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# Variation in Concentrations of Glucose, Oxygen and Lactic Acid with the Growth of Tumor.

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**Abstract**— Malignant cells characteristically exhibit altered metabolic patterns when compared with normal mammalian cells with increased reliance on anaerobic metabolism of glucose to lactic acid even in the presence of abundant oxygen. The inefficiency of the anaerobic pathway is compensated by increased glucose flux, a phenomenon first noted by Otto Warburg , some 80 years ago and currently exploited for 2-fluoro-2-deoxy-Dglucose-positron emission tomography imaging in clinical radiology.

We investigate the consumption of glucose with varying concentration of oxygen through mathematical models. We propose a one-dimensional time-dependent mathematical model of partial differential equations governing the concentrations of glucose and oxygen in the tumor region and effect of their consumption on the growth of tumor. Numerical methods have been applied to find out the solutions of these equations. This quantification of primary nutrients along with the number of cells in proliferating, quiescent and dead phase will give better assessment of avascular tumor growth..

**Index Terms**— dead phase ,Malignant cells, primary nutrients proliferating cell, quiescent cell,

## 1 INTRODUCTION

Malignant cells characteristically exhibit altered metabolic patterns when compared with normal mammalian cells with increased reliance on anaerobic metabolism of glucose to lactic acid even in the presence of abundant oxygen.Hence cancer cells are known to consume considerably more glucose than normal cells under identical conditions ([1]. While tumor cells oxidize a portion of the glucose they uptake, a large fraction is converted to lactate. Analysis of tumor interstitial fluid suggests that the tricarboxylic acid (TCA) cycle is saturable, which could explain the high rate of lactate production ([2]. Two independent clinical trials have shown that high lactate [3] and low oxygen concentrations [4] in in vivo tumors are each correlated with increased likelihood of metastases, tumor recurrence, and reduced patient survival. The presence of hypoxia is known to reduce the effectiveness of radiation therapy, as this treatment strategy is dependent on presence of oxygen radicals [5]. We believe that the correlating the spatial concentration profile of each of oxygen, glucose and lactic acid will definitely give an insight about their interplay vis-a vis yhe growth of tumor.

## 2 MATHEMATICAL FORMULATION:

Two important nutrients required for growth of tumor cell are oxygen and glucose whose concentrations are mutually dependant in the tumor region. It is found by biology that the consumption of glucose increases with the absence of oxygen because of glycolysis process. The uptakes of both nutrients follow Michaelis-Menten kinetics. The original expression for consumption of glucose was introduced by Casciari at,el[6]) as given below.

where a,b,c ,kg , k and m are constants , G is the concentration of glucose and O is the concentration of oxygen , L is the concentration of H+ ions. We take a modified and simpler form of the above form.

Growth or decay of concentrations of nutrient is represented by reaction-diffusion equation as given below.

$$\frac{dG}{dt} = L^{-m}\left(a + \frac{cb}{O + k}\right)\left(\frac{G}{G + k_g}\right) \qquad (1)$$

where a,b,c ,kg , k and m are constants , G is the concentration of glucose and O is the concentration of oxygen , L is the concentration of H+ ions. We take a modified and simpler form of the above form.

Growth or decay of concentrations of nutrient is represented by reaction-diffusion equation as given below

$$\frac{\partial \Phi}{\partial t} = \nabla\ D_{\Phi}.\nabla\Phi\ - \frac{k_1\Phi}{\Phi + k_{\Phi}} \qquad (2)$$

Glucose consumption rate has been taken as function of oxygen concentration .Similarly lactic acid formation rate in tumor region is function of both existing oxygen and glucose concentrations at that point of time.

The governing equations are

$$\frac{\partial G}{\partial t} = \nabla\ D_g.\nabla G\ - \frac{k_2 G}{(G + k_g)}.\frac{a + \Phi}{(\Phi + b)} \qquad (3)$$

$$\frac{\partial H}{\partial t} = \nabla\ D_h.\nabla H\ - k_h\frac{k_2 G}{(G + k_g)}.\frac{a + \Phi}{(\Phi + b)} \qquad (4)$$

$\Phi$ = Concentration of oxygen.
$D_{\Phi}$ = Coefficient of diffusivity of oxygen.
$G$ = Concentration of glucose.
$D_g$ = Coefficient of diffusivity of glucose.
$H$ = Concentration of lactic acid.
$D_h$ = Coefficient of diffusivity of lactic acid.

$k_g$, $k_\Phi$, $k_h$, $k_1$, $k_2$, a and b are constants signifying consumption rate of glucose and oxygen and lactic acid.
G , Φ and H are functions of x and t, the space and time dependent.
G'' < G'.
x is normalized distance from tumor center.

