CHAPTER 4

MODEL OF THE IMMERSION OF A SPHERICAL TUMOUR WITH A NECROTIC CORE INTO A NUTRIENT BATH

4.1 Introduction

This chapter presents avascular tumour models that have been studied extensively in the last three decade (Adams & Maggelakis, 1989; Ward & King, 1997; Ward & King, 1999; Sherrat & Chaplain, 2001; Ward & King, 2003; Jiang et al, 2005). Although almost all studies reach similar conclusions that avascular tumour can only grow up to a limited size, the saturation mechanisms that are assumed in different models are not same. Depending on nutrients concentration tumour cells are supposed to be in one of the three or stages: proliferating, resting or dead. While the tumour expands, the nutrient concentration at the center falls below a critical level. The cell proliferation rate will be decrease which causes a slow growth rate. Eventually, these interior cells can die off, creating what is known as a necrotic core. Although a significant progress in modeling tumour has been achieved by now, most of the solving methods are based on numerical approach. Hence, an analytical approach is strongly needed.

In recent years, approximate analytical schemes such as Adomian Decomposition Method (ADM) (Adomian, 1988) and Homotopy Perturbation Method (HPM) (He, 1999) have been the source of a lot of research activity. The schemes generate an infinite series of solutions to a wide class of linear and nonlinear differential equations and do not have the problem of rounding error (Adomian, 1988; He, 1999; He, 2006a; He, 2006b; Wazwaz, 2005; He, 2008; Wu et al, 2009). However, only few works deal with the comparison of these methods (Sadighi & Ganji, 2007; Biazar et al, 2008; Saghi & Ganji, 2008; Oziso & Yildirim, 2008; Siddiqui et al, 2010). In this work, we examine the performance of the ADM and HPM when applied to spherical tumour with a necrotic core when immersed in the nutrient bath.

4.2 Mathematical background

The model presented in this chapter is a continuum, deterministic and time-dependent problem for nutrient diffusion given as (Bellomo, 2006):

$$\frac{\partial C}{\partial t} = D\Delta^2 C - \gamma C \quad , \quad a < r < b \quad , \quad t > 0 \tag{4.1}$$

$$\frac{\partial C}{\partial r} = 0 \quad , \quad r = a \quad , \quad t > 0 \tag{4.2}$$

$$C(b,t) = C_E \quad , \quad r = b \quad , \quad t > 0 \tag{4.3}$$

$$C(r,0) = \sum_{i=0}^{3} \alpha_i r^i \quad , \quad a < r < b \quad , \quad t = 0 \tag{4.4}$$

where D ia a diffusion coefficient, γ is a depletion rate, C is a nutrient concentration and $\Delta^2 C = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial C}{\partial r}\right)$ represents the Laplacian in spherical coordinates. Eq. (4.2) represent a no flux condition on the interior boundary where there is no flux of nutrient into the core of the tumour. Eq. (4.3) represents an external nutrient concentration of C_E and Eq.(4.4) represents an initial distribution function with the flexibility of using a polynomial of degree 1, 2 or 3. The polynomials evaluate to C_a at $r = a$, and C_b at $r = b$ .It can be seen that α_i , i = 1, 2 and 3 are defined as:-

$$\text{Linear:} \quad \alpha_3 = \alpha_2 = 0 \ , \ \alpha_1 = \frac{C_a - C_b}{a - b} \ , \ \alpha_0 = C_b - b\alpha_1 \tag{4.5}$$

$$\text{Quadratic:} \ \alpha_3 = 0 \ , \ \alpha_2 = \frac{C_b - C_a}{(a-b)^2} \ , \ \alpha_1 = -2a\alpha_2 \ , \ \alpha_0 = C_a - a^2\alpha_2 - a\alpha_1 \tag{4.6}$$

