

A MODEL OF OXYGEN DIFFUSION IN ABSORBING TISSUE

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Abstract—A mathematical model is presented which describes the diffusion of oxygen in absorbing tissue, and numerical solutions of its partial differential equation are obtained by orthogonal collocation. The diffusion with absorption model accounts for the presence of a moving boundary which marks the furthest penetration of oxygen into the absorbing medium and also allows for an initial distribution of oxygen through the absorbing tissue. The model predictions may be used in the development of time variant radiation treatments of cancerous tumors, so that the dosage of radiation could be varied with the changing oxygen concentration. Simple expressions are also presented for evaluating the surface oxygen concentration, the rate of consumption of oxygen per unit volume of absorbing tissue, and the point of innermost oxygen penetration.

INTRODUCTION AND PROBLEM STATEMENT

The successful treatment of cancer by radiotherapy is dictated primarily by the ability to apply a radiation dosage large enough to do substantial damage to the cancerous cells without damaging surrounding healthy cells, and still remain within the tissue tolerance level of radiation. The susceptibility of cancerous cells to radiation has been shown to increase with increasing oxygen concentrations within the tumor [1-3].

Alper and Howard-Flanders [1] have shown that the dependence of tissue radiosensitivity, for bacterial cells, indicates a 2-3-fold increase in the radiation dosage would be required to obtain the degree of destruction for cells in the total absence of oxygen in comparison with oxygenated cells. This effect of oxygen allows the use of smaller radiation doses to achieve the desired percentage of destruction of cancerous cells.

The method of interest for introducing oxygen within such tumors involves exposing a surface of the tumor to a high oxygen concentration [3, 4], often under high pressure, and allowing the tumor to absorb oxygen until a steady-state condition is reached where no further penetration of oxygen into the tissue occurs. This steady state is characterized by a particular oxygen profile within the tumor resulting from internal consumption of the absorbed oxygen by cancerous cells and the diffusional resistance to oxygen transport within the tumor. Therefore, the surface may be considered to have an oxygen concentration proportional to that of the oxygen source and a point exists within the tissue at which the oxygen concentration has dropped to zero, marking the point of

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innermost penetration. Once this steady state occurs, the outer surface is sealed off and radiation treatments may begin. At the same time, the oxygen within the tissue continues to be absorbed and consumed. This removal of oxygen alters the initial steady-state profile and gradually the point of zero concentration (innermost penetration) will recede toward the originally exposed surface until no oxygen remains.

The present paper concerns itself with the modelling and solution of this combined diffusion and absorption problem; the predictions of the model would allow time variant radiation treatment of cancerous tumors. In such treatments, the radiation dosage would be varied with the oxygen concentration so as to compensate for the lost killing effectiveness resulting from oxygen consumption by the tumor.

It should be noted that the application of the model presented in the following sections, is not limited to cancerous tumors, but the model may be used in describing the diffusion of oxygen in absorbing tissues in general.

MATHEMATICAL FORMULATION

The complex transport mechanisms of oxygen in absorbing tissue may be simplified by assuming that the transport is governed by diffusion in the "solid" sections of the tissue and on the surfaces of its porous networks. These two diffusional mechanisms are treated as one in this work as their mathematical descriptions are identical. The transport mechanism is taken to be one-dimensional and it is assumed that local equilibrium exists between the tissue and oxygen at each point, since the process of absorption is rarely rate limiting [4, 5, 6]; also the diffusion with absorption process is taken to be isothermal, since available data [3, 4] seem to confirm the validity of this assumption.

The continuity equation derived from a differential mass balance in the absorbing tissue, is given by the partial differential equation

$$\frac{\partial c}{\partial t} = \frac{1}{x^\alpha} \frac{\partial}{\partial x} \left(x^\alpha D \frac{\partial c}{\partial x} \right) - f(c), \quad (1)$$

where $c(t, x)$ denotes the concentration of the oxygen free to diffuse at a distance x from the outer surface of the absorbing medium at time t , D is the diffusion coefficient, and $f(c)$ represents the rate of consumption of oxygen per unit volume of the absorbing medium and this rate may be a function of the oxygen concentration. Equation (1) is applicable for a slab, cylinder or sphere by putting $\alpha = 0, 1, \text{ or } 2$.