**Boundary Conditions –**

$$x = 1,\ G = G_0,\ \Phi = \Phi_0,\ \text{and}\ H = H_0$$

$G_0$, $\Phi_0$ and $H_0$ are the bulk concentrations of glucose and oxygen and lactic acid respectively where x =1 signifies the boundary of tumor.

$$\frac{\partial \Phi}{\partial t} = 0 \quad at\ x = 1. \qquad (5)$$

$$\frac{\partial G}{\partial t} = 0 \quad at\ x = 1$$

**Initial Conditions**

At $t = t_0, G = G_0, \Phi = \Phi_0, H = H_0$. $t_0$ signifies the initial time.

## 3 NUMERICAL SOLUTION

The whole tumor region is divided in five linear spatial layers and total time frame is also broken in five time steps ,each of length t =1/10 of total tumor life. n and j indices represent time and space steps respectively.
At these five positions, we have evaluated concentration of oxygen at different time steps. At same nodes, the concentrations of glucose and lactic acid have been measured at the same time steps.
In order to construct an unconditionally stable method for reaction diffusion, systems have to treat both reaction and diffusion terms implicitly. A Crank- Nicholson approximation for the diffusion and reaction terms leads to a fully implicit scheme:
For oxygen concentration we discretize (2) as given below

$$\frac{\Phi_j^{n+1} - \Phi_j^n}{\Delta t} = \left[\frac{\Phi_{j+1}^{n+1} - 2\Phi_j^{n+1} + \Phi_{j-1}^{n+1}}{(\Delta x)^2}\right] + \left[\frac{\Phi_{j+1}^{n} - 2\Phi_j^{n} + \Phi_{j-1}^{n}}{(\Delta x)^2}\right] - \frac{\Phi_j^n}{k_\Phi + \Phi_j^n}$$

For j=0, 1, 2, 3, 4 and n=0, 1, 2, 3, 4.

$$\alpha_1 = \frac{D_\Phi \Delta t}{2(\Delta x)^2},\ \beta_1 = t k_1,$$

**(7)**

$$-\alpha_1 \Phi_{j-1}^{n+1} + (1+2\alpha_1)\Phi_j^{n+1} - \alpha_1 \Phi_{j+1}^{n+1} =$$

Rearranging (2) we get

$$\alpha_1 \Phi_{j-1}^{n} + (1-2\alpha_1)\Phi_j^{n} + \alpha_1 \Phi_{j+1}^{n} + \beta_1 \frac{\Phi_j^n}{k_\Phi + \Phi_j^n}$$

**(8)**

For papers accepted for publication, it is essential that the
Each equation (5) for j = -M + 1...,M + 1 cannot be solved individually for the option values at time step n. Instead, they must be considered, together with the boundary conditions

$$\text{(i)}\ \Phi = \Phi_0,\ \text{at}\ x = x_0$$

**(9)**

$$\text{(ii)}\ \Phi_j^{n-1} - \Phi_j^n = 0$$

**(10)**

The set of equations in (8) make up a tridiagonal system of linear equations for each fixed time index n.

Above equations would give rise to 5 linear equations which can be arranged in the following matrix (order 5X5) equation, which happens to be a tridiagonal matrix of the form given as

$$AU = V \qquad (11)$$

where A is a tridiagonal matrix of 5x5 order and

$$A = \begin{bmatrix} 1+2\alpha_1 & -\alpha_1 & 0 & 0 & 0 \\ -\alpha_1 & 1+2\alpha_1 & -\alpha_1 & 0 & 0 \\ 0 & -\alpha_1 & 1+2\alpha_1 & -\alpha_1 & 0 \\ 0 & 0 & -\alpha_1 & 1+2\alpha_1 & -\alpha_1 \\ 0 & 0 & 0 & -\alpha_1 & 1+2\alpha_1 \end{bmatrix} \qquad (12)$$

U is a column matrix of order of 5x1, given by

$$U = \begin{bmatrix} \Phi_0^{n+1} \\ \Phi_1^{n+1} \\ \Phi_2^{n+1} \\ \Phi_3^{n+1} \\ \Phi_4^{n+1} \end{bmatrix} \qquad (13)$$

