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A MATHEMATICAL MODELING OF TUMOR PROGRESSION BASED ON THE AVAILABILITY OF OXYGEN, GLUCOSE, VEGF AND OTHER CONDITIONS

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Abstract. Tumors are one of the most active areas of research in the world, and that is why a lot of research is focusing on mathematical modeling in this area, to help with production, treatment, and finding solutions to help manage tumors, whether malignant or benign. The importance of our model is that it helps to study tumor growth on the basis of several nutritional factors, namely oxygen, glucose, and VEGF. It also uses a generic equation that we have modified to fit our model, the generic equation that deals with tumor growth, the source of which is already cited in the article. So our model was applied to simulate the growth of the tumor, and we found that the size of the tumor increases with time under the triggering of VEGF, the increase in oxygen, its reaction with glucose and then finally by calculating it with the capillary network CN and the flow Q(t).

Keywords: tumor growth; mathematical modeling; nutrient limitation; compartmental model.
2020 AMS Subject Classification: 92C50, 92C75.

1. INTRODUCTION

Cancer is the most common disease in modern times. It is an umbrella term for a group of diseases characterized by the uncontrolled growth of abnormal cells in our bodies. These cells can form malignant tumors, invade nearby tissues, and spread to other parts of the body through

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the blood or lymphatic system, followed by a process called metastasis. It occurs when genetic mutations affect the mechanisms that regulate cell growth, leading to excessive proliferation of abnormal cells. These cells can form solid tumors or, in the case of blood cancers such as leukemia, multiply freely in the blood without forming a solid tumor.

According to recent global statistics:

In 2022, approximately 20 million new cases were diagnosed worldwide, approximately 9.7 million people died [1].

In 2023, the United States estimated that more than 1,958,310 new cancer cases were diagnosed, with 609,820 cancer-related deaths [2]. Global Mortality Rate: Approximately 91.7% of global cancer deaths occur in adults, with higher rates in men than in women [3].

The World Health Organization (WHO) predicts that the global burden of cancer will increase by approximately 60% over the next two decades, reaching approximately 30 million new cases by 2040 [4].

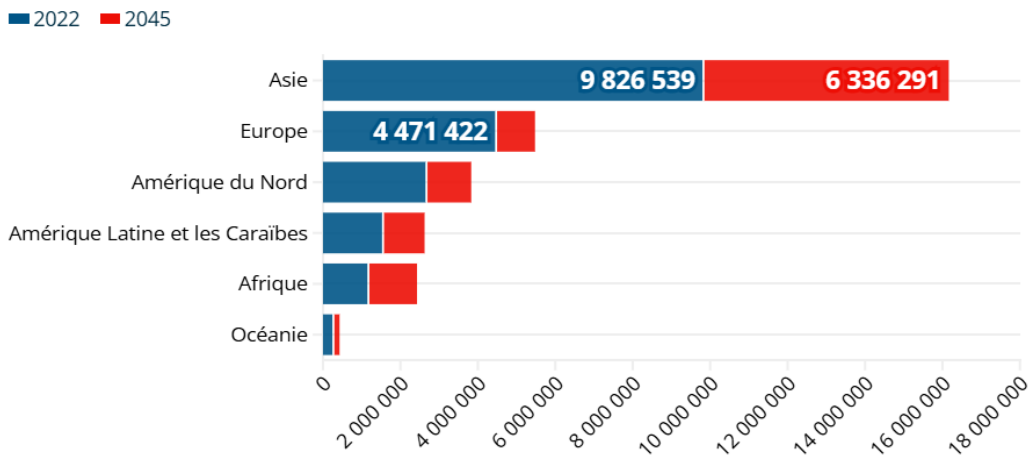

FIGURE 1. Estimated number of new cancer cases by region [4]

In life, every living thing needs nutrients to survive, so at the cellular level, nutrients are essential for survival, growth, and function. They play a central role in maintaining energy balance and building and repairing cellular structures.

Oxygen in the tumor cell, oxygen enables aerobic cellular respiration, this process takes place in the mitochondria, and it enters the oxidation of nutrients(carbohydrates, proteins, and lipids) in order to generate energy in the form of ATP.

Glucose is known as the main and essential energy source, more specifically, in the electron transport chain that takes place in the mitochondria. When the tumor cell detects a need for energy, it begins to break down glucose by a process called glycolysis, which transforms glucose into usable energy and takes place in the cytoplasm. We can see that the availability of nutrients has a significant impact on tumor growth rates.

In mathematics, there are diffusion-reaction models that have dealt with the diffusion of oxygen and glucose and their impact on the tumor cell, these studies have been carried out to understand how varying concentrations of glucose and oxygen affect the growth of tumor cells [5].

In this work, we are going to look at the impact of VEGF (Signal Protein) secreted by cells, particularly tumor cells, in order to communicate with other cells, mainly endothelial cells of blood vessels, which play a crucial role in the availability of oxygen and glucose in the tumor cell and impact tumor progression and have an effect on the metabolic process. It allows tumor cells to consume large amounts of glucose, by this action, the mitochondria rapidly produce ATP which supports the rapid growth of cancer cells. In the event of hypoxia (lack of oxygen), the HIF-1α factor is activated. It stimulates the expression of the VEGF gene, which explains the formation of new blood vessels (angiogenesis), the reception of more oxygen and other nutrients, and ultimately the rapid growth of the tumor [7].

