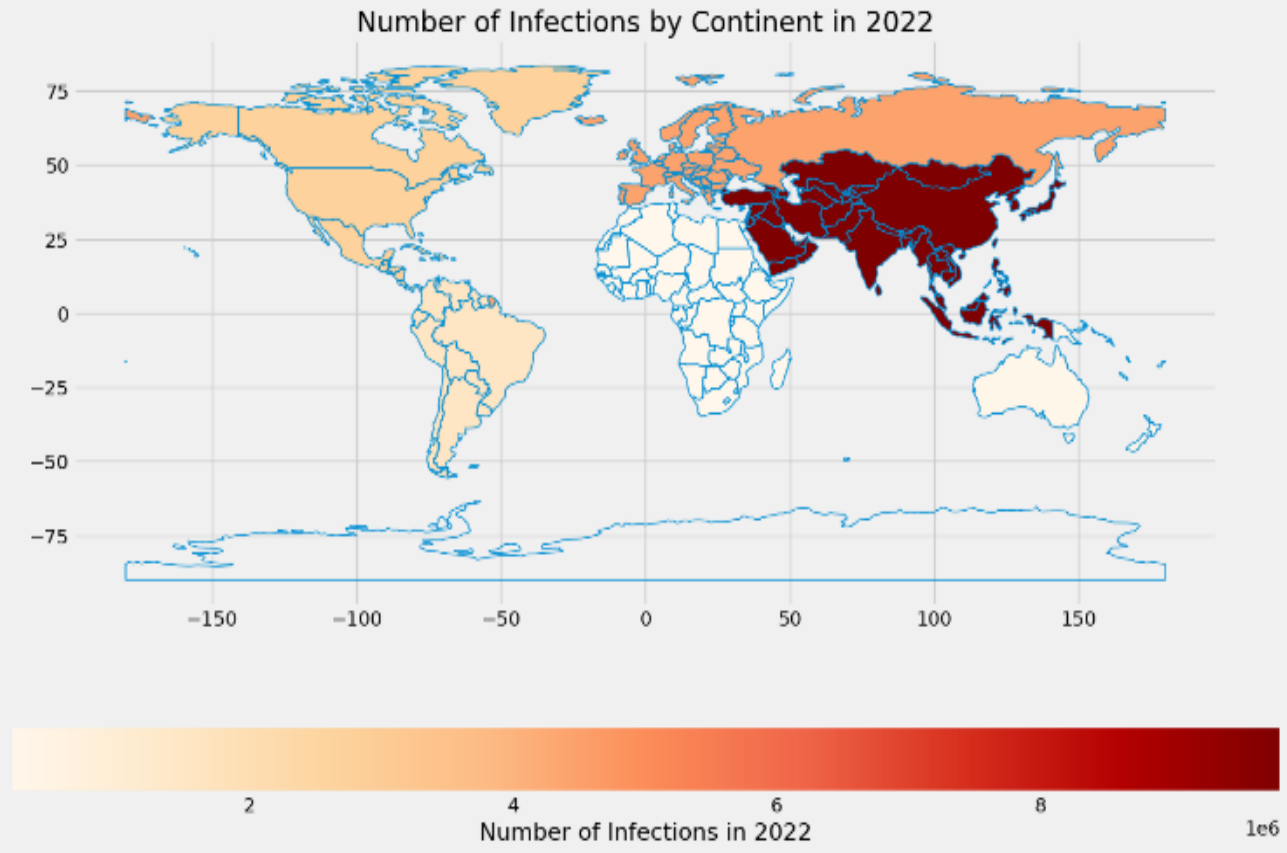

Figure 2. Continents most affected by cancer

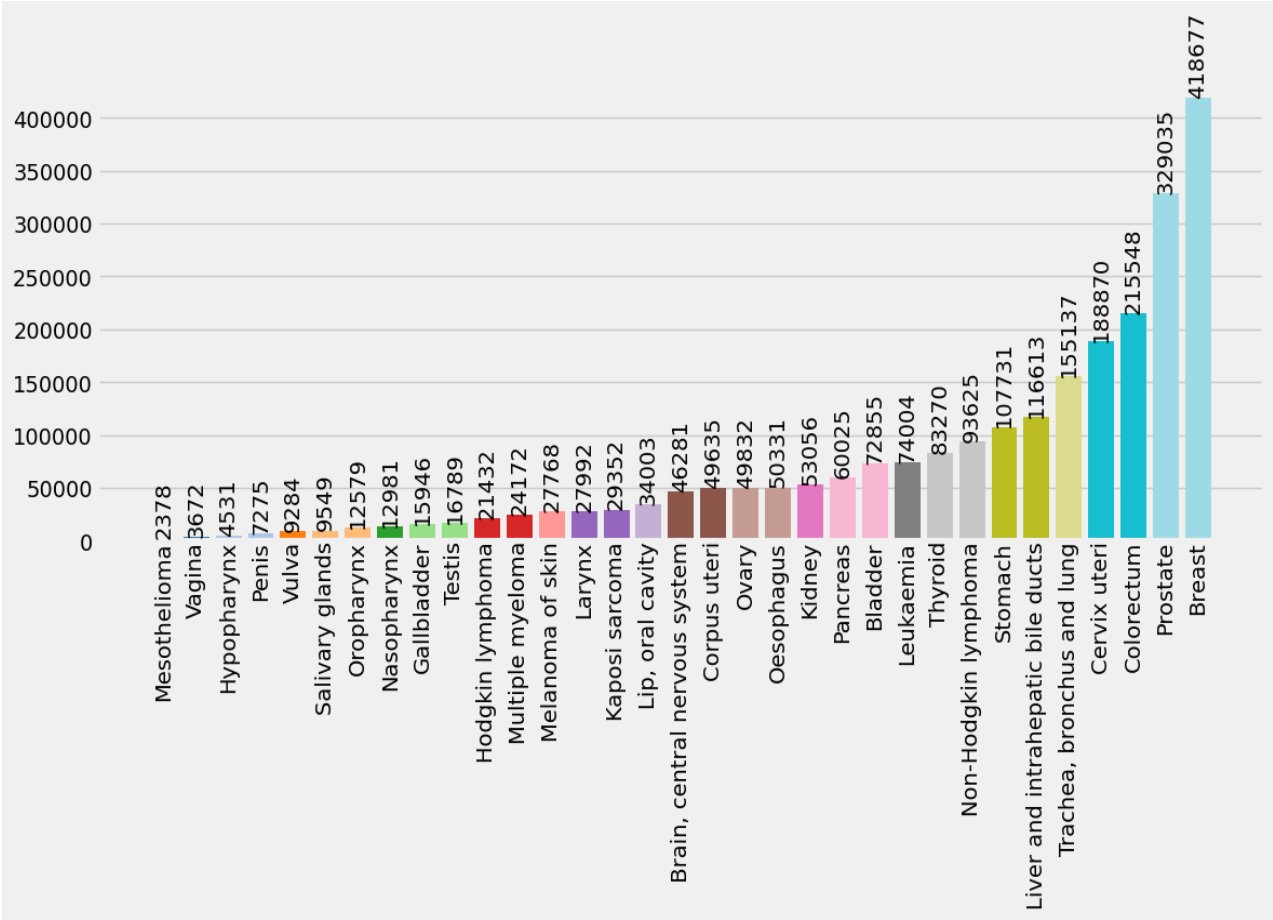

Figure 3. The most common types of cancer in the world

One of the most notable differences is the regulation of the cell cycle, as in normal cells the cell cycle is regulated regularly and precisely programmed through several different mechanisms or checkpoints that ensure that all stages are respected and that the cell is not advanced to the next stage before the specified time, and also if there is a problem in the cell, something like damaged DNA.

In contrast, in cancer cells these control mechanisms are often weakened or removed, allowing the cell to divide in an unfair and uncontrolled manner, and there lies the problem of cancer cells [14].

In normal cells, there is a mechanism called apoptosis or programmed cell death, which eliminates damaged or abnormal cells, which makes the cells work efficiently and regularly. In cancer cells, these cells often develop resistance to apoptosis, which allows them to survive even in the presence of damage or abnormalities, which is the most prominent thing that makes cancer cells this way, i.e., abnormalities and DNA damage [15].

Unlike normal cells, cancer cells can divide indefinitely and more randomly. They ignore the signals and mechanisms that indicate that division in normal cells stops when new cells are not needed or when they are otherwise damaged. Cancer cells act independently and divide more aggressively [16]. This makes cancer cells more powerful and dangerous.

Similar to normal cells, cancer cells can stimulate the formation of new blood vessels to supply themselves with nutrients allowing them to grow strongly and spread to other parts of the body. Cancer cells can also dominate the consumption of nutrients through these blood vessels, which negatively affects normal cells [17].

