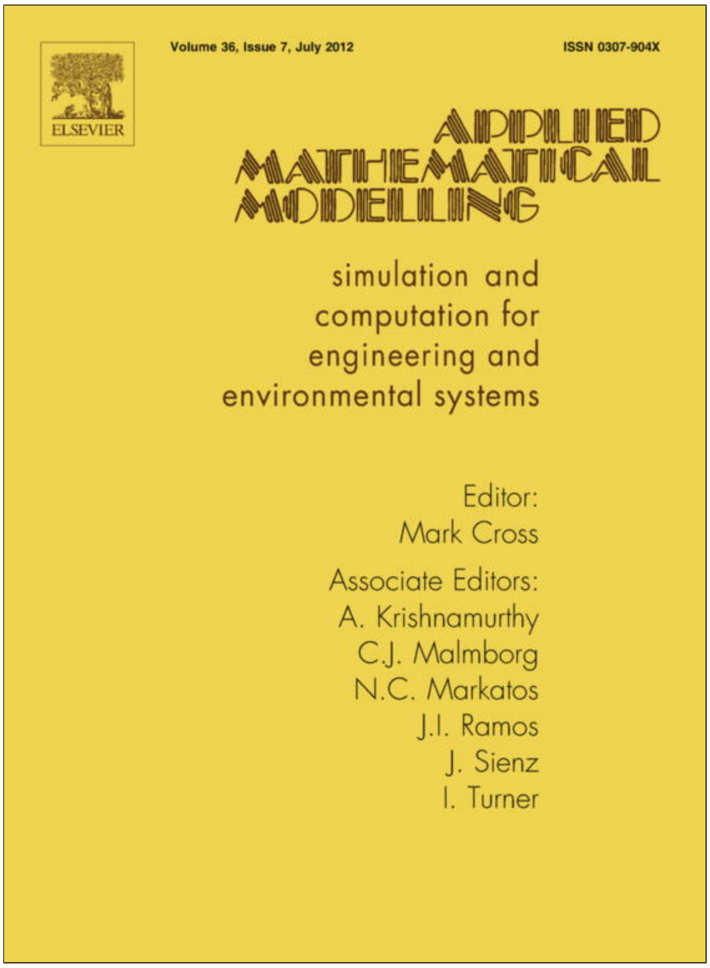
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Short communication

An analytical solution for diffusion and nonlinear uptake of oxygen in a spherical cell

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ABSTRACT

We develop a new analytical solution for a reactive transport model that describes the steady-state distribution of oxygen subject to diffusive transport and nonlinear uptake in a sphere. This model was originally reported by Lin [S.H. Lin, Oxygen diffusion in a spherical cell with nonlinear oxygen uptake kinetics, J. Theor. Biol. 60 (1976) 449–457] to represent the distribution of oxygen inside a cell and has since been studied extensively by both the numerical analysis and formal analysis communities. Here we extend these previous studies by deriving an analytical solution to a generalized reaction–diffusion equation that encompasses Lin's model as a particular case. We evaluate the solution for the parameter combinations presented by Lin and show that the new solutions are identical to a grid-independent numerical approximation.

1. Introduction and background

A model of oxygen diffusion and nonlinear uptake in a sphere was originally proposed and solved by Lin [1]. The same model was then re-examined and re-solved by McElwain [2]. The complete dimensional governing equation can be found in the original manuscripts of Lin and McElwain [1,2]. Here we present and analyze the corresponding nondimensional governing equation and boundary conditions which can be written as,

$$0 = \frac{d^2C}{dR^2} + \frac{2}{R}\frac{dC}{dR} - \frac{\alpha C}{K + C}, \tag{1}$$

subject to

$$\frac{dC}{dR} = 0 \quad \text{at } R = 0 \tag{2}$$

and

$$\frac{dC}{dR} = H(1 - C) \quad \text{at } R = 1. \tag{3}$$

The governing equation is a steady-state reaction–diffusion equation representing oxygen transport by linear diffusion in a sphere with spherical symmetry. The oxygen uptake is described by the nonlinear Michaelis–Menten model [3] with a maximum reaction rate α and the half-saturation concentration K. The boundary condition at $R = 0$ ensures that the oxygen distribution is symmetric at the center of the sphere, and the boundary condition at $R = 1$ specifies a flux of oxygen at the cell

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membrane. This flux is proportional to the difference in oxygen concentration across the cell membrane. The proportionality coefficient, H, represents the membrane permeability [1,2].

