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Numerical study of oxygen diffusion from capillary to tissues during hypoxia with external force effects

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Abstract

A mathematical model to simulate oxygen delivery through a capillary to tissues under the influence of an external force field is presented. The *multi-term general fractional diffusion equation* containing force terms and a time dependent absorbent term is taken into account. Fractional calculus is applied to describe the phenomenon of sub-diffusion of oxygen in both transverse and longitudinal directions. A new computational algorithm, i.e. the New Iterative Method (NIM) is employed to solve the spatio-temporal fractional partial differential equation subject to appropriate physical boundary conditions. Validation of NIM solutions is achieved with a Modified Adomian Decomposition Method (MADM). A parametric study is conducted for three loading scenarios on the capillary- radial force alone, axial force alone and the combined case of both forces. The results demonstrate that the force terms markedly influence the oxygen diffusion process. For example the radial force exerts a more profound effect than axial force on subdiffusion of oxygen indicating that careful manipulation of these forces on capillary–tissues may assist in the effective reduction of hypoxia or other oxygen depletion phenomena.

Keywords: Capillary-tissue diffusion; hypoxia; general fractional diffusion equation; New Iterative Method (NIM); axial-radial forces; spatio-temporal concentration plots.

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1. Introduction

Capillaries are thin and small blood vessels connecting arterioles with venules and forming networks through the body. In abnormal blood circulation, cells in the area most distal to the capillary at the venous end begin to suffer from hypoxia when perfusion levels drop to critically low values [**1-4**]. The insufficient oxygen delivery to tissue may interrupt metastasis and destroy part of the muscle.

The mechanisms controlling oxygen distribution are incompletely understood but involve a series of convective and diffusive processes. Convective oxygen in blood depends on *active, energy consuming processes generating flow in the circulation*. Diffusion transport refers to the *passive movement of oxygen down its concentration gradient across tissue barriers*, including the alveolar capillary membrane, and across the extracellular matrix between the tissue capillaries and individual cells to mitochondria. The amount of diffusive oxygen movement depends on the oxygen tension gradient and the diffusion distance, which is related to the tissue capillary density. The greater the difference between capillary and cellular oxygen concentration and the shorter the distance, the faster the rate of diffusion are reported in [**1, 2**]. However, should the oxygen tension gradient become affected or oxygen concentration levels in capillary become very low, *insufficient oxygenation* may lead to *hypoxia*.

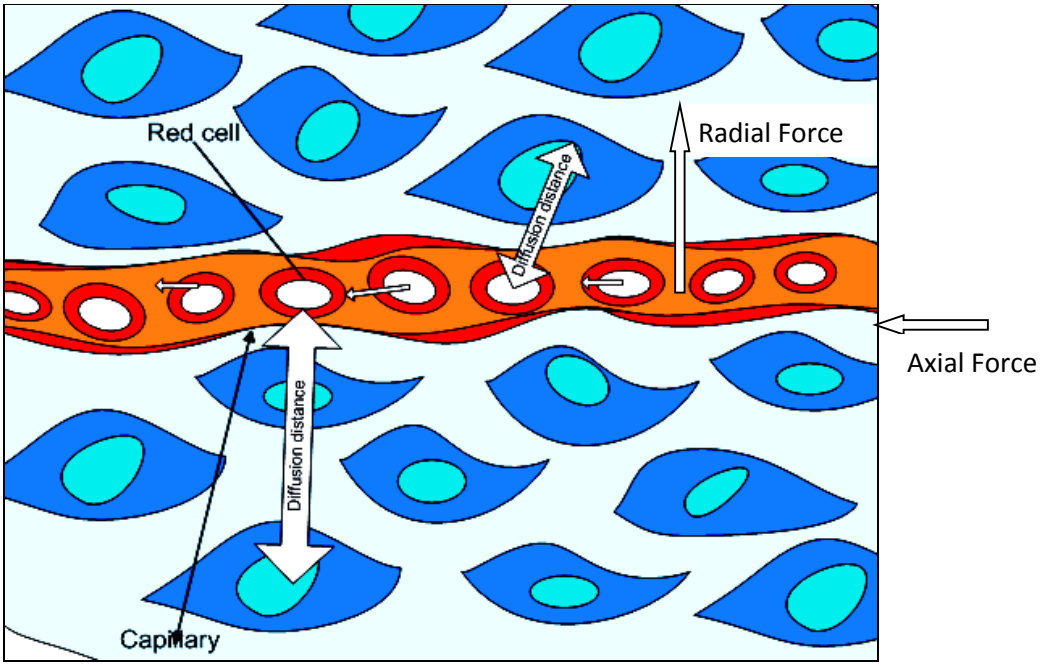

Fig.1. Diffusion of oxygen to tissues through a single capillary.

Previously, Go [**3**] used a mathematical model for oxygen delivery through capillaries in which the longitudinal diffusion of solute in capillaries was neglected and also it was assumed that the diffusion of oxygen and the consumption rate of oxygen are the same everywhere, which is an unrealistic simplification for clinical situations [**1**], as shown in Fig.1. The diffusion processes will differ in different places. Go [**3**] also identified that physical exertion boosts oxygen consumption rate but leads to depletion in oxygen from *some cells* and that cells engulfing capillaries *can* utilize or preserve more oxygen than required for a subsequent cycle. Srivastava and Rai[**4**] removed all the shortcomings discussed above and presented a new mathematical model for diffusion of oxygen of all types, i.e. for sub-diffusion and diffusion processes, using fractional calculus.

Analysis of fractional diffusion equations(which are obtained from the classical diffusion equations of mathematical physics by replacing the ordinary time derivative by a fractional time derivative), constitute a field of growing interest in mathematical biology and other fields. Numerous universal phenomena can be simulated to a greater degree of accuracy by exploiting the properties of these evolution equations. Analytical methods used to solve these equations have very restricted applications and the numerical techniques commonly used give rise to rounding-off errors. Keeping these in mind Srivastava and Rai [**4**] examined the effect of the concentration of the oxygen delivery from the capillary to the tissues by solving the linear and nonlinear multi-term fractional diffusion equations analytically using mathematical tools like the new iterative method (**NIM**) [6] and a modified Adomian decomposition method (MADM) [**5**].**NIM** was first proposed by the Indian mathematicians Daftardar-Gejji and Jafari [**6**] and subsequently implemented by Daftardar-Gejji and Bhalekar [**7,8**] to solve linear and nonlinear partial differential equations and fractional partial differential (diffusion wave) equations. The main advantage of this method is its computational simplicity; the solution obtained by this method is expected to give a better approximation in a straightforward manner.

