CHAPTER 5

THE MULTICELL SPHEROID MODEL FOR AVASCULAR TUMOUR GROWTH

5.1 Introduction

The mathematical model of the solid tumour growth in this chapter focuses on the initial avascular stage of growth. A realistic model of spheroid growth should include certain nonuniformities in the central processes of inhibition of mitosis, consumption of nutrients, cell proliferation, as well as the dependence of cell mitotic rate on growth inhibitor concentration, geometrical constraints and central necrosis. Several papers (Adams, 1986; Adams, 1987a; Adams, 1987b; Chaplain & Britton, 1993) have focused their attention on the chemical inhibition of mitosis within multicell spheroids. The main assumption of the modeling is that a growth inhibitory factor (GIF) is produced within the spheroid in some prescribed spatially-dependent manner to reflect the observed cellular heterogeneity within spheroids. The existence and properties of chemicals which inhibit mitosis are very well documented (Bullogh & Deol, 1971; Folkman & Hochbrg, 1973; Marks, 1973; Iversen, 1985; Iversen, 1991). In this work, we focus on the diffusion of a growth inhibitory factor within a multicell spheroid and its possible effect on cell mitosis and proliferation. The control of mitosis in tissues can be modeled as a schematic mechanism in which self-regulating growth is achieved as a result of negative feedback from the growing tissue (Brugal & Pelmont, 1975). The mitosis is assumed to be controlled by a discontinuous switch-like mechanism, such that if the concentration of the

GIF is less than some threshold level θ, say, in any region within the tissue, mitosis occurs in this region, whereas if the concentration is greater than θ, mitosis is completely inhibited.

In this chapter, we examine the performance of the ADM and HPM when applied to avascular tumour growth model. This is extended model from the previous one which include a source function S(r) and λ as the inhibitor production rate.

5.2 Mathematical background

The differential equation describing the diffusion, production and degradation of the GIF within the spheroid can be written as,

$$\frac{\partial C}{\partial t} = D\nabla^2 C + f(C) + \lambda S(r), \qquad r \in \Omega \tag{5.1}$$

where $C = C(r,t)$ is the concentration of GIF within the spheroid occupying the region $\Omega \in R^3$ and λ is the inhibitor production rate (molecules per unit volume per second). $S(r)$ is a smooth source function of the form (Chaplain & Britton, 1993)

$$S(r) = \begin{cases} 1 - \dfrac{r^2}{R^2}, & 0 \le r \le R, \\ 0, & r > R. \end{cases} \tag{5.2}$$

The model we consider is

$$\frac{\partial C}{\partial t} = D\nabla^2 C - \gamma C + \lambda S(r), \qquad r \in \Omega, \tag{5.3}$$

$$\frac{\partial C}{\partial r} = 0, \qquad r = 0, \tag{5.4}$$

$$D(r)\frac{\partial C}{\partial r} + PC = 0, \qquad \text{on} \qquad \partial\Omega, \quad P \geq 0, \tag{5.5}$$

$$C(r,0) = 0 \qquad , \qquad r \in \Omega, \tag{5.6}$$

where we assume (initially) that production of GIF is via the uniform source function, P is the permeability of the tissue surface, γ is the depletion rate and D is the diffusion coefficient.

Considering the spherical geometry described in the introduction and assuming radial symmetry, the above system reduces to

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D\frac{\partial C}{\partial r}\right) - \gamma C + \lambda, \qquad r \leq R, \tag{5.7}$$

$$\frac{\partial C}{\partial r} = 0, \qquad r = 0, \tag{5.8}$$

$$D(r)\frac{\partial C}{\partial r} + PC = 0, \qquad r = R. \tag{5.9}$$

$$C(r,0) = 0$$

Before continuing with an analysis of the above system, it is appropriate to recast them in terms of dimensionless variables. Denoting by R, θ and t, the radius of the spheroid GIF concentration, and as reference time, we introduce the following dimensionless variables

$$\bar{r} = \frac{r}{R}, \qquad \bar{c} = \frac{C}{\theta}, \qquad \bar{t} = \frac{Dt}{R^2}. \tag{5.10}$$