The solution of this boundary value problem has been studied extensively, beginning with the work of Lin [1] who presented numerical solutions of the governing equation. This first study was re-examined by McElwain [2] who presented new numerical solutions of the governing equation and showed that Lin's [1] previous results were in error. Since this initial controversy, this problem has been studied by many researchers from two different points of view. Firstly, approximate solutions of the governing equation have been studied using a variety of techniques including shooting methods [4], spline approximations [5,6], high-order finite difference methods [7] and regular perturbation methods [2]. Secondly, this problem has also been analyzed formally leading to expressions for upper and lower bounds of the solution [8] as well as proving the uniqueness and existence of the solution [9]. We will build on these previous studies and, for the first time, derive an analytical solution of the model. Our approach [10] is related to the decomposition method [11] and the homotopy analysis method [12–14] since our solution takes the form of a convergent series.

Our solution approach is very flexible and we will demonstrate this by studying a generalization of Eqs. (1)–(3) which we write as

$$0 = \frac{d^2C}{dR^2} + \frac{a}{R}\frac{dC}{dR} - f(C), \tag{4}$$

subject to

$$\frac{dC}{dR} = 0 \quad \text{at } R = 0 \tag{5}$$

and

$$\frac{dC}{dR} = H(1 - C) \quad \text{at } R = 1. \tag{6}$$

Comparing Eqs. (1)–(3) and Eqs. (4)–(6), we see that two generalizations have been made:

(1) Eq. (4) is written in terms of a constant a which can be chosen to reflect Cartesian ($a = 0$), cylindrical ($a = 1$) or spherical ($a = 2$) geometry;
(2) Eq. (4) is relevant for any uptake model $f(C)$.

By setting $a = 2$ and $f(C) = \alpha C/(C + K)$, we recover the original nondimensional model considered by Lin [1] and McElwain [2]. Our aim is now to solve the general problem.

2. General solution

Our strategy is to find the solution of Eqs. (4)–(6) and we begin by assuming that the solution can be written in terms of a series expansion. We note that other researchers are also using series solutions to find analytical solutions to mathematical models that are used to represent various biological and biochemical processes. For example, our previous research has shown that certain steady-state reactive transport problems that arise in the chemical engineering literature can be solved by using series expansions [10]. In this previous work we showed that certain known closed-form solutions correspond to Taylor series solutions when the closed form solution is expanded in a series. Furthermore, we showed that some reactive-transport processes do not appear to have a closed-form solution, however we were able to express and evaluate the solution in a series without any difficulty. Other applications of series solutions include studying susceptible-recovered-infected models of epidemic dynamics [15,16] as well as finding the solution of differential equation models that arise in age-structured models [17].

We assume that the solution of Eqs. (4)–(6) is sufficiently smooth so that it can be expanded in a Maclaurin series given by

$$C(R) = \sum_{i=0}^{\infty} \frac{R^i}{i!}\frac{d^iC}{dR^i}\bigg|_{R=0} = C(0) + R\frac{dC}{dR}\bigg|_{R=0} + \frac{R^2}{2!}\frac{d^2C}{dR^2}\bigg|_{R=0} + \frac{R^3}{3!}\frac{d^3C}{dR^3}\bigg|_{R=0} + \cdots \tag{7}$$