The decomposition method of Adomian has also been applied to solve a wide class of nonlinear differential and partial differential equations (Adomian [**9, 11**], Adomian and Rach [**12**]) etc. Wazwaz [**13,5**] made further progress in this method with some modifications. The modification of the Adomian decomposition method will accelerate the rapid convergence of the series solution. This modified technique has been shown to be computationally efficient for solving several problems in applied fields (Wazwaz [**14-16**], Kaya and Yokus [**17**], Saha Ray [**18**]). Daftardar-Gejji and Bhalekar [**19**] used this method for solving multi-term linear and nonlinear diffusion wave equations of fractional order. Recently diffusion wave like models for physical problems have attracted considerable attention. Many studies have been communicated addressing a diverse range of engineering problems including seismology and acoustics by Manolis [**20**]) and

physiology (peristaltic flow of viscoelastic fluids with various factional models) by Tripathi and Beg [**21, 22**] and Tripathi [**23, 24**] and various numerical techniques have been employed.

In this work, we investigate a *multi-term fractional diffusion equation* which employs time fractional derivative by taking an absorbent term and external forces into account. Recently, Schot*et al.*[**25**] have proposed a generalized diffusion equation which employs space and time fractional derivatives, an absorbent (or source) term, and an external linear force field. This leads us for introducing the external forces along radial vector and axial line in our newly developed multi-term fractional diffusion equation for oxygen delivery through a capillary to tissues [**4**].

In the present article, our aim is to discuss the significant role of external forces on the oxygen delivery from capillary to tissues, considering all kinds of diffusion processes and to show its effect by means of numerical solutions for different conditions and their application for the treatment in hypoxia. The new iterative method (NIM) and modified Adomian decomposition method (MADM) are used to obtain the numerical solutions of the multi-term fractional diffusion equation for oxygen delivery from capillary to tissues containing absorbent term and external forces. The expressions for the concentrations for different times, radii and lengths of the capillaries, using the initial and boundary conditions, are deduced .Numerical computations are conducted using Mathematica and presented graphically. Also, comparisons are made between the **NIM** and **MADM** solutions, demonstrating excellent agreement.

2.The New Iterative Method (NIM)

Daftardar – Gejji and Jafari [**6**] have introduced a new iterative method for solving the functional equation:

$$C(\bar{x},t) = f(\bar{x},t) + L\big(C(\bar{x},t)\big) + N(C(\bar{x},t)). \quad \ldots\ldots (1)$$

Here*f* is a given function, *L* and *N* are given linear and nonlinear functions of *C* respectively, $\bar{x} = (r,z)$. We seek solution C of Eq. (1) having the series form

$$C(\bar{x},t) = \sum_{i=0}^{\infty} C_i(\bar{x},t). \quad \ldots\ldots (2)$$

Since *L* is linear, then:

$$L(\sum_{i=0}^{\infty} C_i) = \sum_{i=0}^{\infty} L(C_i). \quad \ldots\ldots (3)$$

The *non-linear* operator *N* is decomposed as follows (see [6]):

$$N(\sum_{i=0}^{\infty} C_i) = N(C_0) + \sum_{i=0}^{\infty}\{N\big(\sum_{j=0}^{i} C_j\big) - N\big(\sum_{j=0}^{i-1} C_j\big)\}. \quad \ldots\ldots (4)$$

From Eqs. (2) – (4), (1) is equivalent to

$$\sum_{i=0}^{\infty} C_i = f + \sum_{i=0}^{\infty} L(C_i) + N(C_0) + \sum_{i=0}^{\infty}\{N(\sum_{j=0}^{i} C_j) - N(\sum_{j=0}^{i-1} C_j)\}. \quad \ldots\ldots (5)$$

We define the recurrence relation

$$C_0 = f \ , \quad \ldots\ldots (6a)$$

$$C_1 = L(C_0) + N(C_0) \ , \quad \ldots\ldots (6b)$$

$$C_2 = L(C_1) + N(C_0 + C_1) - N(C_0), \quad \ldots\ldots (6c)$$

$$\vdots$$

$$C_{m+1} = L(C_m) + N(C_0 + C_1 + \cdots + C_m) - N(C_0 + C_1 + \cdots + C_{m-1}), \ m = 1,2, \ldots \ . \quad \ldots\ldots (6d)$$

Then,

$$(C_1 + \cdots + C_{m+1}) = L(C_0) + L(C_1) + \cdots + L(C_m) + N(C_0 + C_1 + \cdots + C_m), m = 1,2, \ldots\ldots (7)$$

and

$$\sum_{i=0}^{\infty} C_i = f + L(\sum_{i=0}^{\infty} C_i) + N(C_0) + N(\sum_{i=0}^{\infty} C_i). \quad \ldots\ldots (8)$$

For the convergence, see Ref. [6]. The k – term approximation solution of (1) and (2) is given by $C = C_0 + C_1 + \cdots + C_{k-1}$.

3. Mathematical Model for Oxygen Diffusion

A cylindrical capillary of radius, *R*, containing solute, is studied as a geometric model of the system. We assume that the rate of consumption by surrounding tissue is given by $\int_0^t \mu(t-x) \cdot C(r,z,x)dx$ [22].Here we present a new general mathematical model for diffusion of oxygen under the influence of external forces, i.e. *radial* force and *axial* force. Also, we discuss the effect of the *fractional order* of the derivatives as well as the influence of external forces on delivery of oxygen from capillary to tissues. Previously, the general mathematical model for diffusion of oxygen, as given by Srivastava and Rai [3] omitted external force.