The system now becomes, upon dropping the tildes for notational convenience,

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D\frac{\partial C}{\partial r}\right) - B^2 C + aB^2\left(1 - r^2\right), \tag{5.11}$$

$$\frac{\partial C}{\partial r} = 0, \qquad r = 0, \tag{5.12}$$

$$\frac{\partial C}{\partial r} + \frac{B}{\eta}C = 0, \qquad r = 1. \tag{5.13}$$

$$C(r,0) = 0 \tag{5.14}$$

where $\kappa^2 = \frac{\gamma}{D}$, $B = \kappa R$, $a = \frac{\lambda}{\gamma\theta}$ and $\eta = \frac{(\gamma D)^{\frac{1}{2}}}{P}$. With this non-dimensionalisation, we see that once the parameters for a particular spheroid are determined, the only undetermined parameter is the radius R. The solutions to the above equation can therefore be monitored for different size of spheroids. Thus we can analyse the system using different values for the spheroid radius R while holding constant the various observable parameters associated with the system, i.e., D, γ, P and $\frac{\lambda}{\theta}$ (Brugal & Pelmont, 1975).

Let $r = x$ and using the transformation

$$u(x,t) = xC(x,t) \tag{5.15}$$

Then,

$$\begin{aligned} \frac{\partial u}{\partial x} &= C + x\frac{\partial C}{\partial x} \\ \frac{\partial^2 u}{\partial x^2} &= 2\frac{\partial C}{\partial x} + x\frac{\partial^2 C}{\partial x^2} \\ \frac{\partial u}{\partial t} &= x\frac{\partial C}{\partial t} \end{aligned} \tag{5.16}$$

Eqs. (5.15) – (5.16) substituted into Eq. (5.11) becomes

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - B^2 u + aB^2 x\left(1 - x^2\right) \tag{5.17}$$

Subject to initial condition

$$u(x,0)=0 \tag{5.18}$$

The approximate solution to Eq. (5.17) is obtained by integrating Eq. (5.17) once with respect to t and using the initial condition, where we obtained

$$u(x,t)= f(x)+D\int_0^t \frac{\partial^2 u(x,t)}{\partial x^2}dt - B^2\int_0^t u(x,t)dt + aB^2\int_0^t x(1-x^2)dt \tag{5.19}$$

We set $g(x)= f(x)+D\int_0^t \frac{\partial^2 u(x,t)}{\partial x^2}dt - B^2\int_0^t u(x,t)dt$ (5.20)

In Eq. (5.20), we assume $g(x)$ is bounded for all x in $J=[0,T],(T\in\Re)$ and

$$|t-T|\le m', \forall 0\le t\,,\tau\le T \tag{5.21}$$

We also set

$$F(u)=B^2u \tag{5.22}$$

The terms $\frac{\partial^2 u}{\partial x^2}$ and $F(u)$ are Lipschitz continuous with

$$\left|\frac{\partial^2 u}{\partial x^2}-\frac{\partial^2 u*}{\partial x^2}\right|\le L_1|u-u*|,$$

$$|F(u)-F(u*)|\le L_2|u-u*|,$$

and

$$\alpha = T(m'L_1+m'L_2)$$

$$\beta = 1-T(1-\alpha) \tag{5.23}$$

5.3. Adomian Decomposition Method (ADM)

The Adomian Decomposition Method is applied in Eq. (5.17) to get

$$L_t u = D\frac{\partial^2 u}{\partial x^2} - B^2 u + aB^2 x\left(1 - x^2\right) \tag{5.24}$$

where

$$L_t = \frac{\partial}{\partial t} \tag{5.25}$$

is an integrable differential operator with

$$L_t^{-1} = \int_0^t (.)dt \tag{5.26}$$

Operating on both sides of Eq. (5.24) with the integral operator L^{-1} defined by Eq. (5.26) leads to

$$u(x,t) = f(x) + L_t^{-1}\left(D\frac{\partial^2 u}{\partial x^2} - B^2 u + aB^2 x\left(1 - x^2\right)\right)$$

(5.27)

where $f(x) = u(x,0)$

The Adomian decomposition method assumes the solution in the series form (Adomian, 1994):

$$u(x,t) = \sum_{n=0}^{\infty} u_n(x,t) \tag{5.28}$$

Substituting Eq. (5.28) into (5.27) gives

$$\sum_{n=0}^{\infty} u_n(x,t) = u(x,0) + L^{-1}\left[D\sum_{n=0}^{\infty} u_{n_{xx}} - B^2 \sum_{n=0}^{\infty} u_n + aB^2 x\left(1-x^2\right)\right] \tag{5.29}$$

The components $u_n(x,t)$ of the solution $u(x,t)$ can be elegantly completed using the recurrence relation.

$$u_0(x,t) = f(x) + \int_0^t aB^2 x\left(1-x^2\right) d\tau \tag{5.30}$$

$$u_{n+1}(x,t) = \int_0^t \left(Du_{n_{xx}} - B^2 u_n\right) d\tau \quad , \ \forall n \geq 0 \tag{5.31}$$

Having determined the components u_0 , u_1, u_2 , … the solution u in a series form defined by Eq. (5.28) follows immediately.