$$\text{Cubic} \ : \ \alpha_3 = \frac{2(C_b - C_a)}{a^3 - b^3 + 3ab^2 - 3ba^2} \ , \ \alpha_2 = \frac{-6\alpha_3(a+b)}{4} \ , \ \alpha_1 = -3a^2\alpha_3 - 2a\alpha_2 \ ,$$

$$\alpha_0 = C_b - b^3\alpha_3 - b^2\alpha_2 - b\alpha_1 \tag{4.7}$$

We defined a new dependent variable as

$$u(x(r),t) = rc(r,t) \tag{4.8}$$

Changing to Cartesian coordinates for $x(r) = r - a$, Eqs. (4.1 - 4.4) are now transformed into,

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - \gamma u \quad , \quad 0 < x < L \quad , \quad t > 0 \tag{4.9}$$

$$\frac{\partial u}{\partial r} - \frac{1}{a}u = 0 \quad , \quad x = 0 \quad , \quad t > 0 \tag{4.10}$$

$$u(L,t) = bC_E \quad , \quad x = L \quad , \quad t > 0 \tag{4.11}$$

$$u(x,0)=(x+a)\sum_{i=0}^{3}\alpha_i (x+a)^i\ , \qquad 0<x<L\ , \qquad t=0 \tag{4.12}$$

where $L=b-a$.

In order to obtain the approximate solution, Eq. (4.9) is integrated once with respect to t and using the initial condition we obtained

$$u(x,t)=f(x)+D\int_0^t \frac{\partial^2 u(x,t)}{\partial x^2}dt-\gamma\int_0^t u(x,t)dt \tag{4.13}$$

We set $F(u)=\gamma u$ (4.14)

In Eq. (4.13), we assume $f(x)$ is bounded for all x in $J=[0,T](T\in\Re)$ and

$$|t-\tau|\le m',\forall 0\le t,\tau\le T \tag{4.15}$$

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

$\left|\frac{\partial^2 u}{\partial x^2}-\frac{\partial^2 u^*}{\partial x^2}\right|\le L_1|u-u*|,\left|F(u)-F(u^*)\right|\le L_2\left|u-u^*\right|$ and

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

$$\beta=1-T(1-\alpha) \tag{4.16}$$

4.3. Adomian Decomposition Method (ADM)

The Adomian decomposition method is applied in Eq. (4.9):

$$L_t u - Du_{xx} + \gamma u = 0 \qquad (4.17)$$

where

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

is an integrable differential operator with

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

Operating on both sides of Eq. (4.13) with the integral operator L^{-1} defined by Eq. (4.15) leads to

$$u(x,t) = f(x) + L_t^{-1}\left(Du_{xx}(x,t) - \gamma u(x,t)\right) \qquad (4.18)$$

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

Following the ADM method, the solution can be defined by the series form (Adomian, 1994).

$$u(x,t) = \sum_{n=0}^{\infty} u_n(x,t) \qquad (4.19)$$

Substituting Eq. (4.17) into (4.16) gives

$$\sum_{n=0}^{\infty} u_n(x,t) = u(x,0) + L_t^{-1} D\left(\sum_{n=0}^{\infty} u_{n_{xx}}(x,t)\right)_{rr} - \gamma L_t^{-1} \sum_{n=0}^{\infty} u_n(x,t) \tag{4.20}$$

In order to solve Eq. (4.18), the following recurrence relation is proposed

$$u_0 = f(x) = u(x,0) \tag{4.21}$$

$$u_{n+1}(x,t) = \int_0^t \left[D(u_n)_{xx} - \gamma u_n\right] d\tau, \qquad \forall n \geq 0 \tag{4.22}$$

Having determined the components u_0, u_1, u_2, …the solution u in a series form defined by Eq. (4.19) follows immediately.