To explain the sub-diffusion and diffusion phenomenon simultaneously, it is necessary to adopt a *fractional* diffusion equation, i.e. instead of $\frac{\partial C}{\partial t}$ as in Eq. (2) of [4] we have to use $\frac{\partial^\alpha C}{\partial t^\alpha}$ where $0 < \alpha < 1$ indicates the sub-diffusion process while $\alpha = 1$ represents the diffusion process, since longitudinal diffusion is also considered. Therefore the *net diffusion of oxygen to tissues* will be $\frac{\partial^\alpha C}{\partial t^\alpha} - \tau \frac{\partial^\beta C}{\partial t^\beta}$,where τ is the time lag in concentration of oxygen along the z-axis and $0 < \beta < \alpha \leq 1$. For this case, along the length of the capillaries, for large values of *z* the concentration of oxygen

C becomes very small due to the consumption of oxygen by the surrounding tissues, i.e. as $z \to \infty, C \to 0$.

Now, for force we have introduced $\frac{\partial}{\partial r}\{F(r) \cdot C(r,z,t)\}$**,** the force term along radial vector *r*, and $\frac{\partial}{\partial z}\{F(z) \cdot C(r,z,t)\}$, the force term along z – axis. Therefore, the new general equation for conveying oxygen from the capillary to the surrounding tissue is obtained:

$$\frac{\partial^{\alpha} C}{\partial t^{\alpha}} - \tau \frac{\partial^{\beta} C}{\partial t^{\beta}} = \nabla(d \cdot \nabla C) - \frac{\partial}{\partial r}\{F(r) \cdot C(r,z,t)\} - \frac{\partial}{\partial z}\{F(z) \cdot C(r,z,t)\} - \int_0^t \mu(t-x) \cdot C(r,z,x)dx \quad \ldots\ldots (9)$$

Here *C*(*r*, *z*, *t*) is the concentration of oxygen, *d* is the diffusion coefficient of oxygen, and this *d* may be a function of *C*. No flux on the boundary yields the following boundary condition:

$$\left.\frac{\partial C}{\partial r}\right|_{r \to R} = 0. \quad \ldots\ldots (10)$$

Consider at $t = 0$, $C(r, z, t) = g(r, z)$, and according to the condition as $z \to \infty, C \to 0$. Eq. (9) above is equivalent to the following *integral* equation:

$$C(r,z,t) = g(r,z)\left(1 - \tau \frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) + \tau D_t^{-(\alpha-\beta)} C + D_t^{-(\alpha-\beta)}\left(\nabla(d \cdot \nabla C)\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial r}\{F(r) \cdot C(r,z,t)\}\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial z}\{F(z) \cdot C(r,z,t)\}\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x) \cdot C(r,z,x)dx\right). \quad \ldots\ldots (11)$$

Now for a solution applying the new iterative method (**NIM**); implementing algorithm (6)) in Eq.(11) yields:

$$C_0(r,z,t) = g(r,z)\left(1 - \tau \frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) \quad \ldots\ldots (12a)$$

$$C_1(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_0 + D_t^{-(\alpha-\beta)}\left(\nabla(d \cdot \nabla C_0)\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial r}\{F(r) \cdot C_0(r,z,t)\}\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial z}\{F(z) \cdot C_0(r,z,t)\}\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x) \cdot C_0(r,z,x)dx\right) \quad \ldots\ldots (12b)$$

$$C_2(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_1 + D_t^{-(\alpha-\beta)}\left(\nabla(d \cdot \nabla C_1)\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial r}\{F(r) \cdot C_1(r,z,t)\}\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial z}\{F(z) \cdot C_1(r,z,t)\}\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x) \cdot C_1(r,z,x)dx\right) \quad \ldots\ldots (12c)$$

⋮ ⋮ ⋮ ⋮

$$C_{n+1}(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_n + D_t^{-(\alpha-\beta)}\left(\nabla(d\cdot\nabla C_n)\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial r}\{F(r)\cdot C_n(r,z,t)\}\right) -$$

$$D_t^{-\alpha}\left(\frac{\partial}{\partial z}\{F(z)\cdot C_n(r,z,t)\}\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x)\cdot C_n(r,z,x)dx\right)$$

…… (12d)

Applying the modified Adomian decomposition method (MADM), as elaborated in detail in [5]) to Eq.(11) leads to:

$$\bar{C}_0(r,z,t) = g(r,z)\left(1-\tau\frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) \quad \ldots\ldots \text{(13a)}$$

$$\bar{C}_1(r,z,t) = \tau D_t^{-(\alpha-\beta)}\bar{C}_0 + D_t^{-(\alpha-\beta)}\left(\nabla(d\cdot\nabla\bar{C}_0)\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial r}\{F(r)\cdot\bar{C}_0(r,z,t)\}\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial z}\{F(z)\cdot \bar{C}_0(r,z,t)\}\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x)\cdot\bar{C}_0(r,z,x)dx\right)\ldots\ldots \text{(13b)}$$

$$\bar{C}_2(r,z,t) = \tau D_t^{-(\alpha-\beta)}\bar{C}_1 + D_t^{-(\alpha-\beta)}\left(\nabla(d\cdot\nabla\bar{C}_1)\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial r}\{F(r)\cdot\bar{C}_1(r,z,t)\}\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial z}\{F(z)\cdot \bar{C}_1(r,z,t)\}\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x)\cdot\bar{C}_1(r,z,x)dx\right) \quad \ldots\ldots \text{(13c)}$$

⋮ ⋮ ⋮ ⋮

$$\bar{C}_{n+1}(r,z,t) = \tau D_t^{-(\alpha-\beta)}\bar{C}_n + D_t^{-(\alpha-\beta)}\left(\nabla(d\cdot\nabla\bar{C}_n)\right) - D_t^{-\alpha}\left(\frac{\partial}{\partial r}\{F(r)\cdot\bar{C}_n(r,z,t)\}\right) -$$

$$D_t^{-\alpha}\left(\frac{\partial}{\partial z}\{F(z)\cdot\bar{C}_n(r,z,t)\}\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x)\cdot\bar{C}_n(r,z,x)dx\right)$$

……. (13d)

The bar on *C* (i.e. $\bar{C}$) corresponds to the **MADM** approximation.