V is a column matrix of order of 5x1, given by

$$V = \begin{bmatrix} \Phi_0^n \\ \alpha_1 \Phi_1^n + (1-2\alpha_1)\Phi_2^n + \alpha_1 \Phi_3^n - \beta_1 \left(\frac{\Phi_1^n}{k_\Phi + \Phi_1^n}\right) \\ \alpha_1 \Phi_2^n + (1-2\alpha_1)\Phi_3^n + \alpha_1 \Phi_4^n - \beta_1 \left(\frac{\Phi_2^n}{k_\Phi + \Phi_2^n}\right) \\ \alpha_1 \Phi_3^n + (1-2\alpha_1)\Phi_4^n + \alpha_1 \Phi_5^n - \beta_1 \left(\frac{\Phi_3^n}{k_\Phi + \Phi_3^n}\right) \\ \Phi_4^n \end{bmatrix} \qquad (14)$$

Similarly discretizing (2) by Crank–Nicholson method we get

$$\frac{G_j^{n+1} - G_j^n}{\Delta t} = D_g \left[\frac{G_{j+1}^{n+1} - 2G_j^{n+1} + G_{j-1}^{n+1}}{(\Delta x)^2} + \frac{G_{j+1}^{n} - 2G_j^{n} + G_{j-1}^{n}}{(\Delta x)^2}\right] - k_2 \left(\frac{G_J^n}{(G_J^n + k)}\right)\left(\frac{\Phi_j^n}{a + \Phi_j^n}\right)$$

Defining $\alpha_2 = \frac{D_g \Delta t}{2(\Delta x)^2}$, $\beta_2 = k_2 \Delta t$

We have

$$\alpha_2 G_{j-1}^{n+1} + (1+2\alpha_2) G_j^{n+1} - \alpha_2 G_{j+1}^{n+1} = \alpha_2 G_{j-1}^{n} + (1-2\alpha_2) G_j^{n} + \alpha_2 G_{j+1}^{n} - \beta_2 \left(\frac{a+\Phi_j^n}{b+\Phi_j^n}\right)\left(\frac{G_j^n}{kg+G_j^n}\right) \qquad (16)$$

Applying this equation at each node in the mesh ( 5x5), as described above we get five linear equations , each with five variables ( concentration at each node at a time step).These equations form a matrix equation as given by

$$A_1 U_1 = V_1 \qquad (17)$$

where $A_1$ a tridiagonal matrix of order 5x5, is given by

$$A_1 = \begin{bmatrix} 1+2\alpha_2 & -\alpha_2 & 0 & 0 & 0 \\ -\alpha_2 & 1+2\alpha_2 & -\alpha_2 & 0 & 0 \\ 0 & -\alpha_2 & 1+2\alpha_2 & -\alpha_2 & 0 \\ 0 & 0 & -\alpha_2 & 1+2\alpha_2 & -\alpha_2 \\ 0 & 0 & 0 & -\alpha_2 & 1+2\alpha_2 \end{bmatrix} \qquad (18)$$

and $U_1$, a column matrix of order of 5x1, is given as

$$U_1 = \begin{bmatrix} G_0^{n+1} \\ G_1^{n+1} \\ G_2^{n+1} \\ G_3^{n+1} \\ G_4^{n+1} \end{bmatrix}$$

$$V_1 = \begin{bmatrix} G_0^n \\ \alpha_2 G_0^n + (1-2\alpha_2) G_1^n + \alpha_2 G_2^n - \beta_2 \left(\frac{G_1^n}{G_1^n + k}\right)\left(\frac{a+\Phi_1^n}{b+\Phi_1^n}\right) \\ \alpha_2 G_1^n + (1-2\alpha_2) G_2^n + \alpha_2 G_3^n - \beta_2 \left(\frac{G_2^n}{G_2^n + k}\right)\left(\frac{a+\Phi_2^n}{b+\Phi_2^n}\right) \\ \alpha_2 G_2^n + (1-2\alpha_2) G_3^n + \alpha_2 G_4^n - \beta_2 \left(\frac{G_3^n}{G_3^n + k}\right)\left(\frac{a+\Phi_3^n}{b+\Phi_3^n}\right) \\ G_4^n \end{bmatrix} \qquad (19)$$

Applying following boundary conditions

$$(i)\ G = G_0 + (at\ x = 0) \qquad (20)$$

$$(ii)\ G_j^{n-1} - G_j^n = 0$$

Corresponding values of $\Phi_j$ for (j=0,1,2,3,4 is substituted from the solution of (4.2.5) .Applying Gauss backward substitution method and implementing the same by C++ code, we obtain the results, shown in Table 1 and Table 2 .
Similarly, equation (3) is also solved with the help of discretizing by Crank–Nicolson method while results of corresponding time step of equation (1) and (2) are substituted from the data tabulated in Table 1 and Table 2 , for oxygen and glucose concentrations respectively.
Solving again by implementing the Gauss forward elimination and then backward substitution method implemented through

C++ code, we get following results.