The present work concerns itself with slab geometry and it is assumed that D is constant [4, 6, 7], and the rate of oxygen consumption is also taken to be constant, that is $f(c) = \beta = \text{constant}$; experimental data [4, 5] indicate that $f(c)$ is usually a weak function of oxygen concentration. Then, Eq. (1) reduces to the following expression:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \beta. \quad (2)$$

The diffusion with absorption process, as stated in the previous section, has two parts.

1. Steady state

When the oxygen is entering through the surface, during the initial phase, the boundary condition is given by the expression

$$c = c_0 \text{ at } x = 0, t \geq 0 \quad (3)$$

where the surface concentration c_0 is a constant.

When the gradient of concentration becomes zero at the point, X , in the absorbing tissue where the concentration itself is zero, then a steady state is obtained in which the concentration at every point in the tissue becomes independent of time, that is the accumulation term is zero everywhere. Oxygen can not diffuse beyond the point X and the following conditions exist:

$$c = 0 \text{ at } x \geq X \quad (4)$$

$$\frac{\partial c}{\partial x} = 0 \text{ at } x \geq X \quad (5)$$

for $t \geq 0$.

The steady-state solution of Eq. (2), which satisfies the boundary conditions given by Eqs. (3)–(5), is easily seen to be

$$c = \frac{\beta}{2D}(x - X)^2 \quad (6)$$

and

$$X = \sqrt{\left(\frac{2Dc_0}{\beta}\right)} \quad (7)$$

2. Unsteady state

When the surface $x = 0$ is sealed, oxygen, which is already in the absorbing tissue in the interval $0 \leq x \leq X$, continues to be consumed. Then, the point of zero concentration which, in the initial phase, was given by Eq. (7) moves towards the surface of the absorbing slab. This part of the diffusion with absorption process can be represented by the following equations:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \beta, \quad 0 \leq x \leq X(t) \quad (8)$$

$$\frac{\partial c}{\partial x} = 0 \text{ at } x = 0, \quad t \geq 0 \quad (9)$$

$$c = 0 \text{ at } x = X(t), \quad t \geq 0 \quad (10)$$

$$\frac{\partial c}{\partial x} = 0 \text{ at } x = X(t), \quad t \geq 0 \quad (11)$$

$$c = \frac{\beta}{2D}(x - X)^2, \quad 0 \leq x \leq X, \quad t = 0, \quad (12)$$

where $t = 0$ represents the time at which the surface is sealed. By defining a new set of variables as

$$y = \frac{x}{X}, \quad \tau = \frac{D}{X^2} t, \quad \theta = \frac{c}{2c_0} = \frac{D}{\beta X^2}$$

and denoting by $y_0(\tau)$ the value of y corresponding to $X(t)$, Eqs. (8)–(12) reduce to the

following nondimensional expressions:

$$\frac{\partial \theta}{\partial \tau} = \frac{\partial^2 \theta}{\partial Y^2} - 1, \quad 0 \leq y \leq y_0(\tau) \quad (13)$$

$$\frac{\partial \theta}{\partial y} = 0 \text{ at } y = 0, \quad \tau \geq 0 \quad (14)$$

$$\theta = 0 \text{ at } y = y_0(\tau), \quad \tau \geq 0 \quad (15)$$

$$\frac{\partial \theta}{\partial y} = 0 \text{ at } y = y_0(\tau), \quad \tau \geq 0 \quad (16)$$

$$\theta = 0.5(1 - y)^2, \quad 0 \leq y \leq 1, \tau = 0. \quad (17)$$

The above equations represent a moving boundary problem, and since not only the concentration of oxygen is always zero at the boundary but, in addition, no oxygen diffuses across the boundary at any time, there is no relationship which contains the velocity of the moving boundary explicitly.

Moving boundary problems are often tedious and difficult to solve [8, 14], except in trivial cases [9, 10]. Often, Crank-Nicholson or other finite difference numerical schemes are used [8, 11, 12]; these numerical methods usually require large computation times and are often applicable only when the velocity of the moving boundary is small. They differ in the way they treat the moving boundary and the grid on which numerical values are calculated. In general, the moving boundary will not coincide with a grid line in successive time steps, $\Delta\tau$, if $\Delta\tau$ is taken to be constant and predetermined. Because of these limitations, the solution and parameter estimation of models which involve moving boundaries has been, in most cases, intractable.

In the following section a numerical procedure based on orthogonal collocation [13] is presented, and used to obtain the solution of Eqs. (13)–(17).