2. LITERATURE REVIEW

Researchers have taken interest in tumor cells to understand how they function, how they are affected and what processes they undergo... so that they can finally find and develop suitable treatments to at least limit their progression or make them disappear.

Gordon C Jayson [9] shows in his article that VEGF remains a real key target.

Olach R. has developed a model based on reaction-diffusion equations describing the distribution of nutrients in the tumor tissue, to predict the influence of nutrients on tumor development and how they are transformed into energy.

To predict the influence of nutrients on tumor development and how they are converted into energy [10].

Feng Yu [11] has used a Hele-Shaw type mathematical model to explore how the consumption and intake of nutrients can cause an instability of the tumor boundary, leading to deformations in the shape of the tumor.

Gilardi G. has explored an optimal control problem for a system of partial differential equations to describe tumor evolution, taking into account the biological mechanism of chemotaxis. His system combines a Cahn-Hiliard type model with a Keller-Segel type equation, describing the evolution of a nutrient species and modeling the chemotaxis phenomenon [12].

In 2024, Ouldkhouia N. and Elberrai I. developed a general stochastic mathematical model that simulates tumor growth, in particular cardiac myxoma, to predict the evolution of tumor size as a function of various biological factors [13].

Ferrara N [8] shows that VEGF is an important therapeutic target in cancer and describes the first clinical advances of an anti-VEGF to block tumor growth. He stresses the crucial importance of VEGF, which is one of the various growth factors that regulate angiogenesis (the formation of new blood vessels) see Figure 2, to receive oxygen and other nutrients. He also mentioned how to block VEGF to slow down or even stop tumor growth with the first antibody they have developed, a monoclonal antibody against VEGF that has been approved for many types of cancer, including colorectal and lung cancer. It is called 'Bevacizumad' Avastin, and its role is to prevent VEGF from binding to its receptors in tumor cells.

3. MÉTHODOLOGY

3.1. Some cancer statistics. We will first take a moment to look at some of the statistics we have collected before diving into the details of our model. According to the WHO, our statistical reference, and as shown in Figure (3) [14], which comes from the platform of the International Agency for Research on Cancer and depends on the World Health Organization, represents the incidence of cancer in the world in 2022, combining both sexes (men and women), with a total of 19 976 499 new cases grouping all types of cancer, in each segment we see a different type of cancer. Types that dominate, such as breast cancer for women which is due to changes in lifestyle such as diet, obesity, etc. In addition, lung cancer is due to smoking. The same goes

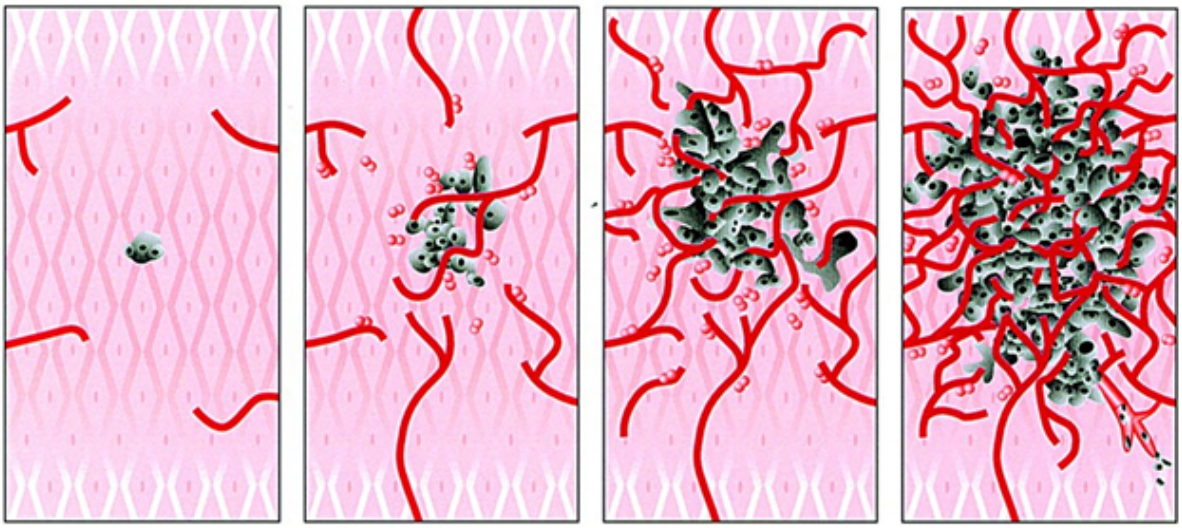

FIGURE 2. Angiogenesis is a necessary condition for sustained tumor growth. [8]

for colorectal cancer, which is mainly due to dietary changes such as low-fiber diets or diets rich in processed meat.