3.1 Case I-Oxygen delivery when only radial force is acting on capillary .

If *F*(*z*) = 0, from Eq.(9)we readily obtain:

$$\frac{\partial^\alpha C}{\partial t^\alpha} - \tau\frac{\partial^\beta C}{\partial t^\beta} = \nabla(d\cdot\nabla C) - \frac{\partial}{\partial r}\{F(r)\cdot C(r,z,t)\} - \int_0^t \mu(t-x)\cdot C(r,z,x)dx \quad \ldots\ldots \text{(14)}$$

Let d define a constant diffusivity. The*force term*, and $consumption\ rate\ parameter$, are defined as $F(r) = -k_1 r\ \ and\ \mu(t) = \frac{\delta}{\Gamma(\gamma)}t^{\gamma-1}$ respectively, following [22], where k_1 and δ are constants. In light of this, eq. (14) reduces to:

$$\frac{\partial^\alpha C}{\partial t^\alpha} - \tau\frac{\partial^\beta C}{\partial t^\beta} = d\nabla^2 C + \frac{\partial}{\partial r}\{k_1 r\cdot C(r,z,t)\} - \int_0^t \frac{\delta}{\Gamma(\gamma)}(t-x)^{\gamma-1}\cdot C(r,z,x)dx \quad \ldots\ldots \text{(15)}$$

which is *linear fraction differential equation*of order α in time t coordinate and of second order in space coordinates (r, z)(i.e. in cylidrical coordinates).

It can be shown that the equivalent *integral equation* of Eq. (15) takes the form:

$$C(r,z,t) = g(r,z)\left(1 - \tau\frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) + \tau D_t^{-(\alpha-\beta)}C + dD_t^{-(\alpha-\beta)}(\nabla^2 C) + k_1 D_t^{-\alpha}\big(C(r,z,t)\big)$$

$$+ k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r}C(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)}(t-x)^{\gamma-1}\cdot C(r,z,x)dx\right) \quad \ldots\ldots (16)$$

Here $g(r,z)$ is an *initial guess*.Now for a solution applying the new iterative method (**NIM**; in view of algorithm (6)) to Eq. (16) leads to:

$$C_0(r,z,t) = \left(r + \frac{R^2}{r}\right)e^{-z}\left(1 - \tau\frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) \quad \ldots\ldots (17a)$$

$$C_1(r,z,t) = \tau D_t^{-(\alpha-\beta)}C_0 + dD_t^{-(\alpha-\beta)}(\nabla^2 C_0) + k_1 D_t^{-\alpha}\big(C_0(r,z,t)\big) + k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r}C_0(r,z,t)\right) -$$

$$D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)}(t-x)^{\gamma-1}\cdot C_0(r,z,x)dx\right) \quad \ldots\ldots (17b)$$

$$C_2(r,z,t) = \tau D_t^{-(\alpha-\beta)}C_1 + dD_t^{-(\alpha-\beta)}(\nabla^2 C_1) + k_1 D_t^{-\alpha}\big(C_1(r,z,t)\big) + k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r}C_1(r,z,t)\right) -$$

$$D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)}(t-x)^{\gamma-1}\cdot C_1(r,z,x)dx\right) \quad \ldots\ldots (17c)$$

$$\vdots \qquad \vdots \qquad \vdots$$

$$C_n(r,z,t) = \tau D_t^{-(\alpha-\beta)}C_{n-1} + dD_t^{-(\alpha-\beta)}(\nabla^2 C_{n-1}) + k_1 D_t^{-\alpha}\big(C_{n-1}(r,z,t)\big)$$

$$+ k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r}C_{n-1}(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)}(t-x)^{\gamma-1}\cdot C_{n-1}(r,z,x)dx\right)$$

$$\ldots\ldots (17d)$$

Effectively the oxygen concentration field solution is:

$$C(r,z,t) = C_0(r,z,t) + C_1(r,z,t) + C_2(r,z,t) + \cdots\cdots + C_n(r,z,t) \quad \ldots\ldots\ldots (18)$$

3.2 Case II- Oxygen delivery when only axial force is acting on capillary

If $F(r) = 0$, from equation (9) we arrive at:

$$\frac{\partial^\alpha C}{\partial t^\alpha} - \tau\frac{\partial^\beta C}{\partial t^\beta} = \nabla(d\cdot\nabla C) - \frac{\partial}{\partial z}\{F(z)\cdot C(r,z,t)\} - \int_0^t \mu(t-x)\cdot C(r,z,x)dx \quad \ldots\ldots (19)$$

Again let *d*define a constant diffusivity. The axial*force term* and *consumption rate parameter,* are defined as$F(z) = -k_2 z \; and \;\; \mu(t) = \frac{\delta}{\Gamma(\gamma)} t^{\gamma-1}$, respectively, following [22], wherek_2 and δ are constants. Now, eq. (19) reduces to:

$$\frac{\partial^\alpha C}{\partial t^\alpha} - \tau \frac{\partial^\beta C}{\partial t^\beta} = d\nabla^2 C + \frac{\partial}{\partial z}\{k_2 z \cdot C(r,z,t)\} - \int_0^t \frac{\delta}{\Gamma(\gamma)} (t-x)^{\gamma-1} \cdot C(r,z,x)dx \qquad \ldots\ldots(20)$$

which constitutes another linear fraction differential equation of order α in time *t* coordinate and of second order in space coordinates (*r*, *z*) i.e. in cylidrical coordinates. As the order α increases, it is anticipated that oxygen delivery concentration will be elevated. The equivalent *integral* equation of Eq.(20) is:

$$C(r,z,t) = g(r,z)\left(1 - \tau \frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) + \tau D_t^{-(\alpha-\beta)} C + d D_t^{-(\alpha-\beta)}(\nabla^2 C) + k_2 D_t^{-\alpha}\big(C(r,z,t)\big)$$

$$+ k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial z} C(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)} (t-x)^{\gamma-1} \cdot C(r,z,x)dx\right) \quad \ldots\ldots (21)$$