4.4 Homotopy Perturbation Method (HPM)

In order to solve Eq. (4.9) with the HPM method, we construct the following homotopy:

$$H(v,p) = (1-p)\left(\frac{\partial v}{\partial t} - \frac{\partial u_0}{\partial t}\right) + p\left(\frac{\partial v}{\partial t} - D\frac{\partial^2 v}{\partial x^2} + \gamma v\right) = 0 \tag{4.23}$$

or

$$\frac{\partial v}{\partial t} - \frac{\partial u_0}{\partial t} = p\left(D\frac{\partial^2 v}{\partial x^2} - \gamma v - \frac{\partial u_0}{\partial t}\right) = 0 \tag{4.24}$$

where $p \in [0,1]$ is an embedding parameter and v_o is an arbitrary initial p approximation satisfying the given initial condition. Suppose the solution of Eq. (4.24) to be in the following form:

$$v = v_0 + pv_1 + p^2v_2 + p^3v_3 + \ldots\ldots \tag{4.25}$$

Substituting Eq. (4.25) into Eq. (4.24) and equating the coefficients of the terms with the identical power of *p*:

$$p^0 : \frac{\partial v_o}{\partial t} - \frac{\partial u_0}{\partial t} = 0$$

$$p^1 : \frac{\partial v_1}{\partial t} - D\frac{\partial^2 v_0}{\partial x^2} + \gamma v_0 + \frac{\partial u_0}{\partial t} = 0$$

$$p^2 : \frac{\partial v_2}{\partial t} - D\frac{\partial^2 v_1}{\partial x^2} + \gamma v_1 = 0$$

$$p^3 : \frac{\partial v_3}{\partial t} - D\frac{\partial^2 v_2}{\partial x^2} + \gamma v_2 = 0$$

.

.

.

$$p^n : \frac{\partial v_n}{\partial t} - D\frac{\partial^2 v_{n-1}}{\partial x^2} + \gamma v_{n-1} = 0 \tag{4.26}$$

Solving Eq. (4.26), we have the recursive relation as follows:

$$v_0 = f(x) = u(x,0) \tag{4.27}$$

$$v_{n+1}(x,t) = \int_0^t \left[D(v_n)_{xx} - \gamma v_n\right] d\tau\,, \qquad \forall n \geq 0 \tag{4.28}$$

4.5 Existence and convergence of ADM and HPM

Theorem 4.1: Let $0<\alpha<1$, then Eq. (4.9) as a unique solution.

Proof: Let u and u^* be two different solutions of Eq. (4.13) then

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

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

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

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

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 this completes the proof.

Theorem 4.2: The series solution $u(x,t)=\sum_{i=0}^{\infty}u_i(x,t)$ of Eq. (4.9) using ADM converges if $0<\alpha<1$, $\left|u(x,t)\right|<\infty$.

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:

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

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

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

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

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

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

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

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

Let $n = m + 1$, then

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

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

.

.

.

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

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

Theorem 4.3: If $|u_m(x,t)| \leq 1,$, then the series solution $u(x,t) = \sum_{i=0}^{\infty} u_i(x,t)$ by using HPM converges to the exact solution of Eq. (4.9).

Proof: We set

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

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

So,

$$\left|\phi_{n+1}(x,t) - \phi_n(x,t)\right| = \left|\phi_n + u_n - \phi_n\right|$$

$$= \left|u_n\right|$$

$$\leq \sum_{k=0}^{m-1} |D| \int_0^t \left| \frac{\partial^2 u_{m-k-1}}{\partial x^2} \right| dt + |\gamma| \int_0^t \left|u_{m-k-1}\right| dt$$

Thus

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

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

4.6 Numerical experiment

In this section, we compute numerically Eq. (4.9) by the ADM and HPM method.