5.4 Homotopy Perturbation Method (HPM)

To solve Eq. (5.17) with the HPM method, we construct the following homotopy:

$$H(\nu, p) = (1-p)\left(\frac{\partial \nu}{\partial t} - \frac{\partial u_0}{\partial t}\right) + \left(\frac{\partial \nu}{\partial t} - D\frac{\partial^2 \nu}{\partial x^2} + B^2 \nu - aB^2 x\left(1-x^2\right)\right) = 0 \tag{5.32}$$

or

$$\frac{\partial \nu}{\partial t} - \frac{\partial u_0}{\partial t} = p\left[D\frac{\partial^2 \nu}{\partial x^2} - B^2 \nu + aB^2 x\left(1-x^2\right) - \frac{\partial u_0}{\partial t}\right] = 0 \tag{5.33}$$

where $p \in [0,1]$ is an embedding parameter and v_o is an arbitrary initial approximation satisfying the given initial condition.

In HPM, the solution of Eq. (5.33) is expressed as

$$v = v_0 + pv_1 + p^2 v_2 + p^3 v_3 + \ldots\ldots \tag{5.34}$$

Hence, the approximate solution of Eq. (5.17) is expressed as a series of the power of *p*, i.e

$$v(x,t) = \lim_{p \to 1} v = v_0 + v_1 + v_2 + v_3 + \ldots\ldots = \sum_{n=0}^{\infty} v_n \tag{5.35}$$

Substituting Eq. (5.34) into Eq. (5.33) and equally the coefficients of the terms with the identical powers of p :

$$p^0: \quad \frac{\partial v_0}{\partial t} - \frac{\partial u_0}{\partial t} = 0 \tag{5.36}$$

$$p^1: \quad \frac{\partial v_1}{\partial t} = D\frac{\partial^2 v_0}{\partial x^2} - B^2 v_0 + aB^2 x(1 - x^2) - \frac{\partial u_0}{\partial t} = 0 \tag{5.37}$$

$$p^2: \quad \frac{\partial v_2}{\partial t} = D\frac{\partial^2 v_1}{\partial x^2} - B^2 v_1 = 0 \tag{5.38}$$

$$p^3: \quad \frac{\partial v_3}{\partial t} = D\frac{\partial^2 v_2}{\partial x^2} - B^2 v_2 = 0 \tag{5.39}$$

$$p^4: \quad \frac{\partial v_4}{\partial t} = D\frac{\partial^2 v_3}{\partial x^2} - B^2 v_3 = 0 \tag{5.40}$$

Solving Eqs. (5.36 – 5.40), we have the recursive relation as follows:

$$v_0 = f(x) = u(x,0) \tag{5.41}$$

$$v_{n+1}(x,t) = \int_0^t \left(D v_{n_{xx}} - B^2 v_n\right) d\tau , \quad \forall n \geq 0 \tag{5.42}$$

5.5 Existence and convergence of ADM and HPM

Theorem 5.1: Let $0 < \alpha < 1$, then Eq. (5.17) as a unique solution.

Proof: Let u and u^* be two different solutions of Eq. (5.17) then

$$\left|u - u^*\right| = \left| D\int_0^t \left[\frac{\partial^2 u(x,t)}{\partial x^2} - \frac{\partial^2 u^*(x,t)}{\partial x^2}\right] dt - \beta^2 \int_0^t \left[u(x,t) - u^*(x,t)\right] dt \right|$$

$$\leq \int_0^t \left| D\left[\frac{\partial^2 u(x,t)}{\partial x^2} - \frac{\partial^2 u^*(x,t)}{\partial x^2}\right]\right| dt + \beta^2 \int_0^t \left|u(x,t) - u^*(x,t)\right| dt$$

$$\leq T\left(m' L_1 + m' L_2\right)\left|u - u^*\right|$$

$$= \alpha \left|u - u^*\right|$$

From which we get $(1-\alpha)\left|u - u^*\right| \leq 0$. Since $0 < \alpha < 1$, then $\left|u - u^*\right| = 0$. Implies $u = u^*$ and completes the proof.

Theorem 5.2: The series solution $u(x,t)=\sum_{i=0}^{\infty}u_i(x,t)$ of Eq. (5.17) using ADM converges if $0<\alpha<1$, $|u(x,t)|<\infty$.