Implementing **NIM** based on the algorithm defined in Eq.(6), the resulting solution of Eq.(21) emerges as:

$$C_0(r,z,t) = \left(r + \frac{R^2}{r}\right) e^{-z}\left(1 - \tau \frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) \quad \ldots\ldots (22a)$$

$$C_1(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_0 + d D_t^{-(\alpha-\beta)}(\nabla^2 C_0) + k_2 D_t^{-\alpha}\big(C_0(r,z,t)\big) + k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial z} C_0(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)} (t-x)^{\gamma-1} \cdot C_0(r,z,x)dx\right) \quad \ldots\ldots (22b)$$

$$C_2(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_1 + d D_t^{-(\alpha-\beta)}(\nabla^2 C_1) + k_2 D_t^{-\alpha}\big(C_1(r,z,t)\big) + k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial z} C_1(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)} (t-x)^{\gamma-1} \cdot C_1(r,z,x)dx\right) \quad \ldots\ldots (22c)$$

$$\vdots \qquad\qquad \vdots \qquad\qquad \vdots$$

$$C_n(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_{n-1} + d D_t^{-(\alpha-\beta)}(\nabla^2 C_{n-1}) + k_2 D_t^{-\alpha}\big(C_{n-1}(r,z,t)\big) + k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial r} C_{n-1}(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)} (t-x)^{\gamma-1} \cdot C_{n-1}(r,z,x)dx\right)$$

…… (22d)

Therefore the complete spatio-temporal oxygen concentration solution is:

$$C(r,z,t) = C_0(r,z,t) + C_1(r,z,t) + C_2(r,z,t) + \cdots\cdots + C_n(r,z,t) \quad \ldots\ldots (23)$$

3.3 Case III- Oxygen delivery when radial and axial both forces are acting on capillary .

For this third and final case, we consider both forces in action.Once again we define a constant diffusivity,*d*. The radial force term, axial *force term* and *consumption rate parameter,* are defined as respectively, $F(r) = -k_1 r,\ \ F(z) = -k_2 z,\ and\ \ \mu(t) = \frac{\delta}{\Gamma(\gamma)} t^{\gamma-1}$, in accordance with [22]. Here k_1, k_2 and δ are all constants.

It follows that Eq.(9) becomes:

$$\frac{\partial^\alpha C}{\partial t^\alpha} - \tau \frac{\partial^\beta C}{\partial t^\beta} = d\nabla^2 C + \frac{\partial}{\partial r}\{k_1 r \cdot C(r,z,t)\} + \frac{\partial}{\partial z}\{k_2 z \cdot C(r,z,t)\} - \int_0^t \frac{\delta}{\Gamma(\gamma)} (t-x)^{\gamma-1} \cdot C(r,z,x)dx$$

……(24)

which is again a *linear* fraction differential equation of order α in time *t* coordinate and of second order in space coordinates (*r*, *z*) i.e. again in cylidrical coordinates. As elaborated earlier, for Cases I and II, *an equivalent integral equation* for Eq.(24) may be derived:

$$\begin{aligned} C(r,z,t) = \quad & g(r,z)\left(1 - \tau \frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) + \tau D_t^{-(\alpha-\beta)} C + d D_t^{-(\alpha-\beta)}(\nabla^2 C) + k_1 D_t^{-\alpha}\left(\frac{\partial}{\partial r} C(r,z,t)\right) + \\ & k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r} C(r,z,t)\right) + k_2 D_t^{-\alpha}\left(C(r,z,t)\right) + k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial z} C(r,z,t)\right) - \\ & D_t^{-\alpha}\left(\int_0^t \frac{\delta}{\Gamma(\gamma)} (t-x)^{\gamma-1} \cdot C(r,z,x)dx\right). \end{aligned} \quad \ldots\ldots (25)$$

Where $g(r,z)$ is initial guess in Eq.(25). Considering$g(r,z) = \left(r + \frac{R^2}{r}\right) e^{-z}$ and $\tau = \frac{1}{3}$ as in [3],we obtain:

$$C_0(r,z,t) = \left(r + \frac{R^2}{r}\right) e^{-z}\left(1 - \tau \frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right) \quad \ldots\ldots.(26a)$$

$$C_1(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_0 + D_t^{-(\alpha-\beta)}\left(\nabla(d \cdot \nabla C_0)\right) + k_1 D_t^{-\alpha}\left(\frac{\partial}{\partial r} C_0(r,z,t)\right) +$$

$$k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r} C_0(r,z,t)\right) + k_2 D_t^{-\alpha}\left(C_0(r,z,t)\right) + k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial z} C_0(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x) \cdot C_0(r,z,x)dx\right) \quad \ldots\ldots..(26b)$$

$$C_2(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_1 + D_t^{-(\alpha-\beta)}\left(\nabla(d\cdot\nabla C_1)\right) + k_1 D_t^{-\alpha}\left(\frac{\partial}{\partial r}C_1(r,z,t)\right) +$$

$$k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r}C_1(r,z,t)\right) + k_2 D_t^{-\alpha}\left(C_1(r,z,t)\right) + k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial z}C_1(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x)\cdot C_1(r,z,x)dx\right) \quad \ldots\ldots(26c)$$

$$\vdots \qquad \vdots \qquad \vdots \qquad \vdots$$

$$C_{n+1}(r,z,t) = \tau D_t^{-(\alpha-\beta)} C_n + D_t^{-(\alpha-\beta)}\left(\nabla(d\cdot\nabla C_n)\right) + k_1 D_t^{-\alpha}\left(\frac{\partial}{\partial r}C_n(r,z,t)\right) +$$

$$k_1 r D_t^{-\alpha}\left(\frac{\partial}{\partial r}C_n(r,z,t)\right) + k_2 D_t^{-\alpha}\left(C_n(r,z,t)\right) + k_2 z D_t^{-\alpha}\left(\frac{\partial}{\partial z}C_n(r,z,t)\right) - D_t^{-\alpha}\left(\int_0^t \mu(t-x)\cdot C_n(r,z,x)dx\right)\ldots\ldots \text{(26d)}$$

The resultingsolution for oxygen delivery concentration is:

$$C(r,z,t) = C_0(r,z,t) + C_1(r,z,t) + C_2(r,z,t) + \cdots\cdots + C_n(r,z,t) \qquad \ldots\ldots \text{(27)}$$

4. Computational Results and Discussion

In this section, we shall examine a range of computations performed using **NIM**. The solutions generated with this algorithm have been shown to demonstrate excellent correlation with the **MADM** algorithm (**Fig.2**). Inspection of this figure reveals that oxygen concentrate depletes rapidly with increasing radial coordinate through the capillary i.e. diffusion across transverse direction of the capillary is inhibited significantly.