Invasion and spread in the body, as cancer cells can spread in the body and invade surrounding tissues in advanced stages, and this characteristic is not present in normal cells.

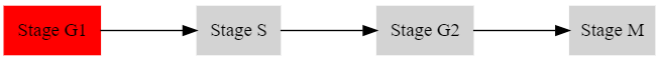

Figure 4. Stages of cell development

3.2.2 Cancer growth model

Definition (Tumor)

We will define a tumor as a mass of cells. Unlike normal cells, tumors are formed when cells multiply excessively and out of control. Cancer cells escape the mechanism of programmed cell death. Tumors can be classified into two main categories:

Benign tumors: This type of tumor is considered cancerous but does not spread in the body, but can cause some problems such as pressure on surrounding organs.

Malignant tumors: These tumors are cancerous, spread in the body, and can invade the surrounding areas [18].

3.2.3 Modeling the amount of blood entering the tumor at moment *t*

To model tumor growth, we first need a general understanding of the model, as the tumor takes all nutrients from the blood. We will rely on this assumption to model tumor growth. In the beginning, at moment *t*, when blood enters the tumor, we assume that a quantity Q of blood enters the tumor through a certain number of capillaries, which we will symbolize as C, as this quantity of blood contains the nutrients that the tumor will use for nutrition. However, we must take into account that the effect of nutrients on the tumor can vary depending on their concentration and other variables. Therefore, we must take into account the effectiveness of nutrients in increasing the size of the tumor, i.e., the percentage of the effect of the type of nutrients entering the tumor on increasing its size and the speed of its growth, which we will symbolize as E_N (see Figure 5).