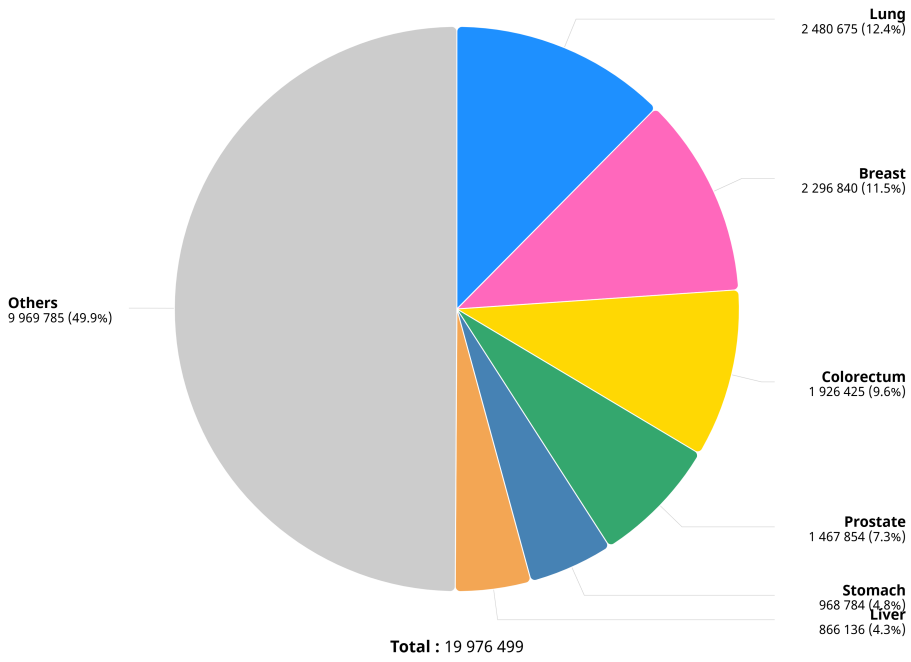

FIGURE 3. Absolute figure, Incidence for both sexes in 2022. [14]

In the article 'American Cancer Society' [15] and as can be seen in Figure (4), there is a list of

the most frequently diagnosed cancers and deaths with an estimate for 2025. It can be seen that lung cancer is still the most deadly cancer, although it is not the most common, while prostate cancer has more cases but is less lethal. Some cancers are ”silent killers”, infrequent but very deadly because of late diagnosis and lack of effective treatment. These analyzes show that there has been a change compared to previous years as a result of progress in the treatment of breast, colorectal, and prostate cancer.

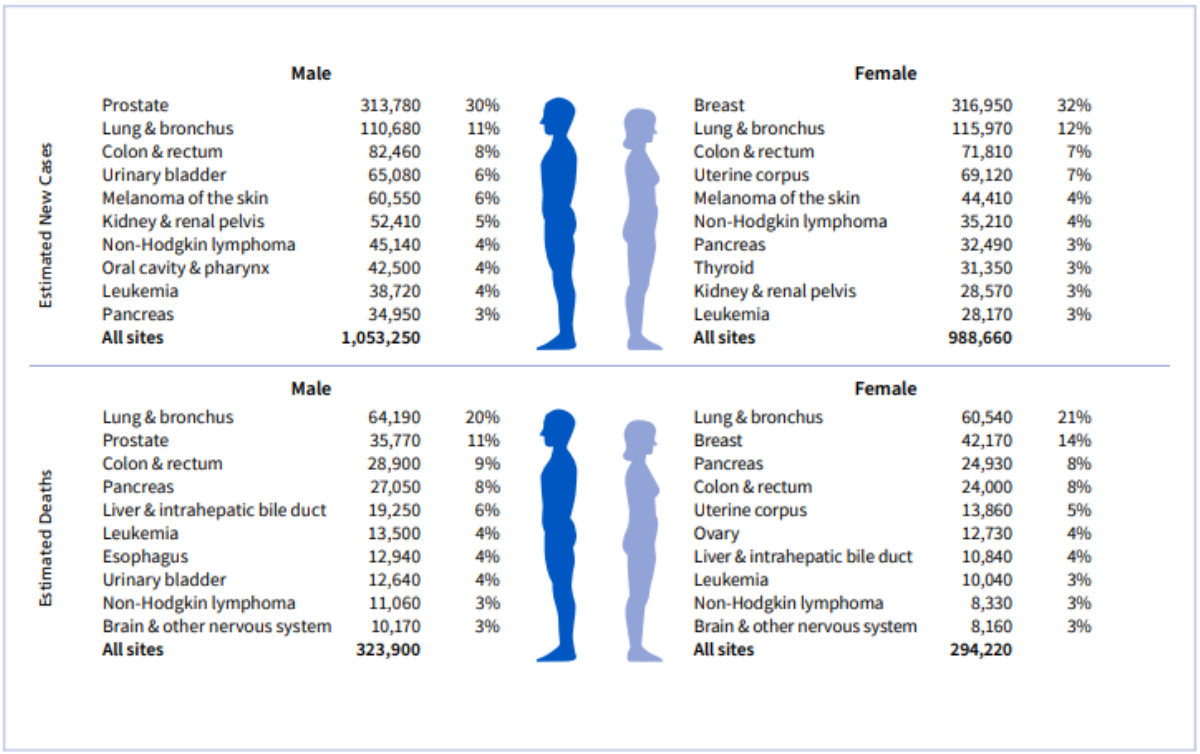

FIGURE 4. Most common and lethal cancers - Predictions for 2025. [15]

3.2. How the tumor develops. The first note is that cancer cells have the same needs as normal cells and need a supply of blood to provide them with oxygen and other nutrients to feed and develop. When the tumor grows large, it declares the need for more blood to supply it with oxygen and nutrients as we have already seen, in which case the tumor cell releases VEGF into its environment, this secretion stimulates angiogenesis by activating neighboring endothelial cells to form new blood vessels [8][16]. To explain figure (5), we will understand each step of the mechanism that allows the tumor to escape the limitations of the environment.

3.2.1. *Hypoxia.* This is what we call a lack of oxygen (anaerobic environment).

