

CHAPTER 6

MODEL FOR TUMOUR ANGIOGENESIS

6.1 Introduction

Tumour angiogenesis factor (TAF) having concentration $c(x,t)$ is secreted by the solid tumour and diffuses into the surrounding tissue. Upon reaching neighbouring endothelial cells situated in the TAF stimulates the release of enzymes by the endothelial cells which degrades their basement membrane. Then, the initial response of the endothelial cells is to migrate towards the source of angiogenic stimulus. Capillary sprouts are formed and cells subsequently begin to proliferate at a later stage. As a results, mitosis is largely confined to a region a short distance behind the sprout tips (Auspruk & Folkman, 1977; Sholley et al, 1984; Paweletz & Knierim, 1989; Stokes & Lauffenburger, 1991; Chaplain, 1996). In this chapter, we introduced a tumour angiogenesis model which is extended from the previous avascular model.

6.2 Mathematical background

The conservation equation for the TAF concentration, under the assumption of linear Fickian diffusion, can be written mathematically as

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - f(c)g(n) - h(c) \quad (6.1)$$

where D_c is the TAF diffusion coefficient, the second and third terms of the left side of equatics are losses due to cells and decay of chemicals, respectively. We assume that the local rate of uptake of TAF by the endothelial cells (modelled by the function $f(c)$) is governed by Michaelis-Menten kinetics (Chaplain & Stuart, 1991; Chaplain, 1996)] and that it also depends on the cells, the more TAF will be removed by the cells acting as sinks (Ausprunk & Folkman, 1977; Chaplain & Stuart, 1991). For simplicity, the actual function used in the model is given by $g(n) = n/n_0$, a simple linear function. We also assume that the decay of TAF with time is governed by first-order kinetics, a standard assumption (Sherrat & Murray, 1990). This leads to the following equation for the TAF in the external tissue:

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \frac{Qcn}{(K_m + c)n_0} - dc \quad (6.2)$$

The initial condition is

$$c(x,0) = c_0(x) \quad (6.3)$$

where $c_0(x)$ is a prescribed function chosen to describe qualitatively the profile of TAF in the external tissue when it reaches the limbal vessels (Chaplain & Stuart, 1991). The TAF is assumed to have a constant value c_b on the boundary of the tumour and to have decayed to zero at the limbus giving the boundary conditions as

$$c(0,t) = c_b \quad c(L,t) = 0 \quad (6.4)$$

The endothelial cells are the principal characters in the drama of angiogenesis and are always centre stages (Paweletz & Knierim, 1989). It is therefore highly desirable and logical to include in our model an equation modeling the endothelial cells. We will thus follow the route of the endothelial cells from their origin in their parent vessel (e.g., the limbus), their crossing of the extracellular matrix and other material in the surrounding host tissue to their destination within the tumour.

The first events of angiogenesis are rearrangements and migration of endothelial cells rather than induction of cell division (Paweletz & Knierim, 1989; Paku & Paweletz, 1991). In response to the angiogenic stimulus, endothelial cells in the neighbouring normal capillaries which do not possess a muscular sheath are activated to stimulate proteases and collagenases. The endothelial cells which are recruited from the parent vessel and the sprouts grow in length by migration of the endothelial cells (Cliff, 1963; Schoefl, 1963; Warren, 1966; Sholley et al, 1984).

The main event we are modeling are the migration and proliferation of the endothelial cells which are not linked together. A general conservation equation for the endothelial cell density $n(x,t)$ (Chaplain, 1996) is given by

$$\frac{\partial n}{\partial t} + \nabla \cdot J = F(n)G(c) - H(n) \quad (6.5)$$

where J is the cell flux, $F(n)$ and $H(n)$ are functions representing a normalized growth term and a loss term, respectively. The mitosis is governed by logistic type growth and that cell loss is a first order process (Chaplain, 1996; Sholley et al, 1984). Thus