So we can express the tumor growth with the following equation:

$$TS(t+T) = C_N Q(t) E_N(t) \tag{1}$$

where, TS is the tumor volume and T is the time period between the blood entering the tumor and the effect of nutrients on the tumor volume. We will return to this equation in detail after extracting $Q(t)$ and $E_N(t)$.

In our model we will need to know the amount of blood entering the tumor at each moment *t* (see Figure 6).

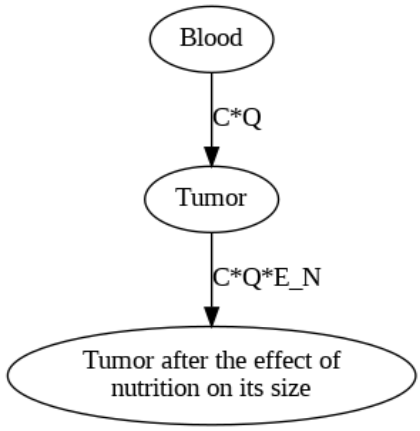

Figure 5. The amount of blood entering the tumor

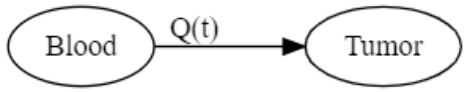

Figure 6. The amount of blood entering the tumor

For this purpose, in this paragraph, we will model the amount of blood entering the tumor at each moment *t*.

For this, we will use the following simplified Navier-Stokes equation:

$$\rho\left(\frac{\partial v}{\partial t} + (v.\nabla)v\right) = -\nabla p + \alpha\nabla^2 v \tag{2}$$

where, ρ: the density of blood in kg/m^3. α: the dynamic viscosity of blood in Pa.s. v: the speed of blood in m/s. p: the pressure in Pa.

The Navier-Stokes Equation is a basic equation for studying the behavior of fluids and liquids. What is important to us here is using it to extract the speed of blood entering the tumor. Since blood is a fluid, we can apply this equation here to extract the speed of blood, which we will need to know the amount of blood entering the tumor.

We assume that the flow of blood is laminar, i.e., $(v.\nabla)v = 0$, where, ∇ is a vector differential operator, we don't need details about it.

The equation becomes as follows:

$$\rho\frac{\partial v}{\partial t} = -\nabla p + \alpha\nabla^2 v \tag{3}$$

We assume that the blood flows in one direction x, so the equation becomes as follows:

$$\frac{\partial v_x}{\partial t} = -\frac{1}{\rho}\frac{\partial p}{\partial x} + \frac{\alpha}{\rho}\frac{\partial^2 v_x}{\partial x^2} \tag{4}$$

Therefore, the blood velocity is:

$$v_x(t) = -\frac{1}{\rho}\int \frac{\partial p}{\partial x}dt + \frac{\alpha}{\rho}\int \frac{\partial^2 v_x}{\partial x^2}dt \tag{5}$$

Blood enters the tumor through the capillaries (see Figure 7) at a speed v_x at time t.

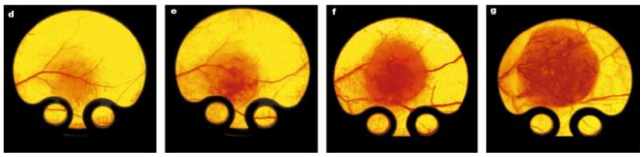

Figure 7. Tumor capillaries [19]

We assume that the average width of the capillaries is C_m and that the average radius of the capillaries is R_m by meter (We chose the meter only to unify the units, but on the practical level we will work with the millimeter). Then we can express the average amount of blood Q_m (by m^3/s) entering the tumor at time t as follows:

$$Q_m(t) = \pi R_m^2 C_m v_x(t) \tag{6}$$

Finally, we get the equation for blood entering the tumor at moment t.

$$Q_m(t) = -\frac{\pi R_m^2 C_m}{\rho}\int \frac{\partial p}{\partial x}dt + \frac{\pi R_m^2 C_m \alpha}{\rho}\int \frac{\partial^2 v_x}{\partial x^2}dt \tag{7}$$

Definition (Nutrient Efficiency Equation)

We define the Nutrient Efficiency Equation as follows:

$$E_N(\mathrm{t}) = \lambda \frac{N(t)}{K_m + N(t)} \tag{8}$$

where, $N(t)$ represents the nutrient concentration at time t.

λ is constant, as it gives the relationship between the size of nutrients and their effect on tumor growth in grams, as its unit is grams per liter (L/g).

K_m is the half-saturation constant, which indicates the effectiveness of nutrients on cell growth at half.

This equation is derived from the Michaelis-Menten Equation [20].

3.2.4 Tumor growth model

In this section, we will model the evolution of tumor size over time.

To model the development of tumor size, we will develop a simplified algorithm for how tumor size develops (see Figure 8). At first, the tumor takes blood through the capillaries, then processes it and extracts the nutrients and oxygen carried by the blood, as the blood contains a concentration of C_n of nutrients and also a concentration of oxygen. It also gets rid of waste and carbon dioxide through the blood that comes out of the tumor [21].