NUMERICAL PROCEDURE

The advantages of orthogonal collocation over finite difference methods with respect to stability, convergence, and computation time of the solutions are discussed extensively by Villadsen and Michelsen [15], and Finlayson [16]. The method of orthogonal collocation is more straightforward in application to problems with model equations of fixed extent [15, 17, 18] than it is to problems with changing domains. Consequently, we use a particularly simple and useful preliminary device for the numerical solution of one-dimensional moving boundary problems, a change of space variable in order to fix the position of the moving boundary $y_0(\tau)$.

Transformation to the independent variable,

$$\xi = \frac{y}{y_0(\tau)}, \quad (18)$$

leads to the relations

$$\left(\frac{\partial \theta}{\partial y}\right)_\tau = \frac{1}{y_0(\tau)} \left(\frac{\partial \theta}{\partial \xi}\right)_\tau \quad (19)$$

$$\left(\frac{\partial^2 \theta}{\partial y^2}\right)_\tau = \frac{1}{(y_0(\tau))^2} \left(\frac{\partial^2 \theta}{\partial \xi^2}\right)_\tau \quad (20)$$

$$\left(\frac{\partial \theta}{\partial \tau}\right)_y = \left(\frac{\partial \theta}{\partial \tau}\right)_\xi - \frac{\xi}{y_0(\tau)} \frac{dy_0(\tau)}{d\tau} \left(\frac{\partial \theta}{\partial \xi}\right)_\tau \quad (21)$$

The relations of Eqs. (18)–(21) transform the moving boundary problem given in Eqs. (13)–(17) into a problem of fixed extent since the position of the moving boundary is always at $\xi = 1$. The transformed model equations are

$$\frac{\partial \theta}{\partial \tau} = \frac{\xi}{y_0(\tau)} \frac{dy_0(\tau)}{d\tau} \left(\frac{\partial \theta}{\partial \xi}\right) + \frac{1}{(y_0(\tau))^2} \left(\frac{\partial^2 \theta}{\partial \xi^2}\right) - 1, \quad 0 \leq \xi \leq 1 \quad (22)$$

$$\frac{\partial \theta}{\partial \xi} = 0 \text{ at } \xi = 0, \quad \tau \geq 0 \quad (23)$$

$$\theta = 0 \text{ at } \xi = 1, \quad \tau \geq 0 \quad (24)$$

$$\frac{\partial \theta}{\partial \xi} = 0 \text{ at } \xi = 1, \quad \tau \geq 0 \quad (25)$$

$$\theta = 0.5(1 - \xi y_0(\tau))^2, \quad 0 \leq \xi \leq 1, \tau = 0, \quad (26)$$

where $y_0(0) = 1$.

The application of orthogonal collocation on the space variable of Eq. (22) yields the following set of ordinary differential equations:

$$\frac{d\theta_i}{d\tau} = \frac{\xi_i}{y_0(\tau)} \frac{dy_0(\tau)}{d\tau} \left(\sum_{j=1}^{N+2} A_{ij}\theta_j\right) + \frac{1}{(y_0(\tau))^2} \left(\sum_{j=1}^{N+2} B_{ij}\theta_j\right) - 1, \quad i = 2, 3 \dots N + 1. \quad (27)$$

The rate of change of $y_0(\tau)$ is approximated using

$$\frac{dy_0(\tau)}{d\tau} \approx \frac{y_0(\tau + \Delta\tau) - y_0(\tau)}{\Delta\tau} \quad (28)$$

The concentrations at the external collocation points, $\xi_1 = 0$ and $\xi_{N+2} = 1$, can be eliminated from Eq. (27) by use of the boundary conditions, Eqs. (23) and (25), which give

$$\theta_1 = \frac{\left(\sum_{j=2}^{N+1} A_{1,j}\theta_j + A_{1,N+2}\theta_{N+2}\right)}{A_{1,1}} \quad (29)$$

$$\theta_{N+2} = -\frac{\left(\sum_{j=2}^{N+1} A_{N+2,j}\theta_j + A_{N+2,1}\theta_1\right)}{A_{N+2,N+2}} \quad (30)$$

It is readily seen that the simultaneous solution of Eqs. (29)–(30) provides the values of θ_1 and θ_{N+2} when the values of $\theta_2, \theta_3 \dots \theta_{N+1}$ are known from the integration of Eq. (27) with the initial condition

$$\theta_i = 0.5(1 - \xi_i)^2, \quad i = 1, 2, 3 \dots N + 2, \tau = 0. \quad (31)$$

It should be noted that only the values of $\theta_2, \theta_3 \dots \theta_{N+1}$ from Eq. (31), are used in the integration of Eq. (27).