$$F(n) = rn \left(1 - \frac{n}{n_0} \right) \quad (6.6)$$

$$H(n) = -k_p n \quad (6.7)$$

where r is a positive constant related to the maximum mitotic rate and k_p is the proliferation rate constant which is taken to be the reciprocal of the endothelial cell doubling time (Stokes & Lauffenburger, 1991; Sherrat & Murray, 1990). Further we assume that the endothelial cell proliferation is controlled in some way by the TAF (Paweletz & Knierim, 1989; Paku & Paweletz, 1991). Thus in the present model, we chose $G(c)$ to be of the form

$$G(c) = \begin{cases} 0, & c \leq c^*, \\ \frac{c - c^*}{c_b}, & c^* < c, \end{cases} \quad (6.8)$$

where $c^* \leq c_b$.

We assume that the flux J of endothelial cells consists of two parts, one representing random motion and the other chemotactic motion of the cells (Auspruk & Folkman, 1977; Sholley et al, 1984; Stokes & Lauffenburger, 1991). Thus

$$J = J_{diffusion} + J_{chemotaxis} . \quad (6.9)$$

We assume linear diffusion so that

$$J_{diffusion} = -D_n \nabla n \quad (6.10)$$

where D_n is the diffusion coefficient of the endothelial cells and

$$J_{chemotaxis} = n\chi(c)\nabla c \quad (6.11)$$

the well-known form for the chemotactic flux. Various functional forms have been proposed for $\chi(c)$ including a logarithmic law

$$\chi(c) = \frac{\chi_0}{c} \quad (6.12)$$

a receptor kinetic law

$$\chi(c) = \frac{\chi_0 k}{(k + c)^2} \quad (6.13)$$

and a constant law

$$\chi(c) = \chi_0 \text{ (a constant)}. \quad (6.14)$$

For mathematical simplicity we take $\chi(c) = \chi_0$, a constant. The cell conservation equation can be written

$$\text{Rate of increase of cell density} = \text{cell migration} + \text{mitotic generation} - \text{cell loss} \quad (6.15)$$

With the above assumption, we thus have the following population diffusion-chemotaxis equation for the endothelial cells as

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \chi_0 \nabla \cdot (n \nabla c) + rn \left(1 - \frac{n}{n_0} \right) G(c) - k_p n \quad (6.16)$$

We assume that initially the endothelial cell density at the limbus is a constant n_0 and zero elsewhere, giving initial condition

$$n(x,0) = \begin{cases} n_0, & x = L \\ 0, & x < L \end{cases} \quad (6.17)$$

We assume that throughout the subsequent motion, the cell density remains constant at the limbus and hence the boundary condition here becomes

$$n(L,t) = n_0 \quad (6.18)$$

As stated previously, the main aim of the model is to monitor the progress of the endothelial cells (in particular those at the sprouts tip) as they cross the ECM (extra cellular matrix) and eventually reach the tumour. Once they reach the tumour and penetrate it, interactions with the tumour cells become important (Paweletz & Knierim, 1989) and the assumptions of the present model are no longer hold. Thus within the assumption and limitations of the present model, we consider the following boundary condition at $x = 0$: (Liotta & Kleinerman, 1977; Chaplain & Sleeman, 1990).

$$n = 0 \quad \text{at } x = 0 \quad (6.19)$$

We normalize the equations using the following reference variables:

- reference TAF concentration: c_b , the value of the TAF concentration at the tumour boundary,
- reference cell density: n_0 , the value of the endothelial cell density at the limbus,
- reference length: L , the distance from the tumour boundary to the limbal vessels,
- reference time unit: $\tau = L^2 / D$.