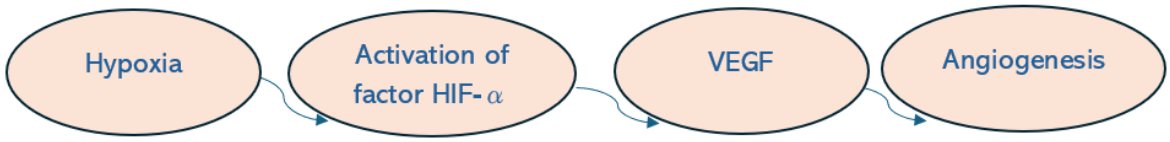

FIGURE 5. Explanatory diagram of the process of nutritional recovery by the tumor cell.

3.2.2. *HIF (Hypoxia-inducible factor 1-alpha).* This is a transcription factor that rapidly degrades (aerobic environment) under normal conditions, but accumulates in the cell under hypoxia and enters the cell nucleus to activate the expression of the hypoxia response gene (VEGF).

3.2.3. *VEGF (Vascular Endothelial Growth Factor).* It stimulates the growth of new blood vessels to improve the supply of oxygen and nutrients, causing tumor progression.

3.2.4. *Angiogenesis.* In this stage, when VEGF is released, it binds to VEGFR receptors, triggering proliferation and formation of new capillaries, which then supplies more oxygen and nutrients (tumor progression).

From this, we conclude that VEGF is the main mediator of angiogenesis, which is why we are going to model tumor progression by modeling VEGF and its impact on the tumor cell.

Without VEGF, there will be no secularization (insufficiency), so tumor growth will be limited. Several studies [7] [8] [16] [17] have been carried out on this, and even the development of anti-VEGF treatments, which have taken VEGF as a logical target to inhibit its action to starve the tumor.

In many types of cancer, they found abnormally high expression of VEGF (e.g. colorectal, lung, breast, kidney, and glioblastoma), so they found that it is easily targeted by antibodies (bevacizumab / Avastin) and less complex than targets of intracellular pathways.

3.3. Mathematical modeling of tumor progression. To better understand the mechanism of tumor growth and help predict their evolution, mathematical modeling of tumor progression has become an active field that brings together several disciplines, including biology, mathematics, and physics. Exponential and logistic models have been used, but they remain among

the classic approaches. However, Cristini, V., and Li, X. [20] have combined metabolic effects such as glucose and oxygen in a model based on the Cahn-Hilliard equations to describe tumor development, taking into account the gradients of nutrients in the tumor environment. Similarly, Hahnfeldt, P., and Panigrahy, D. [21] have developed a dynamic model to describe growth under angiogenic influence, incorporating a differential equation for tumor volume coupled to the evolution of vascular density induced by VEGF. Gatenby, R. A. and Gawlinski, E. T. [22] also proposed a reaction-diffusion model by coupling tumor proliferation to acidification of the extracellular medium. All of these studies and others prove that the integration of biochemical and vascular factors greatly improves the predictive capacity of tumor models and provides a solid basis.

4. MATHEMATICAL MODEL

First, we are going to define a tumor cell to use its supply/impact of nutrients and oxygen through VEGF, and finally have a general model of tumor progression taking these into account. In a hypoxic environment, the tumor cell declares a lack of oxygen, so as I have already mentioned in Figure 5, there is an activation of HIF-α and then the secretion of VEGF, which stimulates the growth of new blood vessels to obtain oxygen.

4.1. VEGF modeling (V). This impact has been modeled using the following equation:

$$\frac{\partial \mathbf{V}}{\partial t} = \alpha V - \lambda(1 - O/K), \tag{1}$$

with:

- V: VEGF concentration.
- O: Oxygen concentration in the tumor cell.
- K: Oxygen threshold.
- α: Natural production rate of VEGF.
- λ: Rate of regulation of VEGF by oxygen.

In this equation, we have modeled the evolution of VEGF concentration over time as a function of αV and oxygen regulation -$\lambda(1-\frac{O}{K})$, this linear form was chosen because it is biologically coherent.

4.1.1. *Biologic interpretation.* When

$$\frac{O}{K} \approx 1$$

then

$$1 - \frac{O}{K} \approx 0 \text{ which means a low VEGF production.}$$

and when

$O \ll K$ $(hypoxia)$, the ratio $\frac{O}{K}$ is small, then $\left(1 - \frac{O}{K}\right) \approx 1$ which means high VEGF production.

4.2. Oxygen modelling (O). The temporal evolution of oxygen in the tumor cell is modeled using the following equation.

$$\frac{\partial \mathbf{O}}{\partial t} = r\frac{\beta O}{(K_o + O)} - \varepsilon V, \tag{2}$$

According to:

- O: oxygen concentration in the tumor.
- V: VEGF concentration.
- $r, \beta, K_o, \varepsilon$ are constants.

4.2.1. *Using the Michaelis-Menten function for $r\frac{\beta O}{(K_o+O)}$.* According to the general form of Michaelis-Menten [18]:

$$v(O) = V_{\max}\frac{O}{K_m + O}$$

If the oxygen concentration is low then $\frac{O}{K_o + O} \approx \frac{O}{K}$ and if it is high $\frac{O}{K_o + O} \approx 1$

4.2.2. *VEGF as a linear consumption term ($-\varepsilon V$).* Following the indirect demand of angiogenesis as shown in Figure 6, we model the increased oxygen consumption with the term $-\varepsilon V$ proportional to the quantity of VEGF.