## 4 RESULTS AND DISCUSSION

The numerical results of the concentrations of oxygen, glucose and lactic acid are tabulated in Table 1, Table 2 and Table.3 respec
tively.

From Fig 1 we observe a uniform fall in normalized concentration of glucose, as time of growth advances, in the nearer regions to the center of tumor. But fall is very marginal. It also shows a large and uniform upward gradient in the concentration with the increasing distance away from center which suggests that with the growth of tumor , glucose consumption goes up which can be also deciphered by lowering concentration of oxygen at the same position.

Fig 2 shows cell growth dynamics on these same nodes at the same time steps and correlating with glucose concentration, we conclude that cell growth is minimally correlated with the existing concentration of glucose in the tumor region.

Fig 3 represents comparative concentrations of oxygen, glucose and lactic acid with gradually increasing distance away from tumor center and here we find a much larger slumping down in the concentration of oxygen as tumor grows with time while decrease in concentration of glucose at these positions is only marginal. While on the contrast a drastic rise in the lactic acid concentration is observed ,which emphasizes the fact that even though glucose consumption keeps on increasing (as is evident by larger production of lactic acid ) with oxygen concentration continuously falling short but supply of glucose is adjusted according to the requirement. An increasing number of tumor cells adopt the anaerobic glycolysis pathway at this point of progression of tumor.

Fig 3, Fig 4, Fig 5 and Fig 6 compare the concentrations of these three substrates, at positions $x_1$, $x_2$, $x_3$ and $x_4$ respectively .Here we observe that the decline in concentration of glucose is now steeper as compared with corresponding decline in concentration of oxygen with the moving away from center of tumor towards boundary of tumor. The concentration of lactic acid shows decline at distant positions from center of tumor. It gets higher and higher in interior parts, with the advancement of time .At $x_1$, in Fig 3, it rises up to 2.5 times of its bulk value, while at $x_2$ , in Fig 4 ,this rise is about 1.5 times its bulk concentration. The same reduces to 1.2 times at the position $x_3$ ,as shown in Fig 5.And it slumps down to 0.4 times the bulk concentration at
position $x=x_4$. It points towards the fact, that tumor cells habitually adapt to anaerobic glycolysis in hypoxia condition but they adapt to anaerobic glycolysis pathway even in presence of oxygen also. The reduced level of lactic acid near the boun dary may be explained to be due to its chemical reaction with oxygen and partially its gradient flow outside the region of tumor .The lower value of lactic acid at boundary also leads us to another inference that glycolic pathway takes place only when oxygen concentration falls below a certain threshold value.

## 5 CONCLUSIONS

The proposed model allows us to compute the nutrient consumption rates in the spheroid and to determine the radius of the necrotic core, when the concentrations of glucose, lactate and oxygen in the external medium are given. The concentration of lactic acid decreases from the center to the surface of tumor while the concentration of glucose shows steep decline as compared to the oxygen concentration towards the outer boundary of tumor. When the concentration of glucose falls below a threshold values, proliferation of cells stops but they still remain viable and whenever get sufficient concentration of nutrient, they again start proliferating. This state is quiescent state; number of cells in this state has been evaluated from solving equations (4), (5) and (6) as they are simple linear differential equations. We have

$$q= 1-\exp(-GH(G-G')t) \quad \textbf{(21)}$$

q is number of cells in quiescent state ,G is concentration of glucose and H is that of lactic acid, G' is threshold value of glucose under which proliferation stops.

Different parameter settings of this model may represent different cell types, with predominant glycolic or oxidative energy metabolism. Our study confirms the fact that pattern represented by initial adoption of the glycolytic phenotype may well represent a response to hypoxia because of temporal and spatial heterogeneity of intratumor blood flow. This does not, however, explains the constitutive change in metabolism that maintains high glycolytic rates even in the presence of adequate oxygen. An alternative explanation may be that the increased glucose flux imposed by adoption of the glycolytic phenotype increases expression of glucose transporters on the cell membrane and improves the cell's ability to compete for glucose in an environment in which substrate is limited. It nevertheless confirms the fact that glucose consumption may play an essential role in cancer progression.

| ***Frm center / Time steps*** | **x=4** | **x=3** | **x=2** | **x=1** | **x=0** |
|---|---|---|---|---|---|
| | **.465002** | **.578109** | **.70345** | **.839844** | **.986105** |
| | **.459821** | **.572302** | **.697075** | **.832958** | **.978764** |
| | ***.454696*** | **.566552** | **.690755** | **.826126** | **.971478** |
| | **.449625** | **.560857** | **.68449** | **.81935** | **.964246** |
| | **.444606** | **.555213** | **.678275** | **.812622** | **.957068** |