We thus define new variables:

$$\tilde{c} = \frac{c}{c_b}, \quad \tilde{n} = \frac{n}{n_0}, \quad \tilde{x} = \frac{x}{L}, \quad \tilde{t} = \frac{t}{\tau} \quad (6.20)$$

Dropping the tildes and specialising to a one-dimensional geometry, the equations now become

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} - \frac{\alpha n c}{\gamma + c} - \lambda c \quad (6.21)$$

$$\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} - \kappa \frac{\partial}{\partial x} \left(n \frac{\partial c}{\partial x} \right) + \mu n (1 - n) G(c) - \beta n \quad (6.22)$$

where

$$G(c) = \begin{cases} 0, & c \leq c^* \\ c - c^*, & c^* < c \end{cases} \quad (6.23)$$

$$\begin{aligned} \alpha &= \frac{L^2 Q}{D_c c_b}, & \gamma &= \frac{K_m}{c_b}, & \lambda &= \frac{L^2 d}{D_c}, & \beta &= \frac{L^2 k_p}{D_c} \\ D &= \frac{D_n}{D_c}, & \kappa &= \frac{c_b \chi_0}{D_c}, & \mu &= \frac{L^2 r}{D_c}, \end{aligned} \quad (6.24)$$

The initial and boundary conditions become

$$c(x, 0) = c_0(x) = 1 - x^2 \quad (6.25)$$

$$n(x, 0) = \begin{cases} 1, & x = 1 \\ 0, & x < 1 \end{cases} \quad (6.26)$$

$$c(0, t) = 1; \quad c(1, t) = 0 \quad (6.27)$$

$$n(1, t) = 1 \quad (6.28)$$

$$n = 0 \text{ at } x = 0 \quad (6.29)$$

The TAF concentration profile in the external host tissue according to the above model does not vary drastically throughout the complete process (Chaplain et al, 1995). The TAF is estimated to diffuse very much faster than the cells and can be reasonably expected to be in some kind of steady state. In order to simplify the complete system and thus make it amenable to mathematical analysis, we make the assumption that the TAF concentration in the external host tissue does not upon time (Stokes & Lauffenburger, 1991). This has the effect of reducing Eqs. (6.21 – 6.22) to a single equation:

$$\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} - \kappa \frac{\partial n}{\partial x} + \mu(1-x)n(1-n) - \beta n \quad (6.30)$$

Subject to the initial condition

$$n(x,0) = 1 \quad (6.31)$$

To obtain the approximate solution of Eq. (6.30) by integrating one time from Eq. (6.30) with respect to t and using the initial condition, we obtain

$$u(x,t) = f(x) + D \int_0^t \frac{\partial^2 n(x,t)}{\partial x^2} dt - \kappa \int_0^t \frac{\partial n(x,t)}{\partial x} dt + \mu \int_0^t (1-x)n(1-n) dt - \beta \int_0^t n(x,t) dt \quad (6.32)$$

In Eq. (6.32), we assume $f(x)$ is bounded for all x in $J = [0, T]$ ($T \in \mathfrak{R}$) and

$$|t - \tau| \leq m', \forall 0 \leq t, \tau \leq T$$

We set $F(n) = \mu(1-x)n(1-n)$. The terms $\frac{\partial^2 n}{\partial x^2}$, $\frac{\partial n}{\partial x}$ and $F(n)$ are Lipschitz continuous

with

$$\left| \frac{\partial^2 u}{\partial x^2} - \frac{\partial^2 n^*}{\partial x^2} \right| \leq L_1(n - n^*)$$

$$\left| \frac{\partial n}{\partial x} - \frac{\partial n^*}{\partial x} \right| \leq L_2(n - n^*)$$

$$|F(n) - F(n^*)| \leq L_3(n - n^*)$$

and

$$\alpha = T(m' L_1 + m' L_2 + m' L_3)$$

$$\beta = 1 - T(1 - \alpha) \tag{6.33}$$

6.3. Adomian Decomposition Method (ADM)

The Adomian decomposition method is applied in Eq. (6.30):

$$\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} - K \frac{\partial n}{\partial x} + \mu(1-x)n(1-n) - \beta n \tag{6.34}$$

where
$$L_t = \frac{\partial}{\partial t} \tag{6.35}$$

is an integrable differential operator with

$$L_t^{-1} = \int_0^t (\cdot) dt \quad (6.36)$$

Operating on both sides of Eq. (6.34) with the integral operator L^{-1} defined by Eq. (6.36)