Proof: Denote as $(C[J],\|.\|)$ the Banach space of all continuous functions on J with the norm $\|f(t)\|=\max\forall_t\in J$. Define the sequence of partial series $\{S_n\}$; Let S_n and S_m be arbitrary partial sums with $n\geq m.$ We prove that S_n is a Cauchy sequence in this Banach space:

$$\|S_n-S_m\|=\max_{\forall t\in J}|S_n-S_m|$$

$$=\max_{\forall t\in J}\left|\sum_{i=m+1}^{n}u_i(x,t)\right|$$

$$=\max_{\forall t\in J}\left|\sum_{i=m+1}^{n}\left(\int_0^t Du_{i_{xx}}\,dt-\int_0^t\beta^2u_i\,dt\right)\right|$$

$$=\max_{\forall t\in J}\left|D\int_0^t\left(\sum_{i=m}^{n-1}u_{i_{xx}}\right)dt-\beta^2\int_0^t\left(\sum_{i=m}^{n-1}u_i\right)dt\right|$$

From Kalla (2008), we have

$$\sum_{i=m}^{n-1}u_{i_{xx}}=G^2(S_{n-1})-G^2(S_{m-1})$$

$$\sum_{i=m}^{n-1}u_i=F(S_{n-1})-F(S_{m-1})$$

So

$$\|S_n - S_m\| = \max_{\forall t \in J} \left| D\int_0^t [G^2(S_{n-1}) - G^2(S_{m-1})]dt - \beta^2 \int_0^t [F(S_{n-1}) - F(S_{m-1})dt \right|$$

$$\leq |D| \int_0^t |G^2(S_{n-1}) - G^2(S_{m-1})| dt + |\beta^2| \int_0^t |F(S_{n-1}) - F(S_{m-1})| dt$$

$$\leq \alpha \|S_n - S_m\|$$

Let $n = m+1$, then

$$\|S_{m+1} - S_m\| \leq \alpha \|S_m - S_{m-1}\|$$

$$\leq \alpha^2 \|S_{m-1} - S_{m-2}\|$$

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$$\leq \alpha^m \|S_1 - S_0\|$$

From the triangle inequality, we have

$$\|S_n - S_m\| \leq \|S_{m+1} - S_m\| + \|S_{m+2} - S_{m+1}\| + ... + \|S_n - S_{n-1}\|$$

$$\leq \left(\alpha^m + \alpha^{m+1} + ... + \alpha^{n-m-1}\right) \|S_1 - S_0\|$$

$$\leq \alpha^m \left(1 + \alpha + \alpha^2 + ... + \alpha^{n-m-1}\right) \|S_1 - S_0\|$$

$$\leq \alpha^m \left(\frac{1-\alpha^{n-m}}{1-\alpha}\right) \|u_1(x,t)\|$$

Since $0<\alpha<1$, we have $\left(1-\alpha^{n-m}\right)<1$, then $\left\|S_n - S_m\right\| \le \dfrac{\alpha^m}{1-\alpha}\max_{\forall t\in J}\left|u_1(x,t)\right|$. But $\left|u_1(x,t)\right|<\infty$, so as $m\to\infty$ then $\left\|S_n - S_m\right\|\to 0$. We confidence that $\{S_n\}$ is a Cauchy sequence in $C[J]$, therefore the series is converges and the proof is completed.

Theorem 5.3: If $\left|u_m(x,t)\right|\le 1$, , then the series solution $u(x,t)=\sum_{i=0}^{\infty}u_i(x,t)$ of Eq. (5.17) converges to the exact solution by using HPM.

Proof: We set

$$\phi_n(x,t)=\sum_{i=1}^{n}n_i(x,t)$$

$$\phi_{n+1}(x,t)=\sum_{i=1}^{n+1}n_i(x,t)$$

So,

$$\begin{aligned}\left|\phi_{n+1}(x,t)-\phi_n(x,t)\right| &= \left|\phi_n + u_n - \phi_n\right| \\ &= \left|u_n\right| \\ &\le \sum_{k=0}^{m-1}|D|\left|\int_0^t\right|\frac{\partial^2 u_{m-k-1}}{\partial x^2}\left|dt+\left|\beta^2\right|\left|\int_0^t\right|\left|u_{m-k-1}\right|dt\end{aligned}$$

Thus

$$\sum_{n=0}^{\infty}\left\|\phi_{n+1}(x,t)-\phi_n(x,t)\right\|\le (m-1)\alpha\left|f(x)\right|\sum_{n=0}^{\infty}\alpha^n$$

Since $0<\alpha<1$, therefore $\lim_{n\to\infty}u_n(x,t)=u(x,t)$.