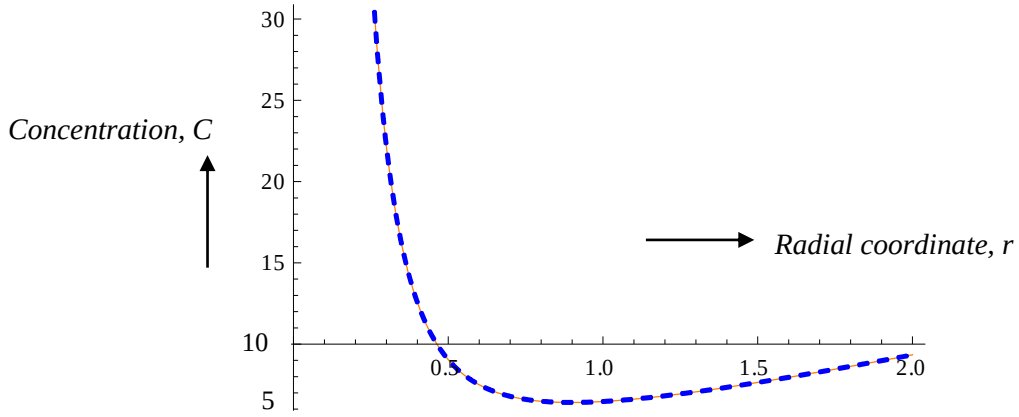

Fig.2. Comparison between **NIM** (orange) and **MADM** (dotted blue) concentration solutions (for $\alpha = 0.9; \beta = 0.4; R = 0.005; \gamma = 2; \mathrm{k}_1 = 1; \mathrm{k}_2 = 1; \tau = \frac{1}{3}; \delta = 1.; d = 1.5; z = 1$).

In **Figs.2-12**, a sufficiently accurate solution (and convergence rate) is achieved with a four term appoximation in all calculations.

As with the radial force scenario (Case I), for numerical solutions (as depicted in **Figs.3-8**), we consider $g(r,z) = \left(r + \frac{R^2}{r}\right)e^{-z}$ and $\tau = \frac{1}{3}$ as in [4], and also consider the case where the following biophysical data applies: $\alpha = 0.9; \beta = 0.4; R = 0.005; \gamma = 2.; \mathrm{k}_1 = 1.; \mathrm{k}_2 = 0 (Since\ F(z) = 0\ taken\ in\ Case\ I); \delta = 1.; d = 1.5$.

Figs 3 and 4 depict the *radial-temporal oxygen concentration distribution* and *axial-temporal oxygen concentration distribution*, at respectively, prescribed axial and radial coordinate locations.

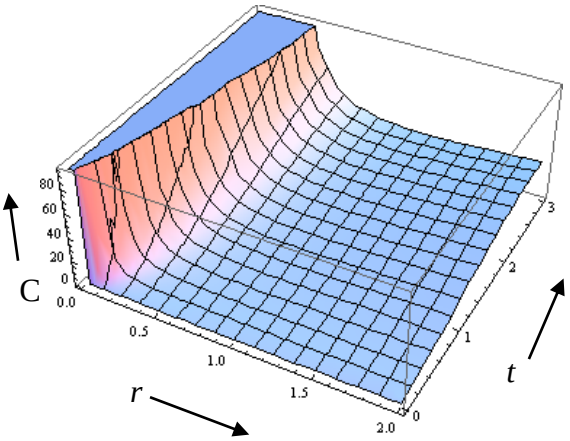

Fig.3. (*C* at *z* = 0.5)

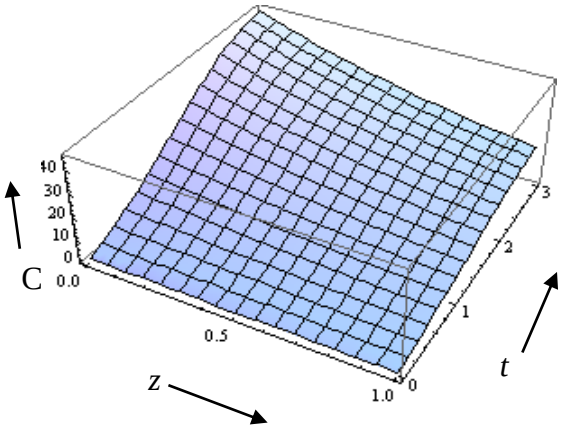

Fig.4. (*C* at *r* = 1)

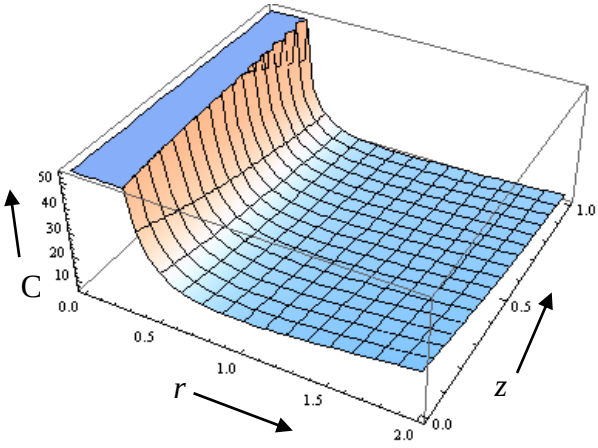

Fig.5. (*C* at *t* = 1.0)