leads to

$$n(x,t) = n(x) + L_t^{-1} \left[D \left(\frac{\partial^2 n}{\partial x^2} \right) - \kappa \left(\frac{\partial n}{\partial x} \right) + \mu N(x,t) - \beta n \right] \quad (6.37)$$

where $n(x) = n(x,0)$ and $N(x,t) = (1-x)n(1-n)$. The solution $n(x,t)$ can be decomposed by an infinite series as follows (Adomian, 1994):

$$n(x,t) = \sum_{i=0}^{\infty} n_i(x,t) \quad (6.38)$$

Substituting Eq. (6.38) into (6.37) gives

$$\sum_{m=0}^{\infty} n_m(x,t) = n(x,0) + L^{-1} \left[D \sum_{m=0}^{\infty} n_{m_{xx}} - \kappa \sum_{m=0}^{\infty} n_{m_x} + \mu N(x,t) - \beta \sum_{m=0}^{\infty} n_m \right] \quad (6.39)$$

The nonlinear term $N(x,t)$ is decomposed by the following infinite series:

$$N_k(x,t) = \sum_{m=0}^{\infty} A_{km} \quad , \quad k = 1, 2 \quad (6.40)$$

where A_{km} is called Adomian's polynomial and define by:

$$A_m = \frac{1}{M!} \left[\frac{d^m}{d\lambda^m} N_k \left(\sum_{i=0}^{\infty} \lambda^i n_i \right) \right]_{\lambda=0}, \quad i \geq 0 \quad (6.41)$$

The components $n_{mm}(x,t)$ of the solution $n(x,t)$ can be elegantly completed by using the following recursive relationships:

$$n_0(x,t) = n(x,0) \quad (6.42)$$

$$n_{m+1}(x,t) = \int_0^t \left[D \frac{\partial^2 n_m}{\partial x^2} - \kappa \frac{\partial n_m}{\partial x} + \mu A_m - \beta n_m \right] d\tau, \quad \forall m \geq 0 \quad (6.43)$$

Having determined the components n_0, n_1, n_2, \dots the solution n in a series form defined by Eq. (6.38) follows immediately.

6.4 Homotopy Perturbation Method (HPM)

To solve Eq. (6.30) with the HPM method, we construct the following homotopy:

$$H(\eta, p) = (1-p) \left(\frac{\partial \eta}{\partial t} - \frac{\partial n_0}{\partial t} \right) + p \left(\frac{\partial \eta}{\partial t} - D \frac{\partial^2 \eta}{\partial x^2} + \kappa \frac{\partial \eta}{\partial x} - \mu(1-x)\eta(1-\eta + \beta\eta) \right) = 0 \quad (6.44)$$

or

$$\left(\frac{\partial \eta}{\partial t} - \frac{\partial n_0}{\partial t}\right) + p \left[-D \frac{\partial^2 \eta}{\partial x^2} + \kappa \frac{\partial \eta}{\partial x} - \mu(1-x)\eta(1-\eta) + B\eta + \frac{\partial n_0}{\partial t} \right] = 0 \quad (6.45)$$

In HPM, the solution of Eq. (6.45) is expressed as

$$\eta = \eta_0 + p\eta_1 + p^2\eta_2 + p^3\eta_3 + p^4\eta_4 + \dots \quad (6.46)$$

where $p \in [0,1]$ is an embedding parameter and η_0 is an arbitrary initial approximation satisfying the given initial condition. Hence, the approximate solution of Eq. (6.30) is expressed as a series of the power of p . As p approaching to 1, we obtained

$$\eta(x,t) = \lim_{p \rightarrow 1} \eta = \eta_0 + \eta_1 + \eta_2 + \eta_3 + \eta_4 + \dots = \sum_{n=0}^{\infty} \eta_n \quad (6.47)$$