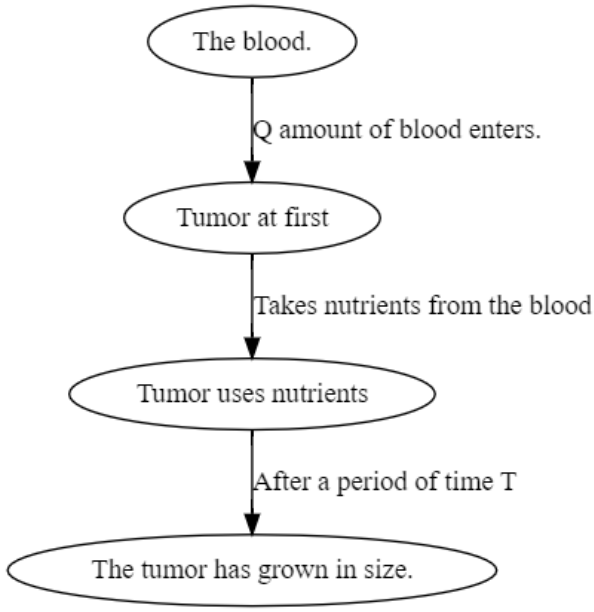

Figure 8. Tumor growth stages

We assume that after a period of time T from the beginning of the tumor's consumption of nutrients, its size increases, i.e., after the consumption of nutrients at moment t, for a period of time T, its effect on the increase in the size of the tumor appears, and thus we can express the development of tumor size growth in the following model:

$$TS(t+T) = C_N Q(t) E_N(t) \tag{9}$$

After using the expressions of Q and E_N from the Eqs. (7) and (8) in TS we get:

$$\begin{aligned} &TS(t+T) \\ &= -\frac{\pi R_m^2 \lambda C_m C_N}{\rho}\frac{N(t)}{K_m + N(t)}\int \frac{\partial p}{\partial x}dt \\ &+ \frac{\pi R_m^2 \lambda C_m C_N \alpha}{\rho}\frac{N(t)}{K_m + N(t)}\int \frac{\partial^2 v_x}{\partial x^2}dt \end{aligned} \tag{10}$$

We put

$$\begin{cases} \xi_1(t) = -\dfrac{\pi R_m^2 \lambda C_m C_N}{\rho}\dfrac{N(t)}{K_m + N(t)} \\ \xi_2(t) = \dfrac{\pi R_m^2 \lambda C_m C_N \alpha}{\rho}\dfrac{N(t)}{K_m + N(t)} \end{cases} \tag{11}$$

Thus, it becomes as follows:

$$TS(t+T) = \xi_1(t)\int \frac{\partial p}{\partial x}dt + \xi_2(t)\int \frac{\partial^2 v_x}{\partial x^2}dt \tag{12}$$

TS is the growth tumor size over time after a period of time T, where the tumor has consumed nutrients from moment t to moment T.

We must take into consideration that the model in our hands does not take into account the fluctuations and random factors that affect the growth of the tumor size. For this reason, we will add the random variable ϵ to the model, as this variable represents natural randomness and we have used this approach previously to express random changes [22].

$$\epsilon \sim \mathcal{N}(0, \sigma^2) \tag{13}$$

where, σ represents the standard deviation of the noise.

Thus, the final model becomes as follows:

$$TS_{\epsilon}(t+T) = \xi_1(t) \int \frac{\partial p}{\partial x} dt + \xi_2(t) \int \frac{\partial^2 v_x}{\partial x^2} dt + \epsilon(t) \tag{14}$$

The reason we chose the random model is to obtain more accurate results and reduce the error rate in predicting the results.

Regarding the random part of the model, which in our case we express as a random variable, it can be expressed in other ways, such as adding the Bruneian motion or adding the stochastic process. As an example of these two uses, see references [23, 24].

3.3 Results and simulation

Before going into details, we point out that the data used here is partial data, meaning that we only have information to clarify more, for example, we found that the growth of tumor size during a year, ranges between 3.053 and 7.238 cubic centimeters (These values were extracted in cubic centimeters and the average tumor growth was estimated) during a year, but we do not have other details [25, 26]. The second type of data is the parameters, which we obtained from articles and which we will refer to in front of each parameter we used. The parameters here are the constants of the model. It should be noted that obtaining more accurate data that contains more details requires clinical trials.

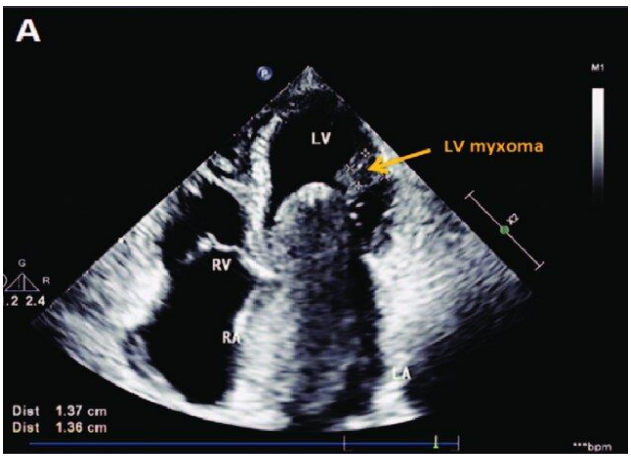

Figure 9. Myxoma of the heart [27]

In this section, we will apply our model to a type of heart tumor called Myxoma (see Figure 9), also called cardiac tumor or heart tumor. This tumor often grows on the wall that separates the two sides of the heart, whether the right or left. About 75 percent of these tumors occur in the left atrium of the heart and can occur in other places in the heart [28, 29].