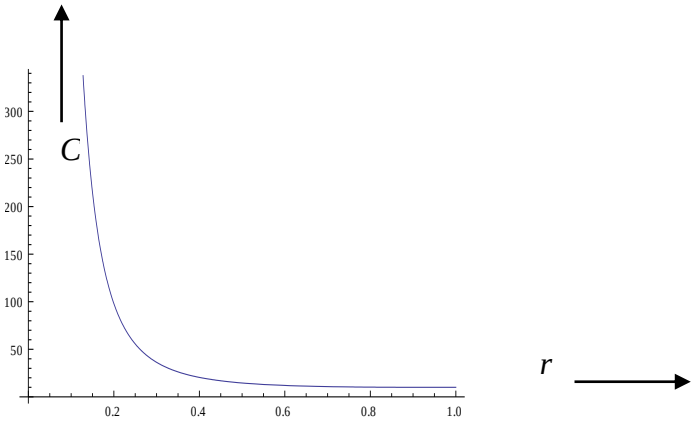

Fig.6. (*C* at *z* = 0.5, *t* = 1)

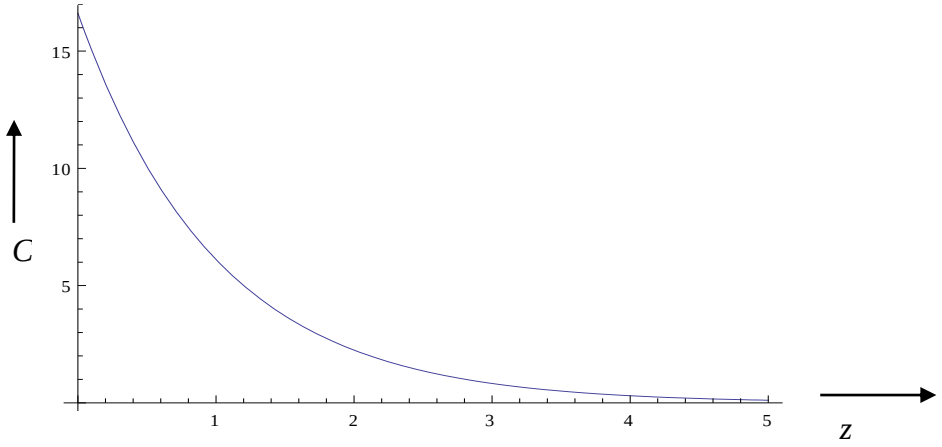

Fig.7. (at r =1,t= 1)

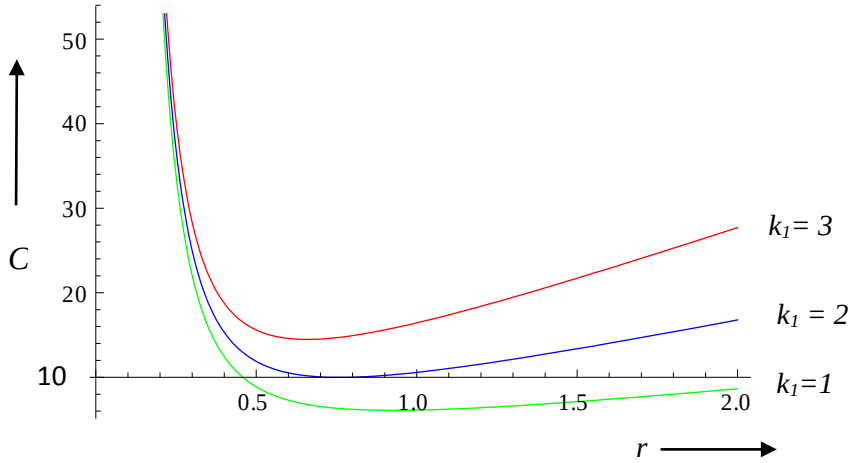

Fig.8 ($at\ z = 1; t = 1; k_2 = 1$)

There is a significant deviation between these profiles. For the radial distribution (**Fig. 3**), a high oxygen concentration is sustained for all time values, at low radial coordinate, but diminishes strongly as the r values increase, reaching a minimum at maximum radial coordinate. Conversely for the axial distribution (**Fig. 4**) concentration is minimized for all values of axial coordinate and is only elevated with passage of time. It is found to be maximized at low z values and high time values, and furthermore although the concentration magnitudes decrease again with increasing z values, they are always greater than for low time values. **Fig. 5** depicts the isochronal radial-axial concentration distribution i.e. at fixed time (t=1). Again we observe that oxygen concentration delivery attains a peak for low radial coordinate values and low axial coordinate, and decays strongly as both coordinates increase. These trends are further confirmed in Figs.6 &7. It is also noteworthy that the values of the concentration are at least an order of magnitude greater in Fig.6 than Fig.7. Therefore although both profiles are depleted rapidly with increasing coordinate values, the radial concentration delivery is greatly in excess of the axial concentration delivery.

Fig.8 illustrates the effect of radial force on oxygen concentration, via the parameter, k_1. It is observed that, when only radial force acting on the capillary – tissues system , the concentration of oxygen is dramatically elevated i.e. consumption of oxygen is greater with radial force present than in the absence of radial force. Also, as force varies concentration of oxygen also varies accordingly. The plots while similar, exhibit an increasingly pronounced peak at large r value and low z value as k_1 increases from 1 through 2 to 3. However k_2 remains the same i.e. equal to 0 since in this case I, *F(z)* is not considered.

As with the axial force scenario (Case II), we develop a numerical solution. We consider (as depicted in **Figs.9-11**) $g(r,z) = \left(r + \frac{R^2}{r}\right)e^{-z}$ and $\tau = \frac{1}{3}$ as in [4], with the following prescribed data:

$\alpha = 0.9; \beta = 0.4; R = 0.005; \gamma = 2.; \mathrm{k}_1 = 0 (since\ in\ this\ case\ F(r) is\ not\ considered); \mathrm{k}_2 = 1; \delta = 1.; d = 1.5.$

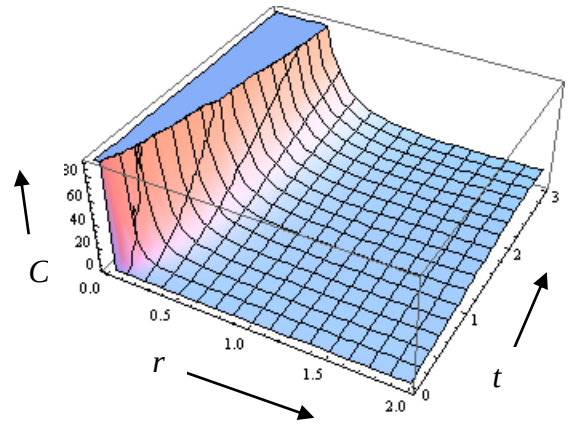

Fig.9. (*C* for *z* = 1)