Substituting Eq. (6.46) into Eq. (6.45) and:

$$\begin{aligned} H(\eta, p) = & \frac{\partial}{\partial t} (\eta_0 + p\eta_1 + p^2\eta_2 + p^3\eta_3 + p^3\eta_4) - \frac{\partial n_0}{\partial t} + p \left\{ -D \frac{\partial^2}{\partial x^2} (\eta_0 + p\eta_1 + p^2\eta_2 + p^3\eta_3 \right. \\ & + p^3\eta_4) + \kappa \frac{\partial}{\partial x} (\eta_0 + p\eta_1 + p^2\eta_2 + p^3\eta_3 + p^3\eta_4) - \mu(1-x)(\eta_0 + p\eta_1 + p^2\eta_2 + p^3\eta_3 + p^3\eta_4) \\ & \left. \times (1 - \eta_0 - p\eta_1 - p^2\eta_2 - p^3\eta_3) + \beta(\eta_0 + p\eta_1 + p^2\eta_2 + p^3\eta_3 + p^3\eta_4) + \frac{\partial n_0}{\partial t} \right\} \end{aligned} \quad (6.48)$$

Equating the coefficients of the terms in Eq. (6.48) with the identical powers of p we get

$$p^0: \frac{\partial \eta_0}{\partial t} - \frac{\partial n_0}{\partial t} = 0 \quad (6.49)$$

$$p^1: \frac{\partial \eta_1}{\partial t} - D \frac{\partial^2 \eta_0}{\partial x^2} + \kappa \frac{\partial \eta_0}{\partial x} - \mu(1-x)(\eta_0 - \eta_0^2) + \beta \eta_0 + \frac{\partial n_0}{\partial t} = 0 \quad (6.50)$$

$$p^2: \frac{\partial \eta_2}{\partial t} - D \frac{\partial^2 \eta_1}{\partial x^2} + \kappa \frac{\partial \eta_1}{\partial x} - \mu(1-x)(\eta_1 - 2\eta_0\eta_1) + \beta \eta_1 = 0 \quad (6.51)$$

$$p^3: \frac{\partial \eta_3}{\partial t} - D \frac{\partial^2 \eta_2}{\partial x^2} + \kappa \frac{\partial \eta_2}{\partial x} - \mu(1-x)(\eta_2 - \eta_1^2 - 2\eta_0\eta_2) + \beta \eta_2 = 0 \quad (6.52)$$

$$p^4: \frac{\partial \eta_4}{\partial t} - D \frac{\partial^2 \eta_3}{\partial x^2} + \kappa \frac{\partial \eta_3}{\partial x} - \mu(1-x)(\eta_3 - 2\eta_0\eta_3 - 2\eta_1\eta_2) + \beta \eta_3 = 0 \quad (6.53)$$

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Solving Eqs. (6.47 – 6.50), we will have the solution of Eq. (6.30).

6.5 Existence and convergence of ADM and HPM

Theorem 6.1: Let $0 < \alpha < 1$, then Eq. (6.30) as a unique solution.

Proof: Let n and n^* be two different solutions of Eq. (6.32) then

$$\begin{aligned}
 |n - n^*| &= \left| D \int_0^t \left[\frac{\partial^2 n(x,t)}{\partial x^2} - \frac{\partial^2 n^*(x,t)}{\partial x^2} \right] dt - \kappa \int_0^t \left(\frac{\partial n(x,t)}{\partial x} - \frac{\partial n^*(x,t)}{\partial x} \right) dt \right. \\
 &\quad \left. + \mu(1-x) \int_0^t [n(1-n) - n^*(1-n^*)] dt - \beta \int_0^t (n - n^*) dt \right| \\
 &\leq \int_0^t \left| D \left[\frac{\partial^2 n}{\partial x^2} - \frac{\partial^2 n^*}{\partial x^2} \right] \right| dt + \kappa \int_0^t \left| \frac{\partial n}{\partial x} - \frac{\partial n^*}{\partial x} \right| dt + \mu(1-x) \int_0^t |n(1-n) - n^*(1-n^*)| dt + \beta \int_0^t |n - n^*| dt \\
 &\leq T(m'L_1 + m'L_2 + m'L_3) |n - n^*| \\
 &= \alpha |n - n^*|
 \end{aligned}$$

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

Theorem 6.2: The series solution $n(x,t) = \sum_{i=0}^{\infty} n_i(x,t)$ of Eq. (6.30) using ADM converges

if $0 < \alpha < 1$, $|n(x,t)| < \infty$.

