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Research Article

Role of Glucose and Oxygen Concentration on Tumor Cell: A Mathematical Model

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Abstract. The paper aims at determining the combined effect of oxygen level and glucose concentration on the growth of tumor cells. The tumor cells were identified by Otto Warburg as the cells with increased glycolysis and decreased mitochondrial activity and described their metabolism. The known fact is that tumor tissues, which are in the form of solid tumors or as ascites cells, display a high rate of aerobic and anaerobic glycolysis. In this paper, one-dimensional mathematical model analysing the concentration of oxygen and glucose in the tumor is developed. The analyses of the effect of glucose and oxygen on tumor cells is done. The correlation between proliferating and quiescent cell number vis-à-vis primary nutrient concentration is found. The proposed model helps us to evaluate the consumption rate of nutrients in the cell when the concentration of glucose, oxygen, and lactic acid in the external medium is given and the radius of the necrotic core can be determined by using the model.

Keywords. Glycolysis, Michaelis-Menten kinetics, Crank-Nicholson approximation, Diffusivity, Tumor cell, Tridiagonal system, Lactic acid, Metabolism

Mathematics Subject Classification (2020). 92D30

1. Introduction

The damaged cells or redundant cells vanish to let healthy cells grow. When the old cells are damaged, the new ones grow. But sometimes there is an uncontrolled growth of abnormal cells. These cells may result in lumps of tissue called tumors. Thus these abnormal cells grow excessively and give rise to tumors. It is a swelling of a part of the body, generally without inflammation. Tumors can be classified as benign (noncancerous) or malign (cancerous). The older cells are replaced by the new ones to perform new functions. A cell uses ATP which is a product of the reaction of glucose with oxygen. Lactic acid along with carbon dioxide and water are byproducts of aerobic cellular respiration. The mechanism of the body is controlled by glucose or blood sugar. When the glucose levels are within required limits, it often goes unnoticed. Unhealthy effects are often noticed when there is fluctuation from the standard limits. As a result, it affects the normal functioning of the body. Normally, growth and division of cells are controlled by our body. It is a known fact that tumor tissues, which are either solid tumors or ascites cells, have the ability of converting glucose to lactate when oxygen is available. This phenomenon is referred to as glycolysis. Warburg *et al*. [10] proposed the theory on the origin of tumor cells, which states that if there is impairment to the respiratory processes of a normal cell it turns out to be malignant. These cells survive on the energy provided by respiration from other metabolic processes. Thus, he stated that the energy for survival of tumor cells depends on the rate of glycolysis though it has never been shown experimentally. The rapid growth of tumor cells, lead to changes in the environment which in turn affect the growth and changes in metabolite concentration. It can also cause the development of micro regions developed by tumor cells of different phenotypes and this may be harmful to the health. One-dimensional mathematical model governing the concentration of oxygen and glucose in the region of the tumor is developed in this paper. The analyses of the effect of glucose and oxygen on tumor cells is done. The correlation between proliferating and quiescent cell number vis-à-vis primary nutrient concentration is found (see Casciari *et al*. [1], Fadaka *et al*. [2], Fitzgibbon *et al*. [3], Goldberg *et al*. [4], Kapur [5], Marušić [6], and Singh [9]).

2. Mathematical Formulation

Tumor growth is facilitated by two main nutrients, oxygen and glucose. Both these are mutually dependent on each other. The uptakes of glucose and oxygen follow Michaelis-Menten's kinetics. Due to glycolysis process, with the lack of oxygen, the glucose consumption increases. Casciari *et al*. [1] introduced the original expression for glucose consumption which is given as:

$$\frac{dg}{dt} = (L^{-m})\left(a_1 + \frac{c_1 b_1}{O+k}\right)\left(\frac{g}{g+K_1 g}\right), \tag{2.1}$$

where

O : Oxygen concentration, g : Glucose concentration, L : Concentration of H^+ ions, K_1, a_1, b_1, c_1, m and k are constants. In this paper, the equation (2.1) is modified.

3. Mathematical Model

The cell growth mechanism is given by following advection-diffusion equations. Glucose is taken as the main nutrient responsible for cell growth. Tumor cells rely more on anaerobic metabolism with or without the presence of oxygen.