These tumors are considered non-cancerous, but they cause serious problems, the most prominent of which is causing blockages, as fluids from the tumor exit into the bloodstream and may cause blockages in the brain, lungs, or one of the extremities, which may lead to a stroke, pulmonary embolism, and others. 40 percent of those infected with these tumors suffer from one of the blockages [30].

The larger the tumor, the greater the likelihood of problems resulting from it, as it can obstruct blood flow inside the heart, especially at the atrioventricular valve. These tumors can also affect the heartbeat, affect the regularity of the heartbeat, and other functions [31, 32].

In order to apply the model to this tumor, we will need the constants and the definitions of the functions that we will need in this case.

Our model is as follows:

$$\begin{aligned} TS\epsilon(t+T) &= C_N Q(t) E_N(t) + \epsilon(t) \\ TS\epsilon(t+T) &= C_N \pi R_m^2 C_m v_x(t) \lambda \frac{N(t)}{K_m + N(t)} + \epsilon(t) \end{aligned} \tag{15}$$

In the following, we will assume that T=0 just to simplify the model.

In order to simplify the model from the practical point of view, we will take

$$N(t) = \exp(at) \tag{16}$$

where, a is a constant, and the form of the function $N(t)$ is chosen [33, 34].

Regarding the concentration of nutrients in the heart or in the vicinity of the tumor, i.e., the concentration of glucose, it is about $C_N = 5.5mM$ (millimoles per liter) or $C_N = 0.991g/L$ [35].

The average Myxoma contains between 30 and 60 microscopically visible capillaries that it forms to obtain nutrients. We will take the average between the two values, i.e., 45 capillaries on average, and thus we will take $C_m = 45$ [36].

The average radius of these capillaries is between 2.5 and 5 micrometers. By taking the average between these two values, we get $R_m = 3.75\mu m$ or $R_m = 3.75 \times 10^{-6}$ m [18].

In general, the blood velocity in the capillaries ranges between 0.03 and 0.1 centimeters per second, i.e., the average between the two values is 0.065 centimeters per second. Thus, $v_x = 0.065$ cm/s, i.e., $v_x = 0.065 \times 10^{-2}$ m/s and $K_m = 0.0036$ L/g [37, 38].

Taking λ=0.84138 L/g, this constant using information about this tumor has been estimated [25].

Figure 10 shows the simulation of the growth of the Myxoma tumor volume over time per day, as we assumed that σ is between 0.15 and 0.20, where we note that the tumor volume may reach 7.65 cubic centimeters in 360 days, and this is consistent with previous studies, which confirm that the tumor volume grows between 3.053 and 7.238 cubic centimeters [25, 26].

To know the change in the size of the tumor diameter, we will use the volume calculation where $V(t) = TS(t)\tau$ and thus we get

$$V(t) = TS_{\epsilon}(t)\tau = \frac{4}{3}\pi r(t)^3 \tag{17}$$

where, $r(t)$ in cm represents the tumor radius at moment t and τ represents the maximum time period we want to simulate the model for, after calculation we get a model for the evolution of the tumor diameter size as follows:

$$r(t) = \sqrt[3]{\tau \frac{3TS_{\epsilon}(t)}{4\pi}} \tag{18}$$

It is noted from Figure 11 that the change in the size of the tumor diameter ranges between 2 and 2.5 cm over a period of

360 days, which is almost consistent with the real data [39]. (Clinical presentation of left atrial Myxoma.) Where the growth rate of the tumor ranges between 1.8 and 2.4 cm per year, meaning that the size of the tumor diameter in the first year, ranges between 1.8 and 2.4 cm, where the growth rate of this tumor is somewhat slow. In Figure 11, the change in the size of a Myxoma in centimeters after 5 years, where its size reaches between 4 and 5 cm, where Reiter et al. [39] confirmed that the size of a Myxoma is 5 cm on average, and it can exceed 5 cm in non-pathological cases, where this is due to complications resulting from other diseases, according to the study conducted by Kato et al. [40]. Through simulation, it appears that the growth of the tumor is slow in the normal state. This is consistent with previous studies, such as the study conducted by Reiter et al. [39] and Kato et al. [40], where this study confirms that the growth of Myxoma tumors as a special case and mucosal tumors in general is slow with the passage of time.

We notice in Figure 12 that the development of the tumor diameter over 5 years increases with time, and this is while maintaining the same conditions in which the tumor appeared. This is what takes us to the following observation: the model measures the average development of either the size or the diameter of the tumor. The model also measures the development of the tumor size in general and not specifically, i.e., the model does not take into account the age of the patient or whether the patient with the tumor has other diseases, etc., but this does not mean that the model is not applicable in special cases. The constants can be determined according to the special case.