Proof: Denote as $(C[J], \|\cdot\|)$ the Banach space of all continuous functions on J with the norm $\|f(t)\| = \max_{t \in J} |f(t)|$. 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:

$$\begin{aligned} \|S_n - S_m\| &= \max_{t \in J} |S_n - S_m| \\ &= \max_{t \in J} \left| \sum_{i=m+1}^n n_i(x, t) \right| \\ &= \max_{t \in J} \left| \sum_{i=m+1}^n \left(\int_0^t D \frac{\partial^2 n_i}{\partial x^2} dt + \kappa \int_0^t \frac{\partial n_i}{\partial x} dt + \mu(1-x) \int_0^t n_i(1-n_i) dt - \int_0^t \beta n_i dt \right) \right| \\ &= \max_{t \in J} \left| D \int_0^t \left(\sum_{i=m}^{n-1} \frac{\partial n_i}{\partial x^2} \right) dt + \kappa \int_0^t \left(\sum_{i=m}^{n-1} \frac{\partial n_i}{\partial x} \right) dt + \mu(1-x) \int_0^t \left(\sum_{i=m}^{n-1} n_i(1-n_i) \right) dt - \beta \int_0^t \left(\sum_{i=m}^{n-1} n_i \right) dt \right| \end{aligned}$$

From Kalla (2008), we have

$$\begin{aligned} \sum_{i=m}^{n-1} \frac{\partial^2 n_i}{\partial x^2} &= G^2(S_{n-1}) - G^2(S_{m-1}) \\ \sum_{i=m}^{n-1} \frac{\partial n_i}{\partial x} &= G(S_{n-1}) - G(S_{m-1}) \\ \sum_{i=m}^{n-1} n_i(1-n_i) &= F_1(S_{n-1}) - F_1(S_{m-1}) \\ \sum_{i=m}^{n-1} n_i &= F_2(S_{n-1}) - F_2(S_{m-1}) \end{aligned}$$

So,

$$\begin{aligned}
\|S_n - S_m\| &= \max_{\forall t \in J} \left| D \int_0^t \frac{\partial^2 n_{k-m-1}}{\partial x^2} dt + \left| \kappa \int_0^t \frac{\partial n_{k-m-1}}{\partial x} dt + \mu(1-x) \int_0^t n_{k-m-1} (1 - n_{k-m-1}) dt + \beta \int_0^t n_{k-m-1} dt \right. \right. \\
&\leq \left| D \int_0^t G^2(S_{n-1}) - G^2(S_{m-1}) dt + \left| \kappa \int_0^t G(S_{n-1}) - G(S_{m-1}) dt + \mu(1-x) \int_0^t F_1(S_{n-1}) - F_1(S_{m-1}) dt \right. \right. \\
&\quad \left. \left| \beta \int_0^t F_2(S_{n-1}) - F_2(S_{m-1}) dt \right. \right. \\
&\leq \alpha \|S_n - S_m\|
\end{aligned}$$

Let $n = m + 1$, then

$$\begin{aligned}
\|S_{m+1} - S_m\| &\leq \alpha \|S_m - S_{m-1}\| \\
&\leq \alpha^2 \|S_{m-1} - S_{m-2}\| \\
&\cdot \\
&\cdot \\
&\cdot \\
&\leq \alpha^m \|S_1 - S_0\|
\end{aligned}$$