The system of reaction-diffusion equations that represent the growth or decay are:

$$\frac{\partial O}{\partial t} = \nabla(D_o \nabla O) - \frac{aO}{(O + kO)}, \tag{3.1}$$

$$\frac{\partial g}{\partial t} = \nabla(D_g \nabla g) - \frac{bg}{(g + kg)}\left(\frac{a_1 + O}{O + b_1}\right), \tag{3.2}$$

$$\frac{\partial L}{\partial t} = (D_L \nabla L) - K_L \frac{Kg}{(g + kg)}\left(\frac{a_1 + O}{O + b_1}\right), \tag{3.3}$$

where

O : Oxygen concentration, g : Glucose concentration,

L : Lactic acid concentration, D_O : Diffusivity coefficient of oxygen,

D_g : Diffusivity coefficient of glucose, D_L : Diffusivity coefficient of lactic acid.

The consumption rate of glucose, oxygen and lactic acid are K_O, K_g, K_L, a, b, a_1, b_1 are constants.

4. Initial and Boundary Conditions

At initial time $t = t_0$ and $x = x_0$ we assume O_0, g_0, L_0 are bulk concentrations of oxygen, glucose and lactic acid and

$$\frac{\partial g}{\partial t} = \frac{\partial O}{\partial t} = 0 \quad \text{at} \quad x = 1$$

which signifies the boundary of the tumor.

5. Numerical Solution

Crank-Nicholson approximation method is used to construct a stable method for reaction diffusion.

For oxygen concentration, discretize the equation (3.1),

$$\frac{O_j^{n+1} - O_j^n}{\Delta t} = \frac{D_O}{2(\Delta x)^2}\{O_{j+1}^{n+1} - 2O_j^{n+1} + O_{j-1}^{n+1} + O_{j+1}^n - 2O_j^n + O_{j-1}^n\} - \frac{aO_j^n}{K_O + O_j^n} \tag{5.1}$$

for $j = 0, 1, 2, 3, 4$ and $n = 0, 1, 2, 3, 4$.

Define $\beta_1 = \dfrac{D_O \Delta t}{2(\Delta x)^2}$ and $\gamma_1 = \Delta t a$. Rearranging the equation (5.1),

$$-\beta_1 O_{j-1}^{n+1} + (1 + 2\beta_1)O_j^{n+1} - \beta_1 O_{j+1}^{n+1} = \beta_1 O_{j-1}^n + (1 - 2\beta_1)O_j^n + \beta_1 O_{j+1}^n - \frac{\gamma_1 O_j^n}{K_O + O_j^n}. \tag{5.2}$$

Each equation for different values of j can not be solved individually at time step n, instead they have to be considered as a system of linear equations along with boundary conditions $O = O_0$ at $x = x_0$ and $O_j^{n-1} - O_j^n = 0$, then applying (5.2) at each node in (5×5) mesh, we get a set of five linear equations with five variables, each representing concentration of oxygen at each time step. Set of five linear equations of (5.2), for each fixed time index form a tridiagonal system of linear equations and which can be expressed as

$$AX = Y, \tag{5.3}$$

where

$$A = \begin{bmatrix} 1+2\beta_1 & -\beta_1 & 0 & 00 & \\ -\beta_1 & 1+2\beta_1 & -\beta_1 & 0 & 0 \\ 0 & -\beta_1 & 1+2\beta_1 & -\beta_1 & 0 \\ 0 & 0 & -\beta_1 & 1+2\beta_1 & -\beta_1 \\ 0 & 0 & 0 & -\beta_1 & 1+2\beta_1 \end{bmatrix}, \quad X = \begin{bmatrix} O_1^{n+1} \\ O_2^{n+1} \\ O_3^{n+1} \\ O_4^{n+1} \\ O_5^{n+1} \end{bmatrix}$$

and

$$Y = \begin{bmatrix} \beta_1 O_0^n + (1-2\beta_1)O_1^n + \beta_1 O_2^n - \frac{\gamma_1 O_0^n}{K_O + O_0^n} \\ \beta_1 O_1^n + (1-2\beta_1)O_2^n + \beta_1 O_3^n - \frac{\gamma_1 O_1^n}{K_O + O_1^n} \\ \beta_1 O_2^n + (1-2\beta_1)O_3^n + \beta_1 O_4^n - \frac{\gamma_1 O_2^n}{K_O + O_2^n} \\ \beta_1 O_3^n + (1-2\beta_1)O_4^n + \beta_1 O_5^n - \frac{\gamma_1 O_3^n}{K_O + O_3^n} \\ \beta_1 O_4^n + (1-2\beta_1)O_5^n + \beta_1 O_6^n - \frac{\gamma_1 O_4^n}{K_O + O_4^n} \end{bmatrix}.$$

Similarly, using Crank-Nicholson approximation and writing in the matrix form for glucose and lactic acid concentration, and applying Gauss backward substitution method and implementing same by using C++, we get the result shown in Table 1 and Table 2 for oxygen and glucose concentration, respectively. Table 3 represents concentration of lactic acid.