Therefore, if Vdecreases , then consumption is low, and if V increases, then consumption is high.

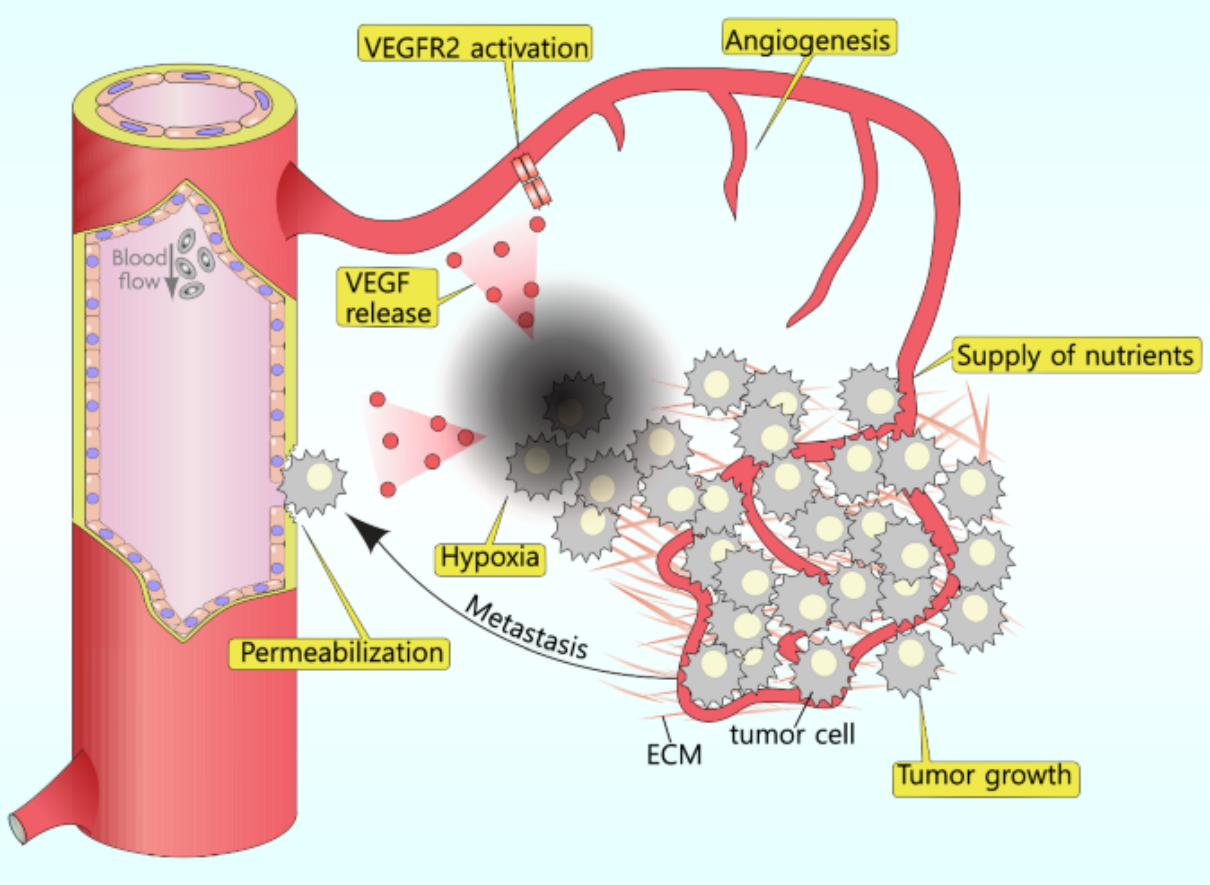

FIGURE 6. VEGF stimulates tumor growth and angiogenesis[19].

4.3. Glucose modeling. Moving on to glucose, here is the equation for the evolution of glucose under the influence of several mechanisms:

$$\frac{\partial \mathbf{g}}{\partial t} = \delta \frac{ag}{(K_g + g)} + bV - \mu O, \tag{3}$$

with:

- g: concentration of glucose (in the Tumor microenvironment).
- V: VEGF concentration.
- O: oxygen concentration.
- δ, a, K_g, b, μ are constants.

Saturable glucose intake $\delta \frac{ag}{(K_g+g)}$ is also described in Michaelis-Menten [18], and bV describes the availability of glucose by VEGF, while $-\mu O$ shows glucose consumption as a function of available oxygen.

4.3.1. *Biologic interpretation.* If VEGF is elevated, glucose intake increases, and if O is elevated, glucose consumption increases, and in the event of hypoxia (lack of oxygen), there is less oxidative glucose consumption.