From Eq. (4.9):

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} - \gamma u \quad , \quad 0 < x < L \quad , \quad t > 0 \tag{4.27}$$

subject to the initial condition:

$$u_0(x,t) = u(x,0) = (x+a)\{\alpha_0 + \alpha_1(x+a) + \alpha_2(x+a)^2 + \alpha_3(x+a)^3\} \tag{4.28}$$

4.6.1 ADM method

From Eqs.(4.21 – 4.22), we can obtain the first four terms of the solution:

$$u_0(x,t) = u(x,0) = \alpha_0(x+a) + \alpha_1(x+a)^2 + \alpha_2(x+a)^3 + \alpha_3(x+a)^4 \tag{4.29}$$

$$u_1(x,t) = \{(2\alpha_1 + 6\alpha_2(x+a) + 12\alpha_3(x+a)^2)D - \gamma(\alpha_o(x+a) + \alpha_1(x+a)^2 + \alpha_2(x+a)^3 + \alpha_3(x+a)^4)\}t \tag{4.30}$$

$$u_2(x,t) = \{24\alpha_3 D - \gamma[(2\alpha_1 + 6\alpha_2(x+a) + 12\alpha_3(x+a)^2)(1+D) - \alpha_o(x+a) + \alpha_1(x+a)^2 + \alpha_2(x+a)^3 + \alpha_3(x+a)^4]\}\frac{t^2}{2} \tag{4.31}$$

$$u_3(x,t) = -\gamma\{24\alpha_3(1+D) + 2\alpha_1 + 6\alpha_2(x+a) + 12\alpha_3(x+a)^2 + 24\alpha_3 D - \gamma[(2\alpha_1 + 6\alpha_2(x+a) + 12\alpha_3(x+a)^2)(1+D) - \gamma(\alpha_0(x+a) + \alpha_1(x+a)^2 + \alpha_2(x+a)^3 + \alpha_3(x+a)^4)]\}\frac{t^3}{6} \tag{4.32}$$

4.6.2 HPM method

Following the HPM method, from Eqs. (4.27 – 4.28), we obtain the first four terms,

$$v_0 = u_0 = \alpha_0(x+a) + \alpha_1(x+a)^2 + \alpha_2(x+a)^3 + \alpha_3(x+a)^4 \tag{4.33}$$

$$v_1 = \int_0^t \left(D\frac{\partial^2 v_0}{\partial x^2} - \gamma v_0 \right) dt$$

$$= \{(2\alpha_1 + 6\alpha_2(x+a) + 12\alpha_3(x+a)^2)D - \gamma(\alpha_o(x+a) + \alpha_1(x+a)^2 + \alpha_2(x+a)^3 +$$

$$\alpha_3(x+a)^4]\}t$$

(4.34)

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

$$= \{24\alpha_3 D - \gamma[(2\alpha_1 + 6\alpha_2(x+a) + 12\alpha_3(x+a)^2)(1+D) - \alpha_o(x+a) + \alpha_1(x+a)^2 +$$

$$\alpha_2(x+a)^3 + \alpha_3(x+a)^4]\}\frac{t^2}{2}$$

(4.35)

$$v_3 = \int_0^t \left(D\frac{\partial^2 v_2}{\partial x^2} - \gamma v_2 \right) dt$$

$$= -\gamma\{24\alpha_3(1+D) + 2\alpha_1 + 6\alpha_2(x+a) + 12\alpha_3(x+a)^2 + 24\alpha_3 D - \gamma[(2\alpha_1 + 6\alpha_2(x+a) +$$

$$12\alpha_3(x+a)^2)(1+D) - \gamma(\alpha_0(x+a) + \alpha_1(x+a)^2 + \alpha_2(x+a)^3 + \alpha_3(x+a)^4)]\}\frac{t^3}{6}$$

(4.36)

It is obvious that the first four terms approximate solutions (Eqs. (4.29 – 4.32)) obtained using ADM are the same as the first four terms (Eqs. (4.33 – 4.36)) of the HPM. Figures 4.1 and 4.2 show the concentration of nutrient for fixed radial distance against time which were plotted from Eqs. (4.29 – 4.32) and Eqs. (4.33 – 4.36) for ADM and HPM, respectively. Both methods show the similar pattern of diffusion of nutrient. The concentration increases as time increases. When placed into a nutrient bath with high concentration levels, the tumour absorbs nutrient quickly. However, different rate of depletion will affect the nutrient absorption. Nevertheless, despite the presence of depletion factor, the tumour still absorb nutrient from its environment and always have more nutrient near the tumour boundary.