5.6 Numerical experiment

In this section, we compute numerically Eq. (5.17) by the ADM and HPM methods.

From Eq. (5.17),

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - B^2 u + aB^2 x\left(1 - x^2\right) \tag{5.43}$$

subject to initial condition

$$u(x,0) = 0 \tag{5.44}$$

5.6.1 ADM Method

From Eqs.(5.30 – 5.31), we can obtain the first four terms of the solution as

$$u_0(x,t) = aB^2 x\left(1 - x^2\right)t \tag{5.45}$$

$$u_1(x,t) = -aB^2 x\left(3D + \frac{B^2}{2}\left(1 - x^2\right)\right)t^2 \tag{5.46}$$

$$u_2(x,t) = aB^2 x\left(2D + \frac{B^2}{6}\left(1 - x^2\right)\right)t^3 \tag{5.47}$$

$$u_3(x,t) = -\frac{aB^6}{4}\left(3D + \frac{B^2}{6}\left(1 - x^2\right)\right)t^4 \tag{5.48}$$

We substitutes Eqs. (5.45) - (5.48) into (5.28), then we obtain the solution of Eq. (5.17) in as below:

$$u(x,t) = aB^2x(1-x^2)t - aB^2x\left(3D+\frac{B^2}{2}(1-x^2)\right)t^2 + aB^4x\left(2D+\frac{B^2}{6}(1-x^2)\right)t^3$$

$$-\frac{aB^6}{6}\left(3D+\frac{B^2}{6}(1-x^2)\right)t^4 + \ldots\ldots\ldots\ldots.. \qquad (5.49)$$

5.6.2 HPM method

Following the HPM method, from Eq. (5.36), we obtain

$$v_0 = u_0(x,t) = aB^2x(1-x^2)t \qquad (5.50)$$

From Eq. (5.37), we obtain

$$v_1 = \int_0^t \left(D\frac{\partial^2 v_0}{\partial x^2} - B^2v_0 + aB^2x(1-x^2) - \frac{\partial u_0}{\partial t}\right)dt$$

$$= -aB^2x\left[3D+\frac{B^2}{2}(1-x^2)\right]t^2 \qquad (5.51)$$

From Eq. (5.38),

$$v_2 = \int_0^t \left(D\frac{\partial^2 v_1}{\partial x^2} - B^2v_1\right)dt$$

$$= aB^4x\left(2D+\frac{B^2}{6}(1-x)^2\right)t^3 \qquad (5.52)$$

From Eq. (5.39),

$$\nu_3 = \int_0^t (D\frac{\partial^2 \nu_2}{\partial x^2} - B^2 \nu_2)dt$$

$$= -\frac{aB^6}{4} x\left(3D + \frac{B^2}{6}\left(1 - x^2\right)\right)t^4 \qquad (5.53)$$

From Eq. (5.40),

$$\nu_4 = \int_0^t (D\frac{\partial^2 \nu_3}{\partial x^2} - B^2 \nu_3)dt$$

$$= -\frac{aB^8}{20} x\left(9D + \frac{B^2}{6}\left(1 - x^2\right)\right)t^5 \qquad (5.54)$$

We substitutes Eqs. (5.50) - (5.54) into (5.35), then we obtain the solution of Eq. (5.17) as

$$\nu(x,t) = aB^2 x\left(1 - x^2\right)t - aB^2 x\left(3D + \frac{B^2}{2}\left(1 - x^2\right)\right)t^2 + aB^4 x\left(2D + \frac{B^2}{6}\left(1 - x^2\right)\right)t^3$$

$$-\frac{aB^6}{6}\left(3D + \frac{B^2}{6}\left(1 - x^2\right)\right)t^4 - \frac{aB^8}{20} x\left(9D + \frac{B^2}{6}\left(1 - x^2\right)\right)t^5 + \ldots\ldots \qquad (5.55)$$

It is obvious that the first four terms approximate solutions (Eqs. (5.45 – 5.48)) obtained using ADM are the same as the first four terms (Eqs. (5.50 – 5.54)) of the HPM.