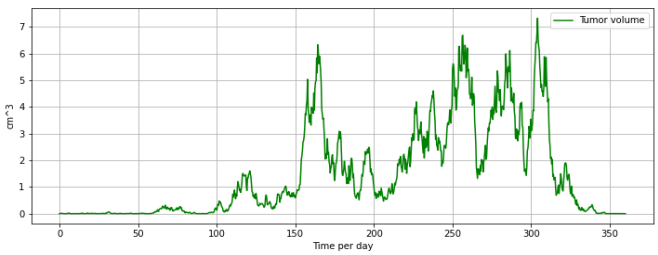

Figure 10. Myxoma volume changes over time in cm^3

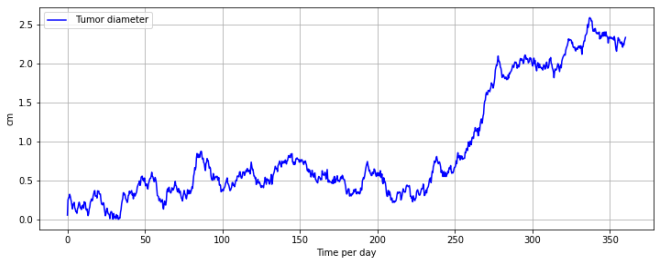

Figure 11. Change in the size of the Myxoma diameter over time in centimeters

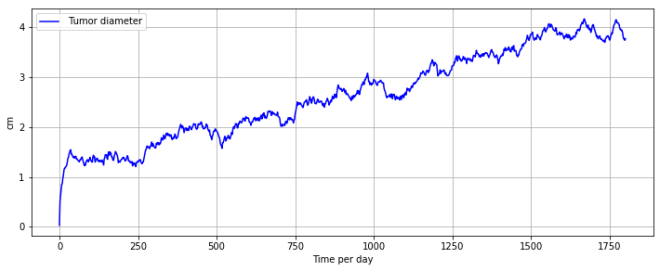

Figure 12. Myxoma size progression over 5 years

4. DISCUSSION

The model we have is still in its infancy and needs more study and development. There are potential applications for the model in clinical studies where the model can be used to predict the development of tumor size through the nutrients the patient takes and the average capillaries that enter the tumor, i.e., the capillaries that the tumor feeds on. Doctors can know this information using devices dedicated to this purpose. The model can also be used to study the effect of the growth of new capillaries on the development of tumor size by taking the constant C as a variable over time, where C represents the number of capillaries that the tumor feeds on. This can be expressed, i.e., the effect of changing capillaries on changing tumor size, with the following coefficient:

$$\frac{\partial TS}{\partial C} \tag{19}$$

In the same way, we can use the model to study other effects such as the effect of the amount of blood entering the tumor and also the effectiveness of nutrients on changing its size in the same previous way, i.e., studying the following coefficients:

$$\frac{\partial TS}{\partial Q} \text{ and } \frac{\partial TS}{\partial E_N} \tag{20}$$

It should be taken into consideration that in this article we are only interested in modeling tumor growth and the mathematical model where researchers can detail the model in the future more than it is on it and its development as we said at the beginning of this section because the model has limits like other models, the most prominent of which is determining the constants according to each tumor, and also some constants cannot be obtained directly by calculation, but there must be clinical trials dedicated to this purpose or obtaining them from previous clinical trials, and this is not an easy matter from an applied point of view. From an ethical point of view, can this model be applied to predict and study tumors and use these predictions for therapeutic purposes or inform the patient of his condition or the size of the tumor in the future? It is a matter related to the sick person, as the patient or the individuals concerned must be informed that the tumor size will be predicted using the model and information related to their bodies will be used, as the tumor is ultimately considered part of the patient's body. For example, when using the number of capillaries that enter the tumor to study it, it is an information related to the patient's body, and in the end, eliminating the disease remains the primary goal, and the disease in our case is the growth of the tumor, which may cause the death of many tumors, as we explained at the beginning of this article through the statistics we listed.

5. CONCLUSIONS

The study of tumor growth in general is a very complex and difficult process from an applied point of view, which does not prevent us from searching for effective methods and approaches to understand the behavior of the latter, and the model in our hands is one of these methods, as it is considered a qualitative model due to its importance, as the model models the growth of tumors in general and it gives the relationship between nutrients and the amount of blood entering the tumor

at each moment, as well as the number of capillaries, which makes it a comprehensive model from an applied point of view, which makes it effective compared to other classical models. We notice this in the applied phase of the article, i.e., the part related to simulation and results, where we notice that the model works well with minimal data, and this can be useful in the case of tumors for which there is not much data available, where the model can be used to predict the behavior of tumors, in our case, Myxoma tumor. We also conclude that the model can be used to study other effects such as the effect of the number of capillaries on tumor growth, the amount of blood entering the tumor, and the effectiveness of nutrients on the development of its size, i.e., the size of the tumor. In conclusion, the model in our hands is a new gateway that opens to the study of tumors and opens with it new visions that will contribute in one way or another to understanding the behavior of tumors and predicting them, thus increasing the chance of finding treatments for them or limiting their development early, which means reducing the victims of these tumors in the case of malignant tumors.