As it was stated in the previous section, there is no relationship which contains the velocity of the moving boundary explicitly and it is necessary to determine $y_0(\tau + \Delta\tau)$ so as to satisfy the remaining boundary condition [Eq. (24)], in this case $\theta_{N+2} = 0$. Thus, the following solution scheme for Eq. (27) is employed; the term $y_0(\tau + \Delta\tau)$ assumes the value y_{01} and then Eq. (27) is integrated using a third order semi-implicit Runge-Kutta method [19] which is also appropriate for integrating systems of stiff ordinary differential equations, and the value of $(\theta_{N+2})_1$ is obtained. If $(\theta_{N+2})_1 \neq 0$, then we let $y_0(\tau + \Delta\tau)$ assume the value y_{02} ; Eq. (27) is integrated again, and the value of $(\theta_{N+2})_2$ is obtained. If $(\theta_{N+2})_2 \neq 0$ then the method of "false position" gives

$$y_{03} = \frac{y_{01}(\theta_{N+2})_2 - y_{02}(\theta_{N+2})_1}{(\theta_{N+2})_2 - (\theta_{N+2})_1} \quad (32)$$

as the next approximation to $y_0(\tau + \Delta\tau)$. The estimate of $y_0(\tau + \Delta\tau)$ corresponding to the larger of the two values $(\theta_{N+2})_1$ and $(\theta_{N+2})_2$ is discarded, and $(\theta_{N+2})_3$ is determined from another integration of Eq. (27). The new estimate, y_{03} , and the one retained from the original pair y_{01} and y_{02} are then used in Eq. (32) to obtain a further estimate y_{04} . This process is repeated until $(\theta_{N+2})_n$ is less than a certain specified quantity $\epsilon \ll 1$; the value used for ϵ was 10^{-6} . Then y_{0n} and $(\theta_{N+2})_n$ represent the solution for the time variable $\tau + \Delta\tau$. When advancing to a new time level, the initial estimate for y_0 is taken to be the final value at the previous time level. In this way, the calculation is progressing until the required time range has been covered, so that $y_0 = 0$.

The approximation order N of the Jacobi orthogonal polynomials $p_N(\xi)$ [15] was tested with $N = 8, 10, 12$. $N = 10$ proved to be sufficient to obtain differences in the oxygen concentration only in the 5th digit as compared to the higher approximation.

RESULTS AND DISCUSSION

In Figs. 1 and 2, the concentration profiles and the position of the moving boundary at different times, τ , are shown; it is seen that as the time increases the profiles become flatter since at $y_0(\tau) = 0$ the concentration profile coincides with the point of origin in Fig. 1. The concentration profile at $\tau = 0$ shows that a negative unit gradient of concentration exists at the surface, but for $\tau > 0$, a zero surface gradient is shown, in accordance with Eq. (14).

In Fig. 2, an interesting result is observed, which is due to the mechanisms of diffusion and absorption in the medium, the moving boundary moves slowly since the process of diffusion acts in the opposite direction to the motion of the boundary whose mobility is induced by the process of absorption. As the time increases, the absorption process overtakes substantially the diffusion, the speed of the moving boundary tends to infinity as τ approaches the time at which there is no longer an oxygen concentration profile in the absorbing tissue.

The variation of the oxygen concentration at the surface with time is shown in Fig. 3. A close examination of the data reveals that the concentration $\theta(\tau, 0)$ varies almost linearly with the square root of the time, τ . The expression,

$$\theta(\tau, 0) = 0.50 - 1.13\sqrt{\tau}, \quad (33)$$

provides the values of $\theta(\tau, 0)$ to an accuracy of 3×10^{-4} as compared with the values of the numerical solution. One may use Eq. (33) to obtain an approximate time for the