Figures 5.1 and 5.2 show the results for ADM and HPM solution for various values of R, which show the development of a spheroid from its early stages of growth to its diffusion-limited size of a stable radius of 0.2 cm. Our results are in good agreement with Chaplain and Britton (1993) where the threshold value for the GIF concentration is C = 1 as shown as horizontal line in Fig. 5.2. Thus if the concentration of GIF is greater than 1 in any region within the spheroid, then mitosis will be inhibited in that region. This enables regions within the spheroid where mitosis is taking place and where mitosis is inhibited (necrotic core) to be easily distinguished. Fig. 5.2 shows that the model predicts that the onset of necrosis occurs in the center of the spheroid (C = 1 at r = 0) at a radius between 0.03 and 0.037 cm. This prediction are well accord with the experimental data of Folkman and Hochberg (1973) which show that necrotic cells first appear at the center when the spheroids are 0.015 – 0.02 cm in radius. Fig. 5.3 shows the GIF concentration is increase as the time increase. This clearly proves the time dependent of GIF concentration which against Chaplain and Britton (1993) steady-state model.

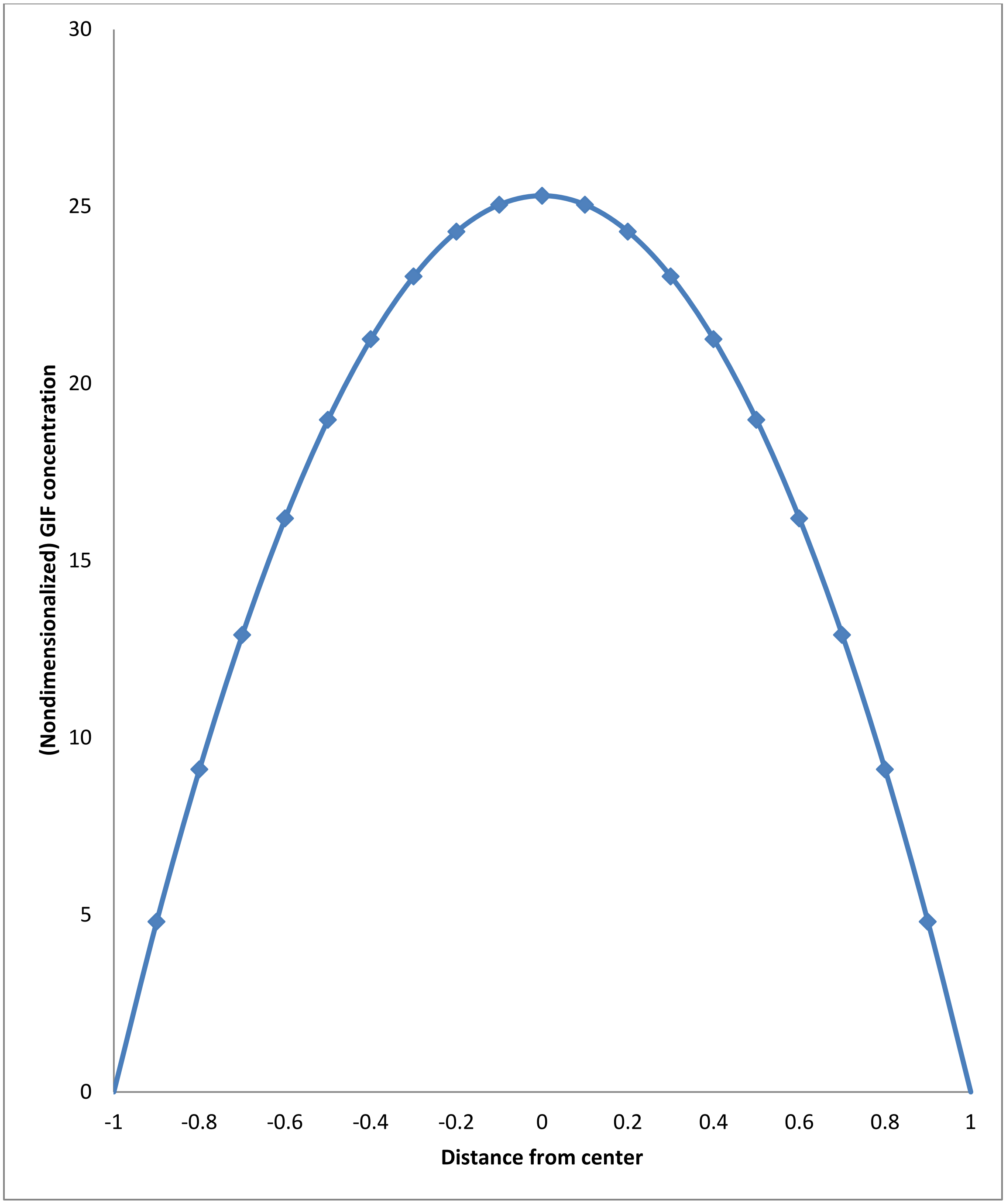

Figure 5.1 Plot of nondimensionalized GIF concentration profile throughout multicell spheroids of size R = 0.2 cm, $D = 5\times10^{-7}\,cm^2 s^{-1}$, t = 10 s and a= 76.764