6. Results

Table 1, Table 2 and Table 3 are the numerical results of the concentration of oxygen, glucose and lactic acid, respectively.

Table 1. Concentration of oxygen at each discretized node

Distance from centre (x)/Time(t)	$X=0$	$X=1$	$X=2$	$X=3$	$X=4$
$t=1$	0.986105	0.839844	0.703450	0.578109	0.465002
$t=2$	0.978764	0.832958	0.697075	0.572302	0.459821
$t=3$	0.971478	0.826126	0.690755	0.566552	0.454696
$t=4$	0.964246	0.819350	0.684490	0.560857	0.449625
$t=5$	0.957068	0.812622	0.678275	0.555213	0.444606

Table 2. Glucose concentration in tumor region at same nodes of time and space frame

Distance from centre (x)/Time(t)	$X=0$	$X=1$	$X=2$	$X=3$	$X=4$
$t=1$	0.985723	0.978385	0.971102	0.963873	0.956698
$t=2$	0.954216	0.946969	0.939777	0.932640	0.924439
$t=3$	0.923105	0.915953	0.908854	0.901811	0.894805
$t=4$	0.892403	0.885347	0.878345	0.871397	0.864489
$t=5$	0.862119	0.855162	0.848259	0.841410	0.834601

Table 3. Lactic acid concentration in tumor region at same nodes of time and space frame

Distance from centre (x)/Time(t)	$X = 0$	$X = 1$	$X = 2$	$X = 3$	$X = 4$
$t = 1$	−0.00550	0.062283	0.194646	0.300387	0.379420
$t = 2$	0.01108	0.124559	0.389275	0.600753	0.758817
$t = 3$	0.01662	0.186820	0.583888	0.901100	1.138192
$t = 4$	0.02216	0.249093	0.778484	1.201426	1.517543
$t = 5$	−0.02770	0.311350	0.973065	1.501731	1.896872

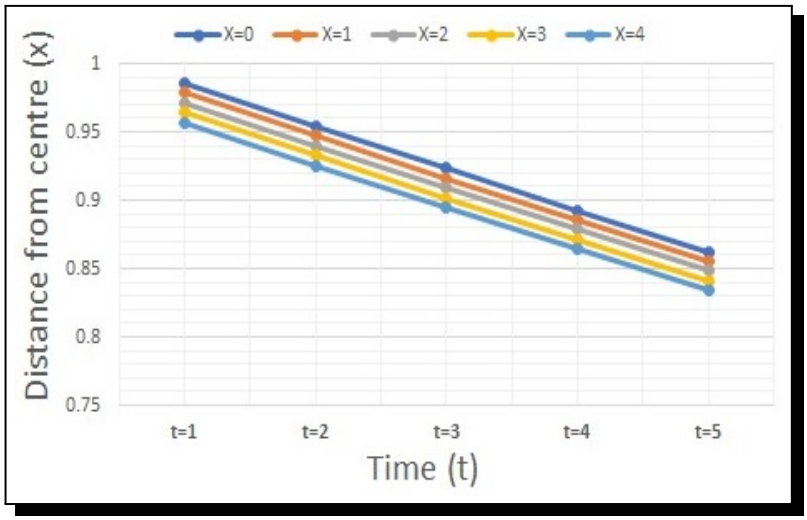

Figure 1. Concentration of glucose at same nodes of time and space frame of tumor region

Figure 1, indicates that the regions close to the centre of tumor shows uniform decline in normalized glucose concentration as the time advances. Sizable and consistent upward gradient in the concentration is observed as it moves away from center which shows that there is an increase in glucose consumption as the tumor grows, which can be also controlled by decreasing the oxygen concentration at the same position.