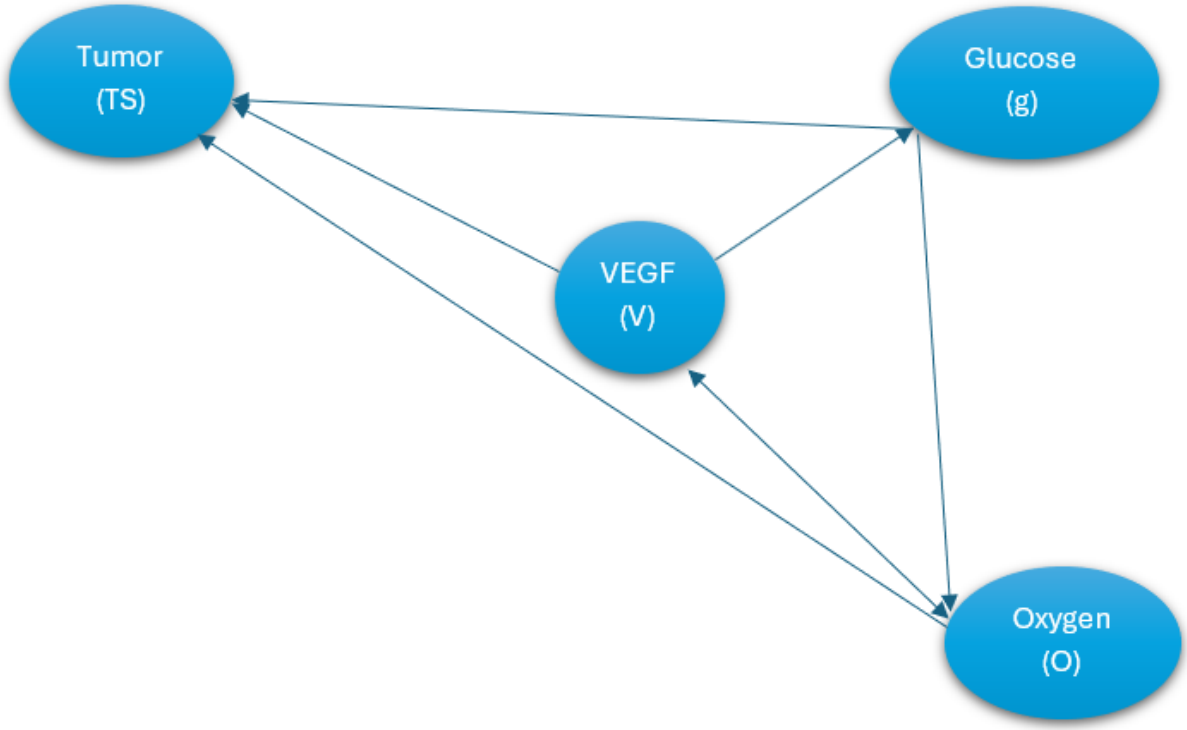

FIGURE 7. Interaction between $g, O, VEGF$ and TS.

4.4. Use of a generic model. In the article [6] Ouldkhouia N. and Elberrai I. developed a general tumor growth model:

$$TS(t+T) = CN * Q(t) * EN(t), \tag{4}$$

in which they took into account the blood flow entering the tumor at time t and the efficiency of nutrients, then the concentration of nutrients.

So, if we use model (7) and integrate glucose dynamics through $\frac{dg}{dt}$ and modify $EN(t)$, we get:

$$TS(t+T) = CNQ(t)(\frac{g(t)}{K_g + g(t)}), \tag{5}$$

with: $EN(t) = \frac{g(t)}{K_g + g(t)}$.

Finally, our complete model is as follows:

$$\begin{cases} \dfrac{\partial \mathbf{V}}{\partial t} = \alpha V - \lambda(1 - O/K), \\ \dfrac{\partial \mathbf{O}}{\partial t} = r\dfrac{\beta O}{(K_o + O)} - \varepsilon V, \\ \dfrac{\partial \mathbf{g}}{\partial t} = \delta\dfrac{ag}{(K_g + g)} + bV - \mu O, \\ TS(t+T) = CNQ(t)(\dfrac{g(t)}{K_g + g(t)}). \end{cases} \tag{6}$$

5. Results and Simulation

5.1. Analysis of Tumor Growth Simulation. In this section, we will simulate the model and to ensure a better understanding of how biological parameters influence tumor progression, we simulated the evolution of tumor size over time under four distinct physiological conditions: baseline, anti-VEGF treatment scenario, hypoxic environment, and high glucose (hyperglycemia) condition.

Where we simulate the model from the following scenarios:

The Basic Scenario: In the basic model, where all parameters reflect normal biological conditions, the tumor exhibits steady, sustained growth. This reflects a balanced supply of oxygen and glucose, accompanied by endogenous production of vascular endothelial growth factor (VEGF), which promotes angiogenesis, as expected, the tumor increases in size gradually over time without sharp acceleration or deceleration.

Anti-vascular endothelial growth factor (VEGF) therapy: In this condition, VEGF production is significantly reduced, as a result, angiogenic signals are impaired, reducing blood vessel growth and, consequently, reducing nutrient delivery to the surrounding tumor, simulations show a significant slowing of tumor growth compared to the baseline condition, the tumor continues to grow, but at a much slower rate, highlighting the potential effectiveness of VEGF-inhibiting therapies in controlling tumor expansion.

Hypoxic Conditions: Under hypoxic conditions, oxygen availability is substantially reduced, despite this, the VEGF concentration increases due to hypoxia-induced activation (consistent with biological mechanisms like HIF-1α activation). However, the tumor's ability to grow is

hampered due to the lack of sufficient oxygen to support cellular proliferation. Consequently, the model shows a slow and constrained tumor growth profile, this result mirrors clinical observations in poorly vascularized tumors that struggle to expand in oxygen-deprived regions. Hyperglycemic Environment: In contrast, the high-glucose scenario leads to accelerated tumor growth. The increased glucose availability enhances the tumor's metabolic efficiency, providing abundant energy for proliferation, combined with VEGF-induced angiogenesis, this environment becomes highly favorable for tumor expansion, the simulation clearly shows that the tumor grows faster and reaches a larger volume than in all other scenarios (See Figure 8).