To determine the values of the derivatives at $R = 0$ we rewrite Eq. (4) as

$$\frac{d^2C}{dR^2} = -\frac{a}{R}\frac{dC}{dR} + f(C). \tag{8}$$

Assuming that $f(C)$ is sufficiently differentiable, we evaluate derivatives of $C(R)$ by recursively differentiating Eq. (8) to give,

$$
\begin{aligned}
\frac{d^2C}{dR^2} &= -\frac{a}{R}\frac{dC}{dR} + f(C),\\
\frac{d^3C}{dR^3} &= \frac{a}{R^2}\frac{dC}{dR} - \frac{a}{R}\frac{d^2C}{dR^2} + \frac{df(C)}{dC}\frac{dC}{dR},\\
\frac{d^4C}{dR^4} &= -\frac{2a}{R^3}\frac{dC}{dR} + \frac{2a}{R^2}\frac{d^2C}{dR^2} - \frac{a}{R}\frac{d^3C}{dR^3} + \frac{d^2f(C)}{dC^2}\left(\frac{dC}{dR}\right)^2 + \frac{df(C)}{dC}\frac{d^2C}{dR^2},\\
&\vdots
\end{aligned} \tag{9}
$$

We now evaluate the derivative expressions in Eq. (9) at the origin by substituting $R = 0$ into Eq. (9) and impose the boundary condition that $\frac{dC}{dR} = 0$ at $R = 0$. By imposing these two conditions simultaneously, we see that many terms in Eq. (9) must be evaluated using L'Hopital's rule [18] in the limit that $R \to 0^+$, which gives:

$$
\begin{aligned}
\left.\frac{dC}{dR}\right|_{R=0} &= 0,\\
\left.\frac{d^2C}{dR^2}\right|_{R=0} &= \frac{f(C_0)}{1+a},\\
\left.\frac{d^3C}{dR^3}\right|_{R=0} &= 0,\\
\left.\frac{d^4C}{dR^4}\right|_{R=0} &= \frac{\left.\frac{d^2C}{dR^2}\right|_{R=0}\left.\frac{df}{dC}\right|_{C=C_0}}{1+\frac{a}{3}},\\
\left.\frac{d^5C}{dR^5}\right|_{R=0} &= 0,\\
\left.\frac{d^6C}{dR^6}\right|_{R=0} &= \frac{3\left.\frac{d^2C}{dR^2}\right|_{R=0}\left.\frac{d^2f}{dC^2}\right|_{C=C_0} + \left.\frac{d^4C}{dR^4}\right|_{R=0}\left.\frac{df}{dC}\right|_{C=C_0}}{1+\frac{a}{5}},\\
&\vdots
\end{aligned} \tag{10}
$$

where $C_0 = C(0)$. These derivative terms evaluated at $R = 0$ allow us to express the Maclaurin series solution (Eq. (7)) as

$$
C(R) = C_0 + \frac{R^2}{2!}\left[\frac{f(C_0)}{1+a}\right] + \frac{R^4}{4!}\left[\frac{\left.\frac{d^2C}{dR^2}\right|_{R=0}\left.\frac{df}{dC}\right|_{C=C_0}}{1+\frac{a}{3}}\right] + \frac{R^6}{6!}\left[\frac{3\left.\frac{d^2C}{dR^2}\right|_{R=0}\left.\frac{d^2f}{dC^2}\right|_{C=C_0} + \left.\frac{d^4C}{dR^4}\right|_{R=0}\left.\frac{df}{dC}\right|_{C=C_0}}{1+\frac{a}{5}}\right] + \mathcal{O}(R^8) \tag{11}
$$

2.1. Convergence and limitations

The i^{th} term in the Maclaurin series is

$$
\frac{R^i}{i!}\left(\frac{\partial^{i-2}}{\partial R^{i-2}}\left[-\frac{a}{R}\frac{dC}{dR} + f(C)\right]\right)\Bigg|_{R=0}, \quad i \geqslant 2. \tag{12}
$$