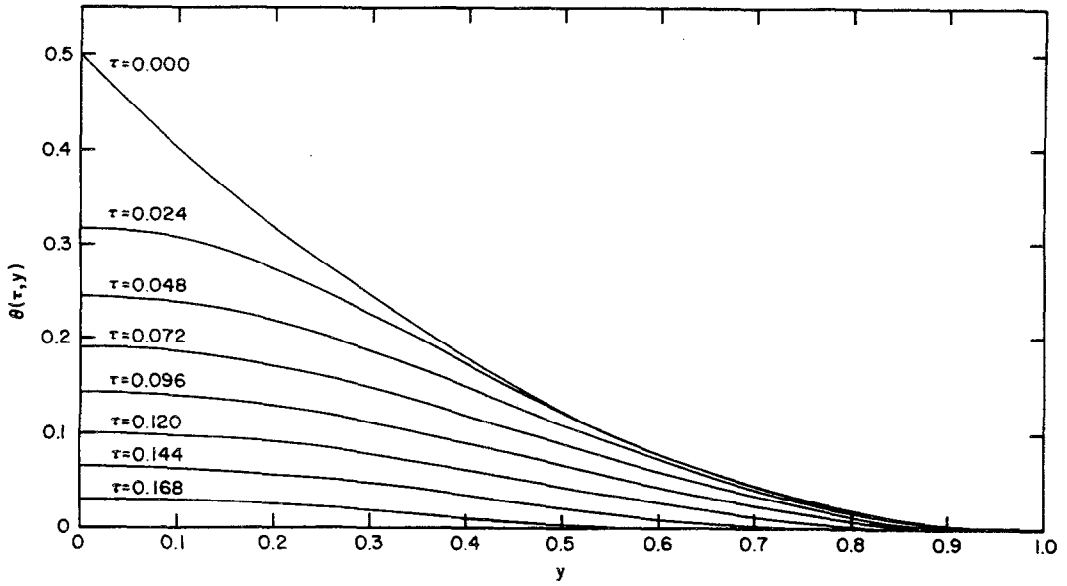


Fig. 1. Oxygen concentration profiles for different times τ .

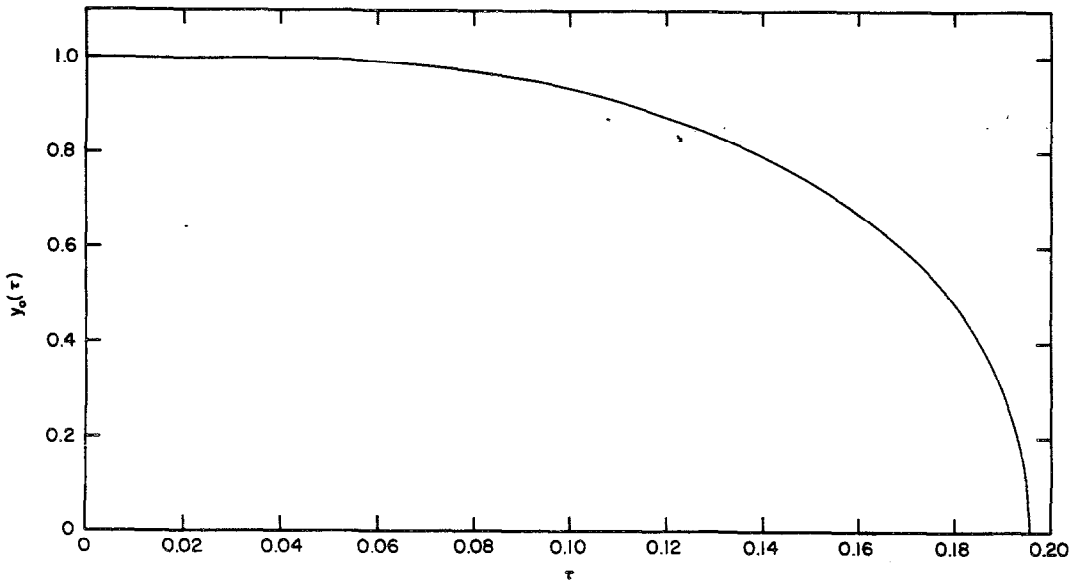


Fig. 2. Position of the moving boundary with respect to time.

oxygen concentration everywhere to become zero; one sets $\theta(\tau, 0) = 0$ in Eq. (33), and the total time of the diffusion with absorption process is equal to 0.196. This number agrees very well with that obtained by the numerical solution. Thus, Eq. (33) may be used as a good approximation for predicting the oxygen concentration at the surface, and the establishment of a correlation between radiation dosage and surface concentration may allow time variant radiation treatments of cancerous tumors. Equation (33) may also be used in estimating the rate of consumption of oxygen per unit volume of absorbing tissue; one may experimentally [4] measure the oxygen concentration at the