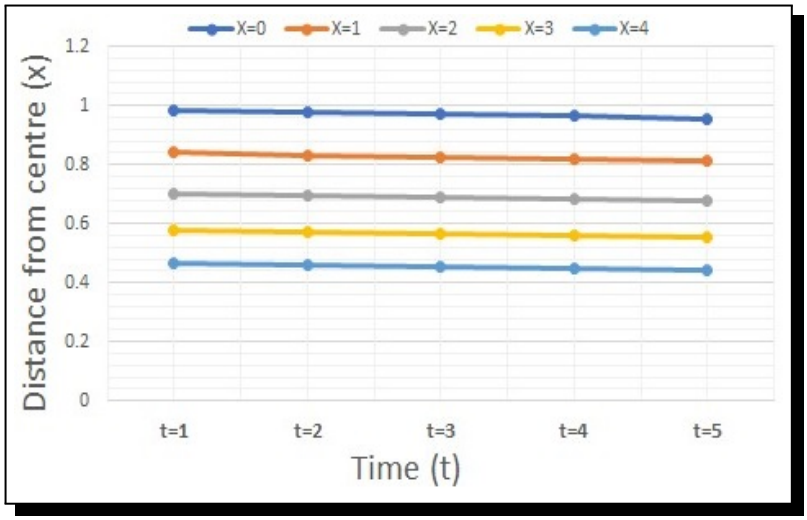

Figure 2. Concentration of oxygen at each discretized node

The dynamics of cell growth with oxygen concentration at the same time steps on these same nodes is shown in Figure 2 There is hardly any correlation between and the existing concentration of oxygen and cell growth in the tumor region.

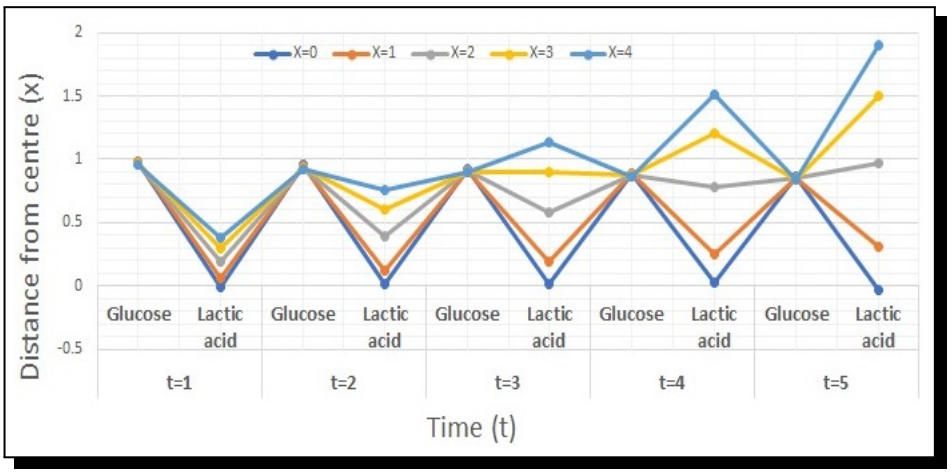

Figure 3. Concentration of glucose at same nodes of time and space frame of tumor region and corresponding concentration of lactic acid at same nodes of time and space frame of tumor region

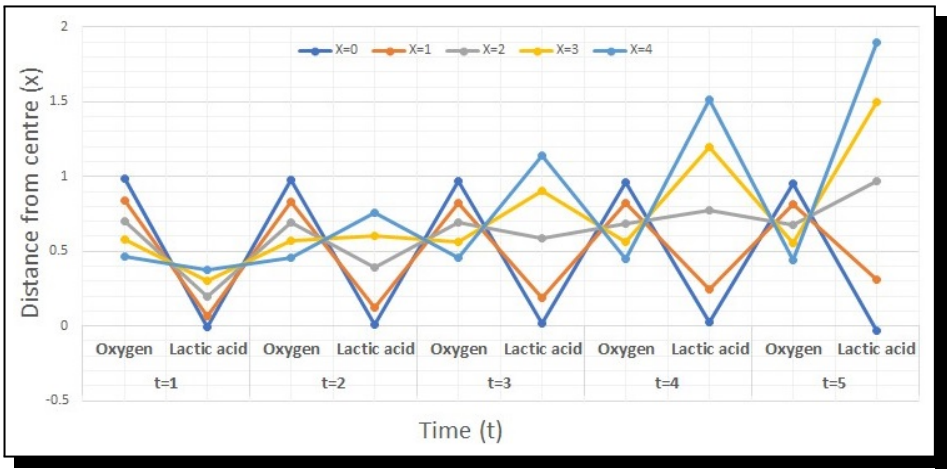

Figure 4. Concentration of oxygen at each discretized node and corresponding concentration of lactic acid at same nodes of time and space frame of tumor region

Figure 3 and Figure 4 depicts the comparison of concentrations of oxygen and glucose along with lactic acid. As the distance from the center of the tumor increases, there is a greater drop in oxygen concentration as the tumor grows with time but the concentration of glucose decreases marginally at these nodes. There is a drastic rise in the concentration of lactic acid which shows that although glucose consumption keeps increasing with the gradual decrease in the concentration of oxygen, the glucose supply is adjusted according to the requirement. At this point of progression of the tumor, every cell adopts the anaerobic glycolysis pathway.