The derivative expressions in Eq. (12) can be evaluated at $R = 0$ by applying L'Hopital's rule as we previously demonstrated. The resulting derivative expressions are combinations of derivatives of the functions $C(R)$ and $f(C)$ evaluated at $R = 0$ and $C = C(0)$, respectively. Since we have assumed that $C(R)$ and $f(C)$ are everywhere sufficiently differentiable, applying the ratio test to this series shows that the radius of convergence is infinite [18]. This means that the series will converge for all values of R and this will be true for all standard forms of the uptake function $f(C)$ (e.g. polynomial functions and certain rational

Table 1
Four different sets of parameters, used by Lin [1] and McElwain [2], are given to define solutions labeled (b), (c), (d) and (e). The value of C_0 obtained from the series solutions truncated after the R^6 term and the corresponding value of C_0 obtained from the fine-mesh numerical simulations are given.

Solution	α	K	H	C_0 (Numerical)	C_0 (Series)
(b)	0.38065	0.03119	5.0	0.91404	0.91404
(c)	0.38065	0.03119	0.5	0.69583	0.69583
(d)	0.76129	0.03119	5.0	0.82848	0.82848
(e)	0.38065	0.31187	5.0	0.93311	0.93311

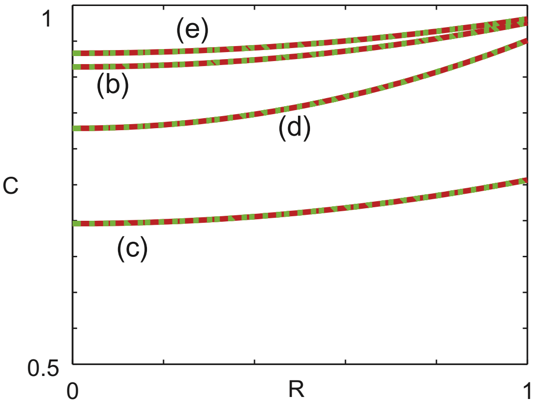

Fig. 1. Comparison of the Maclaurin series solutions (solid red) and the fine-mesh numerical solutions (dotted green) of Eqs. (1)–(3). Four different solutions labeled (b), (c), (d) and (e) are presented with the corresponding parameter values in Table 1. These parameter values corresponded to various experimentally-motivated conditions described in Lin [1] and McElwain [2]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

functions such as the Michaelis–Menten model). Therefore the Maclaurin series is an exact solution that always converges for all practical choices of $f(C)$, furthermore we can implement the series solution by truncating the series after a finite number of terms [10,19]. The question of how to determine the level of truncation will be addressed in Section 2.2.

2.2. Boundary condition at R = 1

To implement the series solution for a particular problem we must determine C_0 by applying the remaining boundary condition at $R = 1$, given by $\frac{dC}{dR} = H(1 - C)$. To satisfy this condition, we differentiate the general series with respect to R to obtain $\frac{dC}{dR}$. After truncating the series expressions for $C(R)$ and $\frac{dC}{dR}$, we substitute these truncated series into the boundary condition at $R = 1$ to obtain an algebraic relationship that determines the value of C_0. This algebraic relationship can be solved to find C_0 using any standard root finding technique (e.g. the bisection algorithm, or a standard in-built routine such *fsolve* in Maple). This process gives an approximate value of C_0. However, since the series solution is convergent we can arbitrarily increase the accuracy of this approximation by simply retaining more terms in the truncated series and examine the convergence behavior of C_0 as further terms are retained in the series. Examining the convergence behavior of C_0 as more terms are retained in the truncated series is particularly straightforward provided that the solution is implemented using a symbolic software platform.