6. PERSPECTIVE

In this article, we have only created the model and applied it in general, but the model still needs further study and development. We can also use the model to find the relationship between tumor size and other variables such as the number of capillaries that the tumor feeds on. The model can also be modified from a general model to a specific model by adding factors such as age and whether the patient suffers from other diseases, as well as adding physical factors such as the pressure applied by the body's organs on the tumor and also the location of the tumor in the body, as the location of the tumor can affect the amount of blood entering the tumor, which will affect the development of tumor size over time.

One of the most prominent challenges is how to find constants according to each tumor, and this requires clinical trials to determine them accurately. There may be some tumors whose size cannot be predicted directly by the model, meaning there may be exceptions to the model. In the end, the current model is a model that provides an opportunity for researchers in the field to discover new ways to solve many of the problems raised in tumor modeling and methods of dealing with them and predicting their behavior and how they can develop over time.

REFERENCES

[1] Organisation mondiale de la Santé. (2022). Cancer. https://www.who.int/fr/news-room/fact-sheets/detail/cancer.

[2] Benzekry, S., Lamont, C., Beheshti, A., Tracz, A., Ebos, J.M., Hlatky, L., Hahnfeldt, P. (2014). Classical mathematical models for description and prediction of experimental tumor growth. PLoS Computational Biology, 10(8): e1003800. https://doi.org/10.1371/journal.pcbi.1003800

[3] Ledzewicz, U., Schättler, H. (2015). Optimal Control for Mathematical Models of Cancer Therapies: An Application of Geometric Methods. Springer. https://doi.org/10.1007/978-1-4939-2972-6

[4] Durrett, R., Moseley, S. (2010). Evolution of resistance and progression to disease during clonal expansion of cancer. Theoretical Population Biology, 77(1): 42-48. https://doi.org/10.1016/j.tpb.2009.10.008

[5] Lowengrub, J.S., Frieboes, H.B., Jin, F., Chuang, Y.L., Li, X., Macklin, P., Wise, S.M., Cristini, V. (2010). Nonlinear modeling of cancer: Bridging the gap between cells and tumors. Nonlinearity, 23(1): R1-R91. https://doi.org/10.1088/0951-7715/23/1/R01

[6] Trobia, J., Tian, K., Batista, A.M., Grebogi, C., Ren, H.P., Santos, M.S., Protachevicz, P.R., Borges, F.S., Szezech, J.D., Viana, R.L., Caldas, I.L., Iarosz, K.C. (2021). Mathematical model of brain tumour growth with drug resistance. Communications in Nonlinear Science and Numerical Simulation, 103: 106013. https://doi.org/10.1016/j.cnsns.2021.106013

[7] Khaliq, R., Iqbal, P., Bhat, S.A., Sheergojri, A.R. (2022). A fuzzy mathematical model for tumor growth pattern using generalized Hukuhara derivative and its numerical analysis. Applied Soft Computing, 118: 108467. https://doi.org/10.1016/j.asoc.2022.108467

[8] Ghaffari Laleh, N., Loeffler, C.M.L., Grajek, J., Staňková, K., Pearson, A.T., Muti, H.S., Trautwein, C., Enderling, H., Poleszczuk, J., Kather, J.N. (2022). Classical mathematical models for prediction of response to chemotherapy and immunotherapy. PLoS Computational Biology, 18(2): e1009822. https://doi.org/10.1371/journal.pcbi.1009822

[9] Wei, H.C. (2023). Mathematical modeling of tumor growth and treatment: Triple negative breast cancer. Mathematics and Computers in Simulation, 204: 645-659. https://doi.org/10.1016/j.matcom.2022.09.005

[10] Alinei-Poiana, T., Dulf, E.H., Kovacs, L. (2023). Fractional calculus in mathematical oncology. Scientific Reports, 13(1): 10083. https://doi.org/10.1038/s41598-023-37196-9

[11] Flandoli, F., Leocata, M., Ricci, C. (2023). The Mathematical modeling of Cancer growth and angiogenesis by an individual based interacting system. Journal of Theoretical Biology, 562: 111432. https://doi.org/10.1016/j.jtbi.2023.111432

[12] Azizi, T. (2024). Mathematical modeling of cancer progression. AppliedMath, 4(3): 1065-1079. https://doi.org/10.3390/appliedmath4030057

[13] Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P. (2002). Molecular Biology of the Cell. Garland Science. https://doi.org/10.1002/cbf.1142

[14] Morgan, D.O. (2007). The cell cycle: Principles of control. Oxford University Press. https://doi.org/10.1093/icb/icm066

[15] Elmore, S. (2007). Apoptosis: A review of programmed cell death. Toxicologic Pathology, 35(4): 495-516. https://doi.org/10.1080/01926230701320337

[16] Hanahan, D., Weinberg, R.A. (2000). The hallmarks of cancer. Cell, 100(1): 57-70. https://doi.org/10.1016/S0092-8674(00)81683-9

[17] Folkman, J. (2002). Role of angiogenesis in tumor growth and metastasis. In Seminars in Oncology. WB Saunders, 29(6): 15-18. https://doi.org/10.1016/S0093-7754(02)70065-1

[18] National Cancer Institute. (2020). Tumor. Dans National Cancer Institute Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tumor.