From the triangle inequality, we have

$$\begin{aligned}
\|S_n - S_m\| &\leq \|S_{m+1} - S_m\| + \|S_{m+2} - S_{m+1}\| + \dots + \|S_n - S_{n-1}\| \\
&\leq (\alpha^m + \alpha^{m+1} + \dots + \alpha^{n-m-1}) \|S_1 - S_0\| \\
&\leq \alpha^m (1 + \alpha + \alpha^2 + \dots + \alpha^{n-m-1}) \|S_1 - S_0\| \\
&\leq \alpha^m \left(\frac{1 - \alpha^{n-m}}{1 - \alpha} \right) \|n_1(x, t)\|
\end{aligned}$$

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

Theorem 6.3: If $|n_m(x, t)| \leq 1$, then the series solution $n(x, t) = \sum_{i=0}^{\infty} n_i(x, t)$ of Eq. (6.30)

converges to the exact solution by using HPM.

Proof: We set

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

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

So,

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

$$= |n_n|$$

$$\leq \sum_{k=0}^{m-1} |D| \int_0^t \left| \frac{\partial^2 n_{m-k-1}}{\partial x^2} \right| dt + |\kappa| \int_0^t \left| \frac{\partial n_{k-m-1}}{\partial x} \right| dt + |\mu(1-x)| \int_0^t |n_{k-m-1}(1 - n_{k-m-1})| dt$$

$$+ |\beta| \int_0^t |n_{k-m-1}| dt$$

Thus

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

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

6.6 Numerical experiment

In this section, we compute numerically Eq. (6.30) by the ADM and HPM methods.

6.6.1 ADM method

From Eq.(6.41), we can obtain the first four terms of the Adomian polynomials as

$$A_0 = (1-x)(1-n_0)n_0 \quad (6.54)$$

$$\begin{aligned} A_1 &= \left[\frac{d}{d\lambda} (1-x)(1-(n_0 + \lambda n_1)(n_0 + \lambda n_1)) \right]_{\lambda=0} \\ &= (1-x)n_1(1-2n_0) \end{aligned} \quad (6.55)$$

$$\begin{aligned} A_2 &= \frac{1}{2} \frac{d^2}{d\lambda^2} \left[(1-x)(1-(n_0 + \lambda n_1 + \lambda^2 n_2)(n_0 + \lambda n_1 + \lambda^2 n_2)) \right]_{\lambda=0} \\ &= (1-x)(n_2 - 2n_0 n_2 - n_1^2) \end{aligned} \quad (6.56)$$

$$\begin{aligned} A_3 &= \frac{1}{2} \frac{d^2}{d\lambda^2} \left[(1-x)(1-(n_0 + \lambda n_1 + \lambda^2 n_2 + \lambda^3 n_3)(n_0 + \lambda n_1 + \lambda^2 n_2 + \lambda^3 n_3)) \right]_{\lambda=0} \\ &= (1-x)(n_3 - 2n_0 n_3 - 2n_1 n_2) \end{aligned} \quad (6.57)$$

By the recursive formula in Eq. (6.43), we can obtain directly the components of n_i as

$$n_0 = 1 \quad (6.58)$$

$$n_1 = -\beta t \quad (6.59)$$

$$n_2 = \beta[\mu(1-x) + \beta] \frac{t^2}{2} \quad (6.60)$$

$$n_3 = \beta[\mu\kappa - \beta(\mu(1-x) + \beta) - \mu(1-x)(\mu(1-x) + 3\beta)] \frac{t^3}{6} \quad (6.61)$$

$$n_4 = \beta[\mu^2 D + \mu^2 \kappa(1-x) - 2\mu\kappa + 3\mu(1-x)\beta(\mu(1-x) + \beta) - \frac{1}{2}(\mu\kappa - \mu(1-x)(\mu(1-x) + 3\beta) - \beta(\mu(1-x) + \beta)(\mu(1-x) + \beta))] \frac{t^4}{12} \quad (6.62)$$