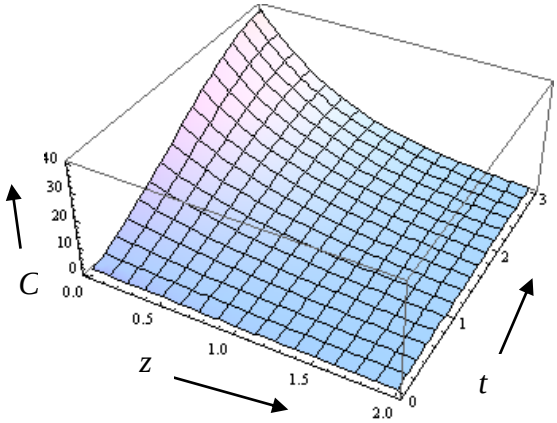

Fig.10. (*C* for *r* = 1)

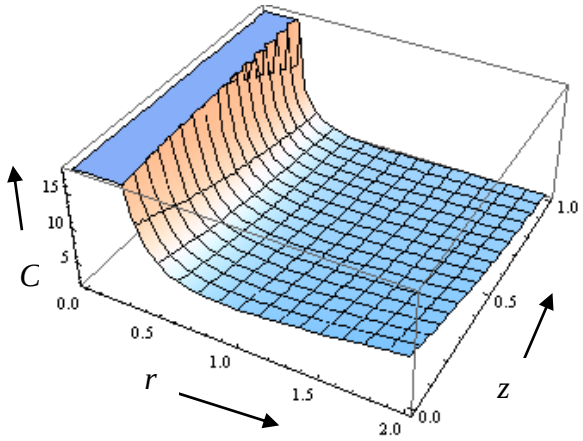

Fig.11. (*C* for *t* = 1)

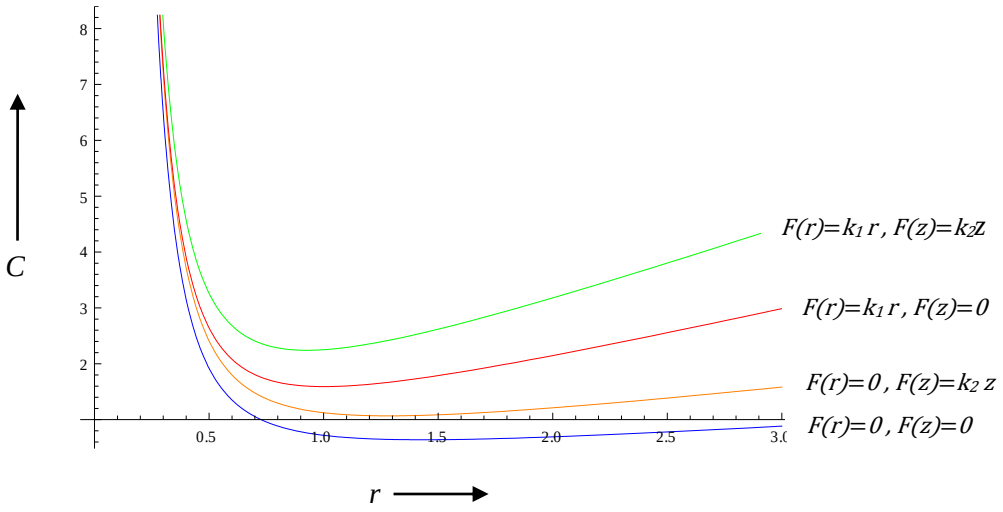

Fig.12. Effect of external forces on sub-diffusion of oxygen at k_1=1,k_2=1.

Figs.9-11 illustrate further computations, similar to those described in **Figs.3-5**, albeit at different *r, z* and *t* values, respectively. Only marginal differences are observed. The general trends are of the same fashion with peaks and troughs in oxygen concentration delivery arising at the same locations.

Finally, from **Fig. 12** it is apparent that, when both the forces (radial force *F(r)* and axial force *F(z)*) are acting simultaneously on the system, the maximum effect is attained i.e. though there is a sub-diffusion of oxygen from capillary to tissues, nevertheless owing to the presence of these forces, tissues will receive much more oxygen than without such forces present, or in the event of only a *single force* (either radial force or axial force) being present. It is also observed that radial force is much effective than axial force in controlling the sub-diffusion of oxygen. This has significant implications for replenishment of oxygen in vital clinical scenarios such as hypoxia.

5.Conclusions

In the present article a generalized diffusion equation has been presented to simulate more accurately the oxygen delivery from capillary to tissues. The new model features both *absorbent* (consumption) terms as well as *force* (radial and axial) terms. The differential form of the new generalized equation describing oxygen transport phenomena has been rendered into a more amenable integral form, subject to pertinent boundary conditions, using fractional calculus. This integral equation has been solved using **NIM** (New Iterative Method) and solutions validated with **MADM** (**M**odified **A**domian **D**ecomposition **M**ethod). The computations have shown that both force terms markedly effect the diffusion of oxygen, although the radial force is found to be more influential and more dramatically enhances concentration of oxygen. Although new parameters

arise in this generalized model, certain refinements are currently being explored to further improve the model. Aspects of this refinement include utilizing a variety of initial guesses for the solution, using force terms which are non-linear and incorporating a variable diffusivity (as a function of concentration). However the present model is sufficiently complex to demonstrate that via judicious manipulation of external forces acting on capillary–tissue oxygen diffusion systems, the detrimental effects of hypoxia associated with subdiffusion of oxygen may be suppressed, if not eliminated entirely. Capillary bed structure [**26**] has also been neglected in the present analysis, and this is also an important area for future investigation.Since oxygen is a crucial factor for metastasis, arteriolar occlusions [**27**], which are also common, serve to decreases oxygen concentration and may contribute to muscle damage. This also remains an important area to analyse, and could be achieved via extending the current work to *multiple non-homogeneous capillaries,* featuring different solutes and via controlling each stable source of oxygen by a transient function to model disturbed hemodynamics.

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