**Table 1 Concentration of Oxygen at each Discretized Node**

| *Diist. Frm center* / *Time steps* | x=4 | x=3 | x=2 | x=1 | x=0 |
|---|---|---|---|---|---|
| | **0.956698** | **0.963873** | **0.971102** | **0.978385** | **0.985723** |
| | **0.925539** | **0.93264** | **0.939777** | **0.946969** | **0.954216** |
| | **0 .894805** | **0.901811** | **0.908854** | **0.915953** | **0.923105** |
| | **0..864489** | **0.871397** | **0.878345** | **0.885347** | **0.892403** |
| | **0.834601** | **0.84141** | **0.848259** | **0.855162** | **0.862119** |

**Table 2 Corresponding Concentrations of Glucose at the Same Nodes of Time and Space Frame of Tumor Region**

| *Diist. Frm center* / *Time* | x=4 | x=3 | x=2 | x=1 | x=0 |
|---|---|---|---|---|---|
| | **0.37942** | **0.300387** | **0.194646** | **0.062283** | **0.00555** |
| | **0.758817-** | **0.6007530** | **0.389275** | **0.124559** | **0.01108** |
| | **1.138192** | **0.9011** | **0.583888** | **0.18682** | **0.01662** |
| | **1.517543** | **1.201426** | **0.778484** | **0.249093** | **0.02216** |
| | **1.896872** | **1.501731** | **0.973065** | **0.31135** | **-0.0277** |

**Table 3 Corresponding Concentrations of Lactic Acid at the Same Nodes of Time and Space Frame of Tumor Region**

**Figure.1** -Relative concentration of glucose ( y-axis) vis-a-vis relative time steps of tumor cycle at $t_1,t_2,t_3,t_4,t_5$ (X-Axis) at different positions from tumor.

**Figure 2-** Cell concentrations (Y-axis) at $x_0,x_1,x_2,x_3,x_4$ positions (X-axis ) at time steps $t_0,t_1,t_2,t_3,t_4,$

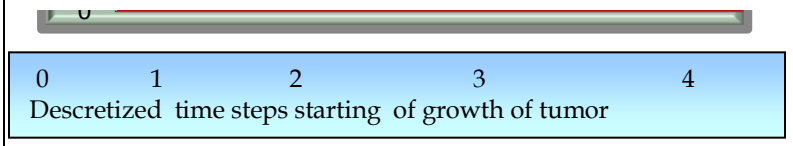


**Figure.3** Comparative concentrations of oxygen, glucose and lactic acid with later stage of tumor growth at position x = $x_1$

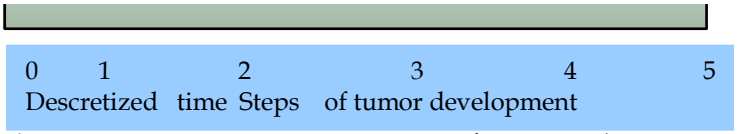


**Figure 4** Comparative concentrations of oxygen ,glucose and lactic acid with later stage of tumor growth at each time step $t_0,t_1,t_2,t_3,t_4$ , at position x = $x_2$ .


**Discretized time steps**

**Fig 5** Comparative concentrations of oxygen, glucose and lactic acid at each time step $t_0,t_1,t_2,t_3,t_4$ ,at position x = $x_3$ .

**Fig 6** Comparative concentrations of oxygen ,glucose and lactic acid at each time step $t_0,t_1,t_2,t_3,t_4$ ,at position x = $x_4$ .

**Appendix- 4.**

The values of oxygen concentration and consumption rates have been reported in the series of experimental papers on the in vitro growth of the Optimal oxygen concentration 0 = 0.28 mM [8]

Max oxygen consumption rate $\eta$ = 2.36 $10^{-7}$ g/(cm3 / s) [8]

Michaelis constant ko = 0.046 mM [9]

Necrotic oxygen level °min = 0.0082 mM, [9]

Diffusion coefficient of glucose Dg= 9.91X$10^{-5}$$cm^2$/sec [6]

Diffusion coefficient of lactic acid Dh= 1.1x$10^{-5}$$cm^2$/sec [6]

The tentative values of other constants used in the model above are given below.

Diffusion coefficient $D_0 = 10^{-6}$ [10]

$K_1$ = 0.6, $K_o$ = 0.05, $K_2$ =0.25, $k_g$ .,a = 0.02,b = 0.7, $k_h$ = 1.5

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