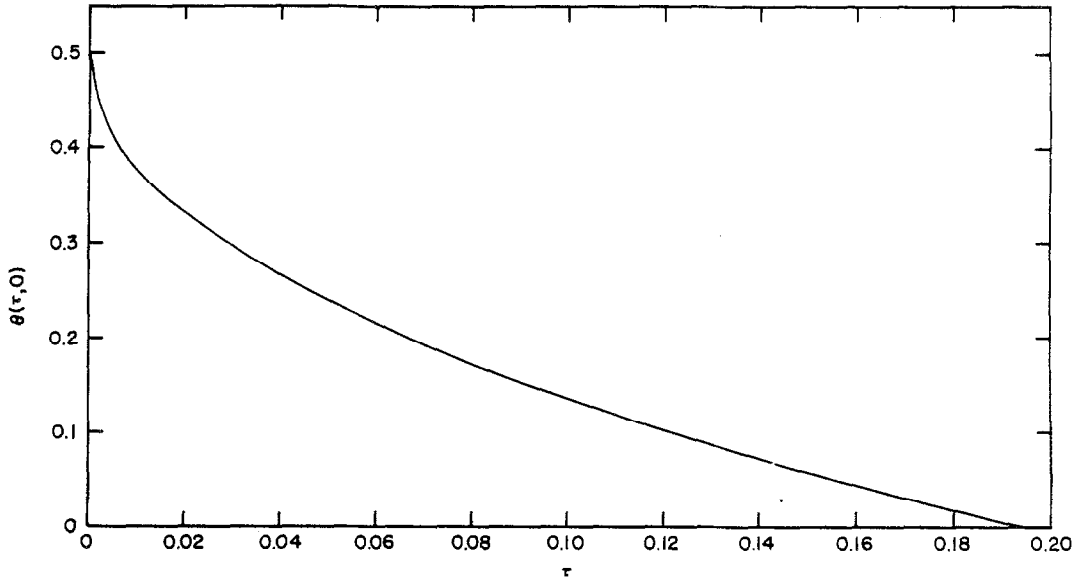


Fig. 3. Variation of the oxygen concentration at the surface with respect to time.

surface, $c(t, 0)$, for a given time $t > 0$, and then obtain β through the use of Eq. (33) which provides the following expression for β :

$$\beta = \frac{2c_0}{t} \left[\frac{0.5 \left(1 - \left(\frac{c(t, 0)}{c_0} \right) \right)}{1.13} \right]^2, \quad t > 0. \quad (34)$$

Knowing β from Eq. (34) and having an estimate of the diffusion coefficient D from a diffusion experiment [1, 4], we can now estimate the point of innermost oxygen penetration, X , through the use of Eq. (7).

It should be noted that if a series of experimental values of $c(t, 0)$, obtained at different times $t > 0$ and used in Eq. (34), give varying values of β , this implies that the assumption of constant absorption rate is not valid and that the oxygen consumption rate may depend on the oxygen concentration. In that case, the function $f(c)$ has to be constructed and replace β in Eq. (2); the resulting new set of model equations should have to be solved in order to obtain the oxygen concentration, $c(t, x)$. It is suggested that the Freundlich Equation [20] may provide an appropriate, as an approximation, functional form of $f(c)$; then the expression for $f(c)$ would have the following form:

$$f(c) = ac^b, \quad (35)$$

where a and b are constants which can be determined by isothermal experiments [20]. A natural extension of the present work is to consider the slab problem when the rate of consumption of oxygen depends on the oxygen concentration, i.e., Eq. (35), as well as the cases at which the geometry of the absorbing medium is cylindrical or spherical.

In Fig. 4, the variation of the average concentration, $\bar{\theta}$ with time is shown; as in the case of $\theta(\tau, 0)$, the establishment of a correlation between radiation dosage and average oxygen concentration may also allow time variant radiation treatments of cancerous tumors. From an experimental point of view, the establishment of a correlation between