Figure 5 compares the concentration of all three substrates at different positions, as we move from the centre towards the boundary. It is observed that there is steep decline in the glucose concentration as compared to that of oxygen, while the concentration of lactic acid increases in interior parts of the tumor with the advancement of time. This proves that the tumor cells habitually adapt to anaerobic glycolysis in hypoxia conditions.

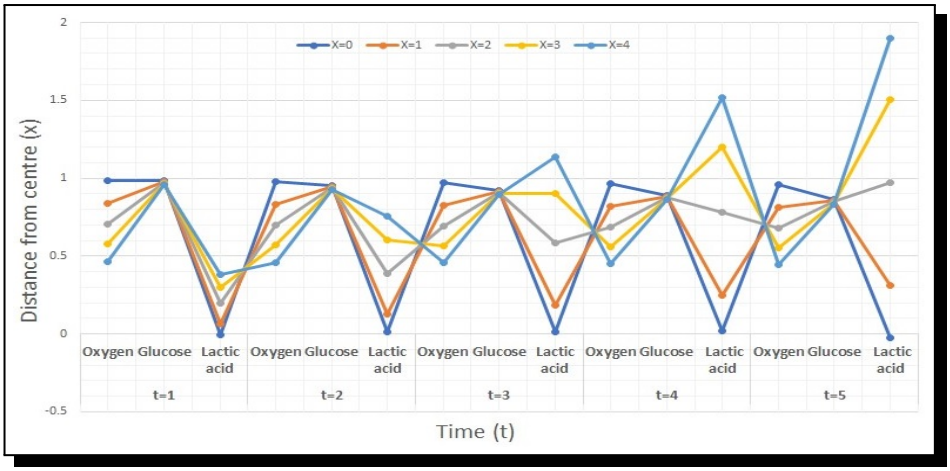

Figure 5. Comparison of concentration of oxygen/glucose and corresponding concentration of lactic acid at the same nodes of time and space frame of tumor region

Lactic acid reacts with oxygen thus reducing its level near the boundary and also due to its flow outside the tumor region. Only when the concentration of oxygen reaches below a certain threshold value, glycolic pathway occurs, this can also attribute to the low concentration of lactic acid.

7. Conclusion

The model proposed in the paper allow us to compute and study the consumption rate of nutrients in the tumor region, also estimation of necrotic core radius can be done if the concentration of oxygen, glucose and lactic acid in the external medium are known. Along the tumor boundary, there is a steep decline in glucose concentration as compared to oxygen concentration. As we move from the centre to the surface of the tumor, there is decrease in lactic acid concentration. The proliferation of the cells stops as the concentration of glucose falls below threshold values, though they still remain viable.

In this model, by using different settings for parameters, we can represent various type of cells with predominant glycolic or oxidative energy metabolism. This study confirms that a response to hypoxia may be represented by initial adoption of glycolytic phenotype due to temporal and spatial heterogeneity of intra-tumor blood flow. Though the constitutive change in metabolism which is responsible to maintain high glycolytic rates even in presence of adequate oxygen cannot be explained by this model. Hence we can conclude that consumption of glucose may play a vital role in progression of cancer.

Appendix A

The concentration and consumption rate values of oxygen have been reported in series of experimental papers of Bertout *et al*. [7], and Warburg *et al*. [10] on the in vitro growth of the optimal oxygen concentration $o = 0.28$ mM.

Coefficient of diffusion of the oxygen: $D_O = 10^{-6}$ cm^2/sec

Coefficient of diffusion of the glucose: $D_G = 9.91 \times 10^{-5}$ cm^2/sec

Coefficient of diffusion of the lactic acid: $D_L = 1.1 \times 10^{-5}$ cm^2/sec

$a = 0.6$, $K_O = 0.05$, $K_g = 0.05$, $K_L = 1.5$, $K = 0.25$, $a_1 = 0.02$, $b_1 = 0.7$ gives values of other constants used in the model.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All the authors contributed significantly in writing this article. The authors read and approved the final manuscript.

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