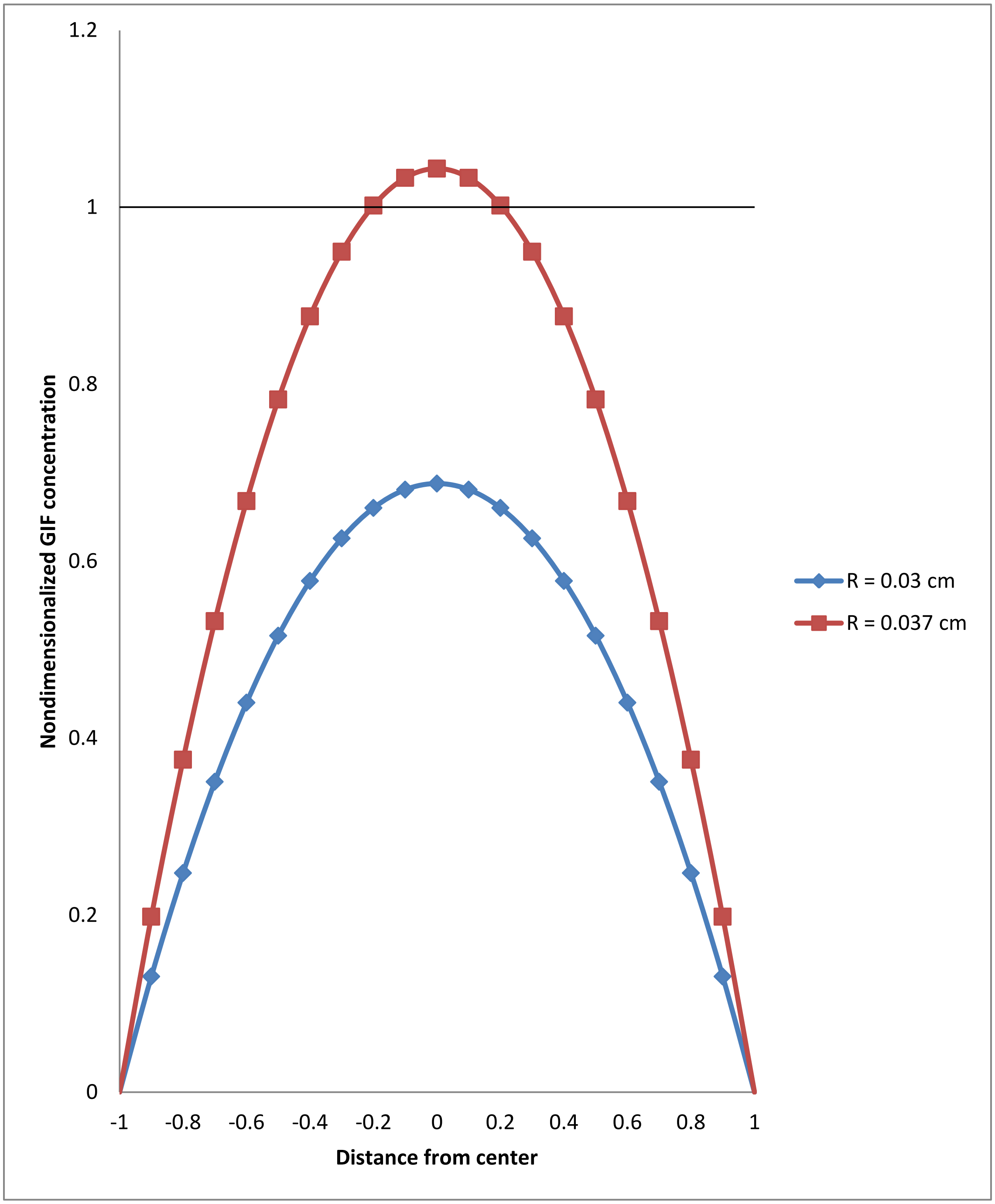

Figure 5.2 Plot of nondimensionalized GIF concentration profile throughout multicell spheroids of size R = 0.03 cm and R = 0.032 cm, $D = 5\times10^{-7} cm^2 s^{-1}$, t = 10 s and a = 76.764