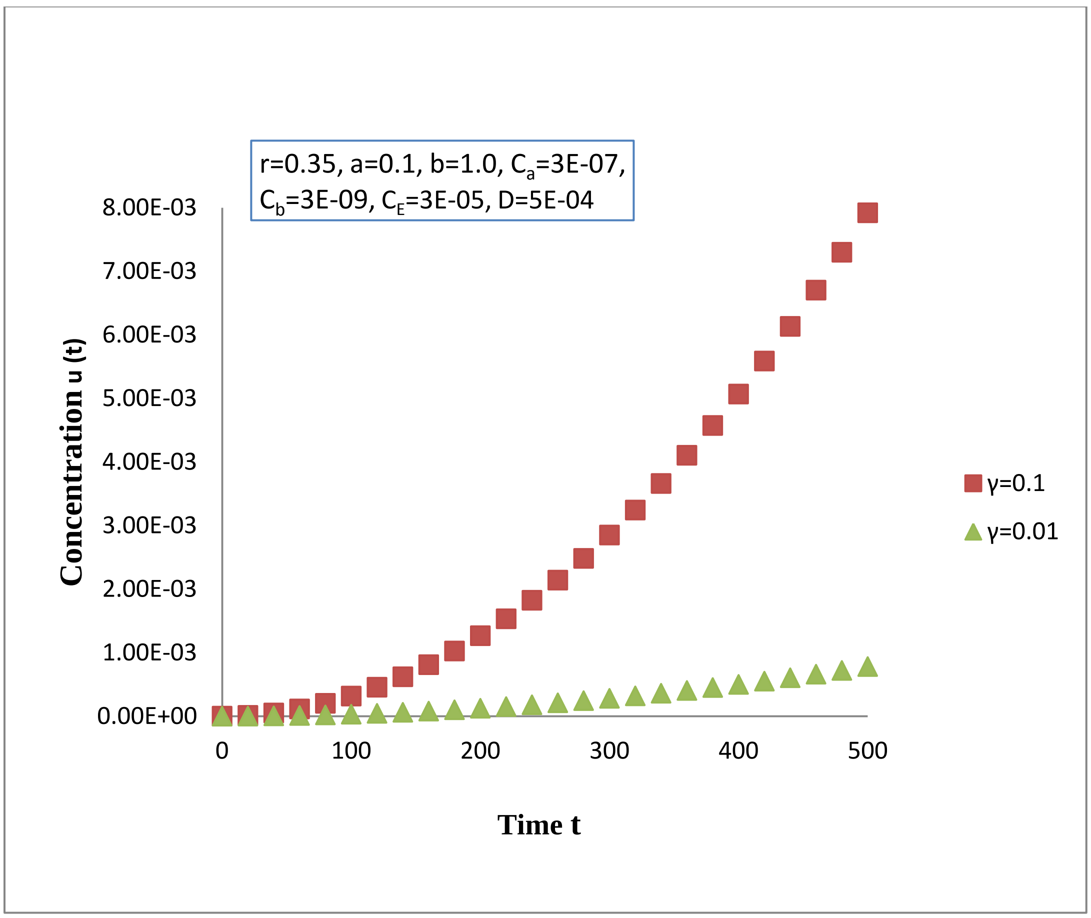

Figure 4.1. Concentration verses time for fixed radial distance of r = 0.35 at different depletion rate values via ADM