This simulation study confirms that tumor growth is highly sensitive to metabolic and vascular

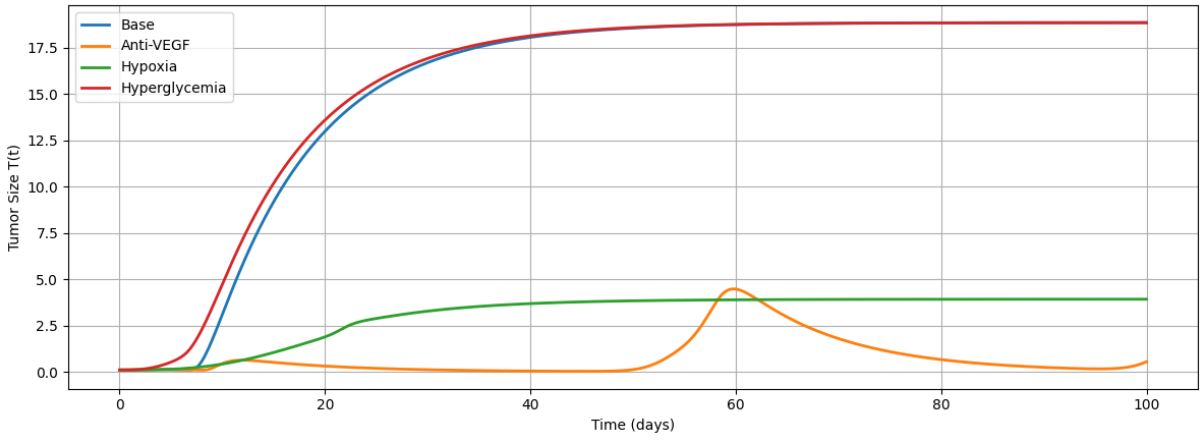

FIGURE 8. Tumor Growth Comparison under Four Scenarios.

conditions. Glucose and oxygen serve as critical substrates for expansion, while VEGF acts as a key regulatory factor for vascular development and nutrient access. Therapeutic strategies that limit glucose uptake or VEGF signaling, or that exacerbate hypoxia, can significantly reduce tumor growth potential. These findings are consistent with current oncological understanding and may serve as a computational foundation for future model-based therapeutic explorations.

5.2. Analysis of Glucose, Oxygen, and VEGF Dynamics. In order to gain a deeper understanding of the metabolic and angiogenic behavior of tumor cells, we analyzed the evolution and interplay of three key biological factors: glucose, oxygen, and VEGF (Vascular Endothelial Growth Factor). Each plays a distinct yet interconnected role in fueling and regulating tumor

progression. The simulations were performed under four conditions: a baseline physiological state, anti-VEGF treatment, hypoxia, and hyperglycemia (see Figure 9). In Figure 9, in the base-