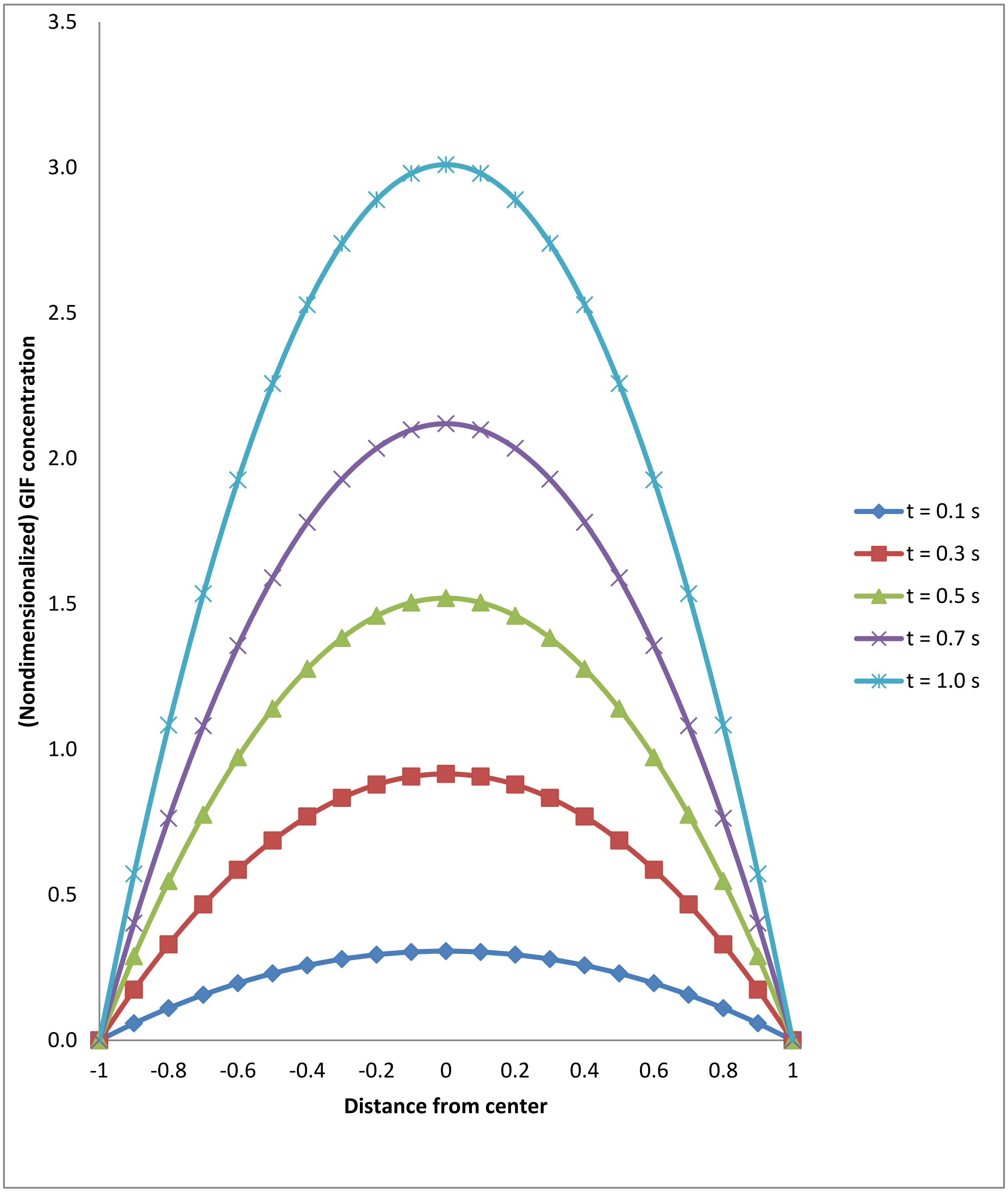

Figure 5.3 Plot of time dependent nondimensionalized GIF concentration profile throughout multicell spheroids of size R = 0.2 cm, $D = 5\times10^{-7} cm^2 s^{-1}$ and a= 76.764

5.7 Summary

This present analysis exhibits the reliable applicability of ADM and HPM methods to solve multicell spheroid model of avascular tumour growth. Our goal has been achieved by formally obtaining series solutions with a high degree of accuracy without any need to linearization , discretization or restrictive assumptions. The computational size has been reduced compared to other existing techniques such as finite different method. Our solutions (Eqs (5.54) and (5.59)) are more general which include the time dependent solution compare to Chaplain and Britton (1993) which simplified the equation into a steady state condition.