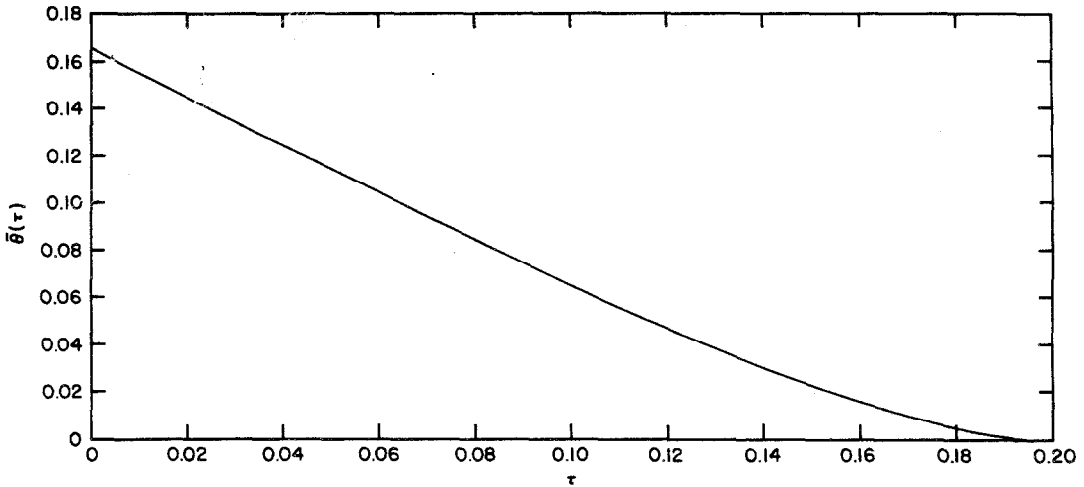


Fig. 4. Variation of the average oxygen concentration in the absorbing tissue with respect to time.

radiation dosage and surface oxygen concentration seems to be easier than one that involves the average oxygen concentration [1, 3].

CONCLUSIONS AND REMARKS

A mathematical model has been presented, which describes the process of oxygen diffusion and absorption in tissue. The unsteady-state part of the model accounts for the presence of a moving boundary which marks the furthest penetration of oxygen into the absorbing medium, and the solution of the model equations is obtained by orthogonal collocation after an appropriate change in the space variable transforms the moving boundary problem into one of fixed extent.

It was found that at the beginning of the diffusion, with absorption process, the motion of the boundary is slow, but as the oxygen continues to be consumed the absorption process substantially overtakes the diffusion and the speed of the moving boundary tends to infinity, as the time is approached at which there is no longer an oxygen concentration profile in the absorbing tissue.

Simple expressions were also presented for evaluating the surface oxygen concentration, the rate of consumption of oxygen per unit volume of the medium, and the point of innermost oxygen penetration.

Finally, approaches were discussed which may use the model predictions in developing time variant radiation treatments of cancerous tumors. In such treatments, the radiation dosage would be varied with the oxygen concentration so as to compensate for the lost killing effectiveness resulting from oxygen consumption by the tumor.

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NOTATION

- A_{ij} \equiv Elements of the discretization matrix A of the differential operator $\partial\theta/\partial\xi$
 a \equiv Constant in Eq. (35)
 B_{ij} \equiv Elements of the discretization matrix B of the differential operator $\partial^2\theta/\partial\xi^2$
 b \equiv Constant in Eq. (35)
 c \equiv Oxygen concentration
 c_0 \equiv Surface oxygen concentration in the steady-state part of the problem
 D \equiv Diffusion coefficient
 $f(c)$ \equiv Rate of consumption of oxygen per unit volume of absorbing tissue
 N \equiv Number of interior collocation points
 $p_N(\xi)$ \equiv Orthogonal polynomial
 t \equiv Time
 X \equiv Innermost oxygen penetration given by Eq. (7)
 $X(t)$ \equiv Position of the moving boundary
 x \equiv Spatial position
 y \equiv Dimensionless spatial position
 $y_0(\tau)$ \equiv Dimensionless position of the moving boundary
 y_{01}, y_{02} \equiv Assumed estimates of $y_0(\tau + \Delta\tau)$
 α \equiv Form factor; 0, 1, and 2 for slab, cylinder and sphere, respectively
 β \equiv Constant rate of consumption of oxygen per unit volume of the absorbing tissue
 $\Delta\tau$ \equiv Dimensionless time increment
 θ \equiv Dimensionless oxygen concentration
 $\bar{\theta}$ \equiv Average dimensionless oxygen concentration in absorbing tissue
 ξ \equiv Variable defined by Eq. (18)
 τ \equiv Dimensionless time
 i \equiv Integer value
 j \equiv Integer value
 n \equiv Integer value