3. Case study: spherical geometry and Michaelis–Menten uptake

By substituting $a = 2$ and $f(C) = \alpha C/(K + C)$, we obtain the solution corresponding to the previous work of Lin [1] and McElwain [2]. This solution, truncated after the R^6 term, can be written as

$$C(R) = C_0 + \frac{\alpha C_0 R^2}{3!(C_0 + K)} + \frac{\alpha^2 C_0 K R^4}{5!(C_0 + K)^3} - \frac{\alpha^3 C_0 K (10C_0 - 3K) R^6}{7![3(C_0 + K)^5]} + \mathcal{O}(R^8). \tag{13}$$

Although we have truncated the solution after the R^6 term, it is straightforward to extend this solution to include any higher order terms if necessary. To apply the boundary condition at $R = 1$, we differentiate Eq. (13) with respect to R to obtain an expression for $\frac{dC}{dR}$. To find C_0 we substitute these truncated series into the boundary condition $\frac{dC}{dR} = H(1 - C)$ at $R = 1$ and solve the resulting algebraic expression for C_0 using the *fsolve* command in Maple. We now apply the solution to study four different parameter combinations given by Lin [1] and McElwain [2]. The parameter combinations are summarized in Table 1 and the corresponding solution profiles are given in Fig. 1.

To demonstrate the accuracy of the Maclaurin series solution, we generated numerical solutions of Eqs. (4)–(6) and compare these with the Maclaurin series solutions in Fig. 1. To generate the numerical solutions, spatial derivatives in Eqs. (4)–(6) were replaced with a standard centered in space finite difference approximation on a uniform grid with spacing δx [20–22]. This gives a tridiagonal system of nonlinear algebraic equations. The nonlinear algebraic system was linearized using Picard iteration [23], and the resulting systems of linear equations were solved using the Thomas algorithm [20]. Iterations were performed until the maximum change in the value of the dependent variable between iterations fell below a small tolerance, ϵ_1. For all results presented here we used a fine grid and a strict convergence tolerance by setting $\delta x = 1 \times 10^{-5}$ and $\epsilon_1 = 1 \times 10^{-8}$. The values of C_0 obtained from the truncated series solution and the fine-mesh numerical solutions are given in Table 1 and show that the analytical solution agrees with the numerical solution correct to five decimal places. Furthermore, the numerical profiles are superimposed on the series solutions in Fig. 1 showing that, in all cases considered, the series solutions and the numerical solutions are visually indistinguishable at this scale.

We also generated equivalent numerical results using a finer grid and an even stricter convergence tolerance which, for all problems considered in this work, gave results that were visually indistinguishable from the numerical results on the original fine grid. This grid refinement procedure ensured that our numerical results are grid independent.

4. Conclusion

We have derived an analytical solution of a general reaction–diffusion model in an arbitrary geometry (Cartesian, cylindrical or spherical) with an arbitrary (linear or nonlinear) uptake term. This general solution can be used to represent a number of biological processes including the transport and uptake of oxygen in a spherical cell. This particular problem has received a great deal of interest both from the analysis and numerical communities however we believe that this is the first time that a general solution has been presented.

Our solution is a Maclaurin series, and we obtain expressions for the general term in the Maclaurin series to show that the series is convergent. Numerical simulations of the previous problems considered by Lin [1] and McElwain [2] are reproduced and we show that the series solution is identical to fine-mesh numerical solutions.

The Maclaurin series solution presented here could be further generalized and applied to other spherical reactive-transport problems from the mathematical biology literature. A classical application of spherical reactive-transport models is to consider the growth of a solid tumor [24]. Solid tumor growth models can replicate key experimental observations which include the formation of an oxygen-depleted necrotic core, a quiescent zone and an oxygen-rich proliferation zone [24,25]. These solid tumor growth models are an extension of the type of model considered in this work since they are an example of a multi-species reactive-transport model [25,21,22] involving two (or more) reactive-transport equations for each relevant component and these equations are coupled. For the solid tumor growth models the relevant components are usually the concentration of tumor cells and the concentration of certain growth factors or nutrients such as oxygen and glucose [25]. As far as we are aware the Maclaurin series solution technique has not yet been applied to these kinds of multi-species reactive transport problems and this remains an open question to be explored in the future.

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