[19] Carmeliet, P., Jain, R.K. (2000). Angiogenesis in cancer

and other diseases. Nature, 407(6801): 249-257. https://doi.org/10.1038/35025220
[20] Michaelis, L., Menten, M.L., Johnson, K.A, Goody, R.S. (2011). The original Michaelis constant: Translation of the 1913 Michaelis-Menten paper. Biochemistry, 50(39): 8264-8269. https://doi.org/10.1021/bi201284u
[21] Hanahan, D., Weinberg, R.A. (2011). Hallmarks of cancer: The next generation. Cell, 144(5): 646-674. https://doi.org/10.1016/j.cell.2011.02.013
[22] Ouldkhouia, N., Elberrai, I., Benhachem, A., Sannaky, I., Riouali, M., Hachoum, S. (2024). On stochastic modelling: The impact of advertisement on the consumption-application on ChatGPT-3. Mathematical Modelling of Engineering Problems, 11(10): 2705-2714. https://doi.org/10.18280/mmep.111012
[23] Siva, K., Athithan, S. (2022). Analysis of solution for the stochastic model representing water scarcity in the society. Mathematical Modelling of Engineering Problems, 9(4): 1031-1042. https://doi.org/10.18280/mmep.090421
[24] Chinnadurai, K., Athithan, S. (2023). Poverty and the effects of drug addiction in a deterministic and stochastic model. Mathematical Modelling of Engineering Problems, 10(1): 352-359. https://doi.org/10.18280mmep.100141
[25] Tyebally, S., Chen, D., Bhattacharyya, S., Mughrabi, A., Hussain, Z., Manisty, C., Westwood, M., Ghosh, A.K., Guha, A. (2020). Cardiac tumors: JACC CardioOncology state-of-the-art review. JACC: CardioOncology, 2(2): 293-311. https://doi.org/10.1016/j.jaccao.2020.05.009
[26] Reynen, K. (1995). Cardiac Myxomas. New England Journal of Medicine, 333(24): 1610-1617. https://doi.org/10.1056/NEJM199512143332407
[27] Ji, X., Zhang, X. (2021). Left atrial Myxoma with left ventricular Myxoma diagnosed by ultrasound examination: A case report. Medicine, 100(32): e26903. https://doi.org/10.1097/MD.0000000000026903
[28] Bonow, R.O., Mann, D.L., Zipes, D.P., Libby, P. (2011). Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Elsevier.
[29] Fletcher, C.D.M. (2020). Diagnostic Histopathology of Tumors. 2 Volume Set, 5th Edition. Elsevier.
[30] Malekzadeh, S., Roberts, W.C. (1989). Growth rate of left atrial Myxoma. The American Journal of Cardiology, 64(16): 1075-1076. https://doi.org/10.1016/0002-9149(89)90819-9
[31] Karlof, E., Salzberg, S.P., Anyanwu, A.C., Steinbock, B., Filsoufi, F. (2006). How fast does an atrial Myxoma grow? The Annals of Thoracic Surgery, 82(4): 1510-1512. https://doi.org/10.1016/j.athoracsur.2005.11.014
[32] Lane, G.E., Kapples, E.J., Thompson, R.C., Grinton, S.F., Finck, S.J. (1994). Quiescent left atrial Myxoma. American Heart Journal, 127(6): 1629-1631.
[33] Murray, J.D. (2002). Mathematical Biology: I. An Introduction. Springer. Springer, New York, NY. https://doi.org/10.1007/b98868
[34] Elser, J.J., Nagy, J.D., Kuang, Y. (2003). Biological stoichiometry: An ecological perspective on tumor dynamics. BioScience, 53(11): 1112-1120. https://doi.org/10.1641/0006-3568(2003)053[1112:BSAEPO]2.0.CO;2
[35] Jain, R.K. (2001). Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy. Nature Medicine, 7(9): 987-989. https://doi.org/10.1038/nm0901-987
[36] Hanahan, D., Folkman, J. (1996). Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell, 86(3): 353-364. https://doi.org/10.1016/S0092-8674(00)80108-7
[37] Jain, R.K. (1988). Determinants of tumor blood flow: A review. Cancer Research, 48(10): 2641-2658. https://pubmed.ncbi.nlm.nih.gov/3282647/.
[38] Curcio, E., Piscioneri, A., Morelli, S., Salerno, S., Macchiarini, P., De Bartolo, L. (2014). Kinetics of oxygen uptake by cells potentially used in a tissue engineered trachea. Biomaterials, 35(25): 6829-6837. https://doi.org/10.1016/j.biomaterials.2014.04.100
[39] Reiter, A., Trumm, K., Ballhause, T.M., Weiss, S., Frosch, K.H., Korthaus, A., Bechler, U., Duprée, A., Luebke, A., Bannas, P., Schlickewei, C.W., Priemel, M.H. (2022). Diagnostic and therapeutic pathways of intramuscular Myxoma. Diagnostics, 12(7): 1573. https://doi.org/10.3390/diagnostics12071573
[40] Kato, T., Umeda, E., Suzui, N., Fujii, R., Ogura, H., Sakai, O., Shimabukuro, K., Doi, K. (2024). Rapid expansion of a left atrial Myxoma caused by acute multiple internal hemorrhages: A case report and literature review. Journal of Cardiothoracic Surgery, 19: 13. https://doi.org/10.1186/s13019-024-02495-3