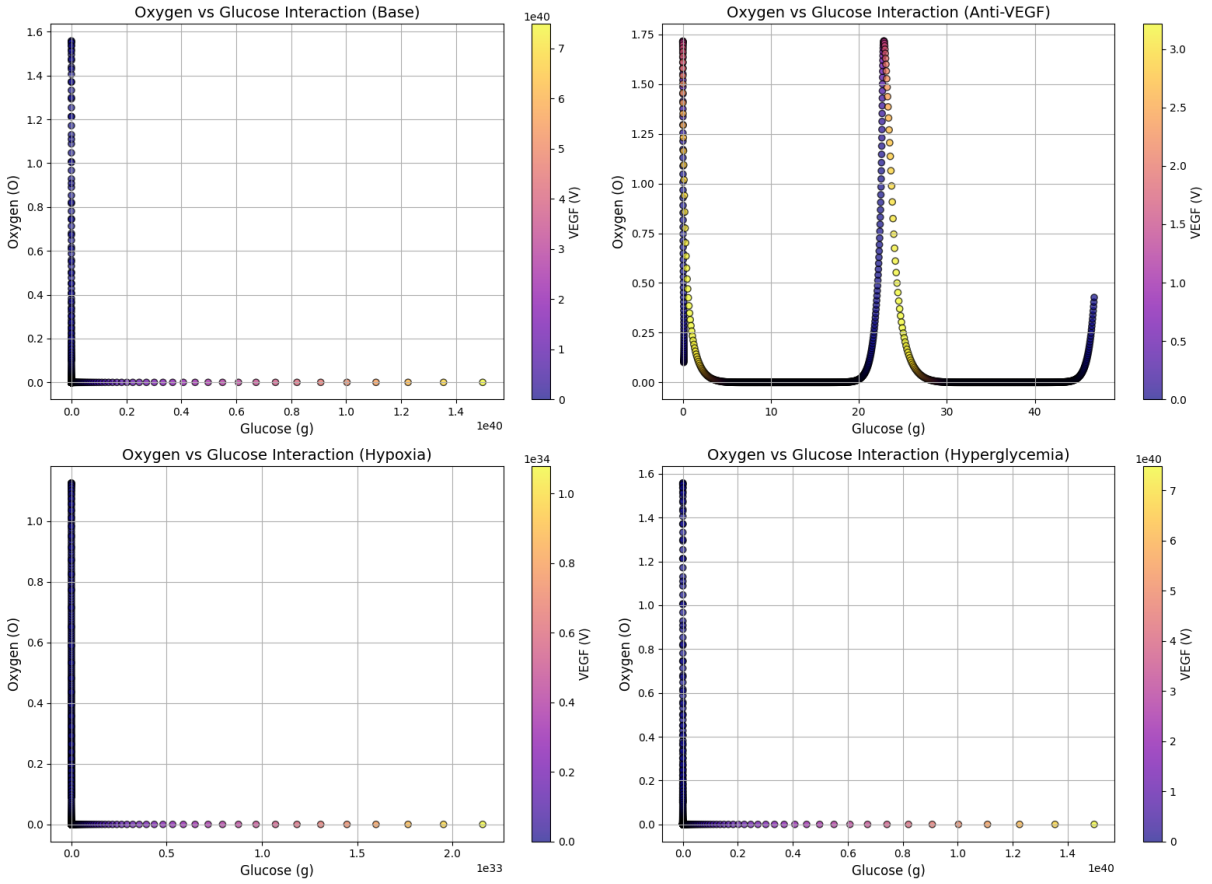

FIGURE 9. Interaction between Glucose, Oxygen and VEGF according to the scenarios.

line case, VEGF concentrations exhibit an initial elevation, then gradually stabilize as oxygen and glucose levels reach dynamic equilibrium. Glucose and oxygen are continuously consumed to support cell proliferation, while VEGF levels increase to support angiogenesis until equilibrium is achieved. This scenario reflects a healthy angiogenesis feedback loop, where nutrient supply and demand are in harmony, leading to moderate and stable tumor growth.

When vascular endothelial growth factor (VEGF) production is pharmacologically inhibited, its concentration remains significantly low throughout the simulation. Interestingly, this decrease also affects glucose and oxygen levels: both exhibit slower consumption rates and lower total concentrations. This is due to a decrease in angiogenic signals, which limits angiogenesis and,

consequently, hinders nutrient delivery to the tumor. The system responds with an overall metabolic slowdown, underscoring the critical role VEGF plays in maintaining tumor metabolism. Under hypoxic conditions, oxygen levels remain low throughout the simulation. As expected, VEGF production is strongly upregulated in response to the lack of oxygen, mimicking the biological activation of the hypoxia-inducible factor (HIF-1α). However, despite the high VEGF levels, the lack of oxygen compromises metabolic efficiency. Glucose consumption is impaired, and the system struggles to compensate for the energy deficit. This condition reflects the biological behavior of tumors in poorly vascularized environments where hypoxia becomes a double-edged sword—promoting VEGF secretion but limiting overall cellular function.

In a glucose-rich environment, glucose levels rise significantly and remain elevated. This leads to enhanced energy availability, which, when coupled with VEGF-driven angiogenesis, creates ideal conditions for tumor growth. Oxygen consumption increases as well, reflecting the higher metabolic rate. VEGF concentration remains elevated due to the increased demand for blood vessels to supply both oxygen and nutrients. The simulation confirms that excess glucose accelerates the entire system, reinforcing the link between hyperglycemia and aggressive tumor progression observed in certain cancer patients.

Visual analysis of the relationship between glucose and oxygen concentrations, with VEGF shown as a color gradient, reveals distinct patterns. In the baseline and hyperglycemic scenarios, glucose and oxygen levels are positively correlated and associated with moderate to high VEGF expression. In contrast, in the hypoxia and anti-VEGF conditions, the interaction space is compressed, indicating constrained metabolic and angiogenic activity. These differences highlight the sensitivity of VEGF-mediated feedback loops to both nutrient supply and oxygen availability.

6. Discussion

Our output model is a novelty that can be improved, yet it is ideal for studying the progression of tumors dependent on vascularization and metabolism, given that the role of VEGF is crucial in angiogenesis to improve the supply of nutrients, and especially when we wish to simulate treatments targeting the tumor environment such as anti-VEGF or metabolic inhibitors. Our model will be particularly useful for hypoxic solid tumors such as pancreatic cancer, breast

cancer, kidney cancer, or glioblastoma [23][24], as well as for studying tumor progression in hypoxic (low oxygen) or low glucose environments. Basically, the model will help predict when the tumor will grow slowly, explore, or stagnate depending on nutritional values, and test the impact of hypoxia or glycolysis inhibitors.

7. Conclusion

Throughout the world, tumor growth represents a major challenge, which is why researchers are interested in carrying out studies in this area despite the complexity of the biological mechanisms involved and the lack of precise data in actual clinical situations.

Our model is not purely qualitative, but quantifies the evolution of variables over time, since we use variables with continuous values and they are calculable.

It is also mechanistic, dynamic, and deterministic as it represents biological interactions and models temporal evolutions through derivatives and it is also non-statistical.

It can be used to monitor the temporal evolution of nutrients, tumor size, and angiogenic signaling.

Our system stands out for its ability to simultaneously integrate the effects of blood supply (from $Q(t)$ flow and VEGF), available nutrients such as those mentioned above (oxygen and glucose), and the Capillary Network (CN).

This is a relevant approach in the context of limited experimental data, as in the case of certain tumors (cardiac myxomas) [6], and the model was run with a minimum of input data.

In short, given that conventional approaches are not sufficient, our model offers a predictive view of tumor progression and a possible key to improving anti-VEGF treatments and possibly developing new treatments.

Conflict of Interests

The authors declare that there is no conflict of interests.

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