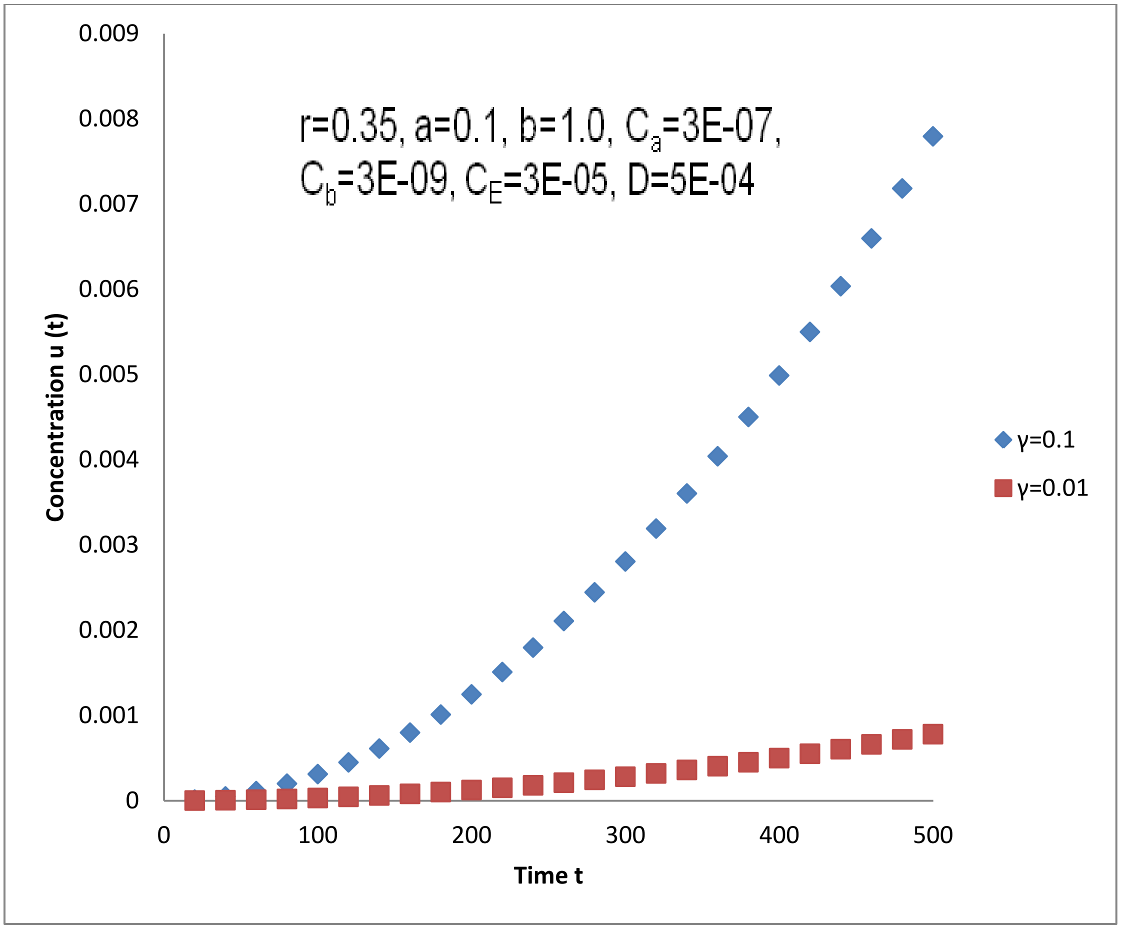

Figure 4.2. Concentration verses time for fixed radial distance of r = 0.35 at different depletion rate values via HPM

4.7 Summary

We have analyzed the behavior of nutrient concentration diffusing into a spherical tumour with a necrotic core via ADM and HPM. The numerical results that we have obtained justify the advantage of both methodologies, even in the few terms, approximation is accurate. Furthermore, as the methods do not require discretization of the variables, i.e. time and space, it is not affected by computation round off errors and one is not faced with necessity of large computer memory and time. A clear conclusion can be drawn from these results that both solutions are identical in form. Our results are more general than Bellomo (2006) since we are taking the depletion term into account which Bellomo (2006) didn’t.