We substitute the components of n_i into Eq. (6.38), then we obtain the solution of Eq. (6.30) as below:

$$\begin{aligned} n(x, t) = & 1 - \beta t + \beta[\mu(1-x) + \beta] \frac{t^2}{2} + \beta[\mu\kappa - \beta(\mu(1-x) + \beta) - \mu(1-x)(\mu(1-x) + 3\beta)] \frac{t^3}{6} \\ & + \beta[\mu^2 D + \mu^2 \kappa(1-x) - 2\mu\kappa + 3\mu(1-x)\beta(\mu(1-x) + \beta) - \frac{1}{2}(\mu\kappa - \mu(1-x)(\mu(1-x) + 3\beta) \\ & - \beta(\mu(1-x) + \beta)(\mu(1-x) + \beta))] \frac{t^4}{12} \end{aligned} \quad (6.63)$$

6.62 HPM method

Following the HPM method, from Eqs. (6.49 - 6.53), we obtain

$$\eta_0 = \eta_0 = 1 \quad (6.64)$$

$$\begin{aligned} \eta_1 = & \int_0^t \left(D \frac{\partial^2 \eta_0}{\partial x^2} - \kappa \frac{\partial \eta_0}{\partial x} - \mu(1-x)(\eta_0^2 - \eta_0) - \beta \eta_0 - \frac{\partial \eta_0}{\partial t} \right) dt \\ = & -\beta t \end{aligned} \quad (6.65)$$

$$\begin{aligned}
\eta_2 &= \int_0^t \left(D \frac{\partial^2 \eta_1}{\partial x^2} - \kappa \frac{\partial \eta_1}{\partial x} - \mu(1-x)(2\eta_0 \eta_1 - \eta_1) - \beta \eta_1 \right) dt \\
&= \beta [\mu(1-x) + \beta] \frac{t^2}{2}
\end{aligned} \tag{6.66}$$

$$\begin{aligned}
\eta_3 &= \int_0^t \left(D \frac{\partial^2 \eta_2^2}{\partial x^2} - \kappa \frac{\partial \eta_2}{\partial x} - \mu(1-x)(2\eta_0 \eta_2 + \eta_1^2 - \eta_2) - \beta \eta_2 \right) dt \\
&= \beta [\mu\kappa - \beta(\mu(1-x) + \beta) - \mu(1-x)(\mu(1-x) + 3\beta)] \frac{t^3}{6}
\end{aligned} \tag{6.67}$$

$$\begin{aligned}
\eta_4 &= \int_0^t \left(D \frac{\partial^2 \eta_3^2}{\partial x^2} - \kappa \frac{\partial \eta_3}{\partial x} - \mu(1-x)(2\eta_0 \eta_3 + 2\eta_1 \eta_2 - \eta_3) - \beta \eta_3 \right) dt \\
&= \beta [\mu^2 D + \mu^2 \kappa(1-x) - 2\mu\kappa + 3\mu(1-x)\beta(\mu(1-x) + \beta) - \frac{1}{2}(\mu\kappa - \mu(1-x)(\mu(1-x) + 3\beta) \\
&\quad - \beta(\mu(1-x) + \beta)(\mu(1-x) + \beta))] \frac{t^4}{12}
\end{aligned} \tag{6.68}$$

We substitute the components of n_i into Eq. (6.47), then we obtain the solution of Eq. (6.30) as below:

$$\begin{aligned}
n(x, t) &= 1 - \beta t + \beta [\mu(1-x) + \beta] \frac{t^2}{2} + \beta [\mu\kappa - \beta(\mu(1-x) + \beta) - \mu(1-x)(\mu(1-x) + 3\beta)] \frac{t^3}{6} \\
&\quad + \beta [\mu^2 D + \mu^2 \kappa(1-x) - 2\mu\kappa + 3\mu(1-x)\beta(\mu(1-x) + \beta) - \frac{1}{2}(\mu\kappa - \mu(1-x)(\mu(1-x) + 3\beta) \\
&\quad - \beta(\mu(1-x) + \beta)(\mu(1-x) + \beta))] \frac{t^4}{12}
\end{aligned} \tag{6.69}$$

It is obvious that the first five terms approximate solutions (Eqs. (6.58 – 6.62)) obtained using ADM are the same as the first four terms (Eqs. (6.64 – 6.68)) of the HPM.

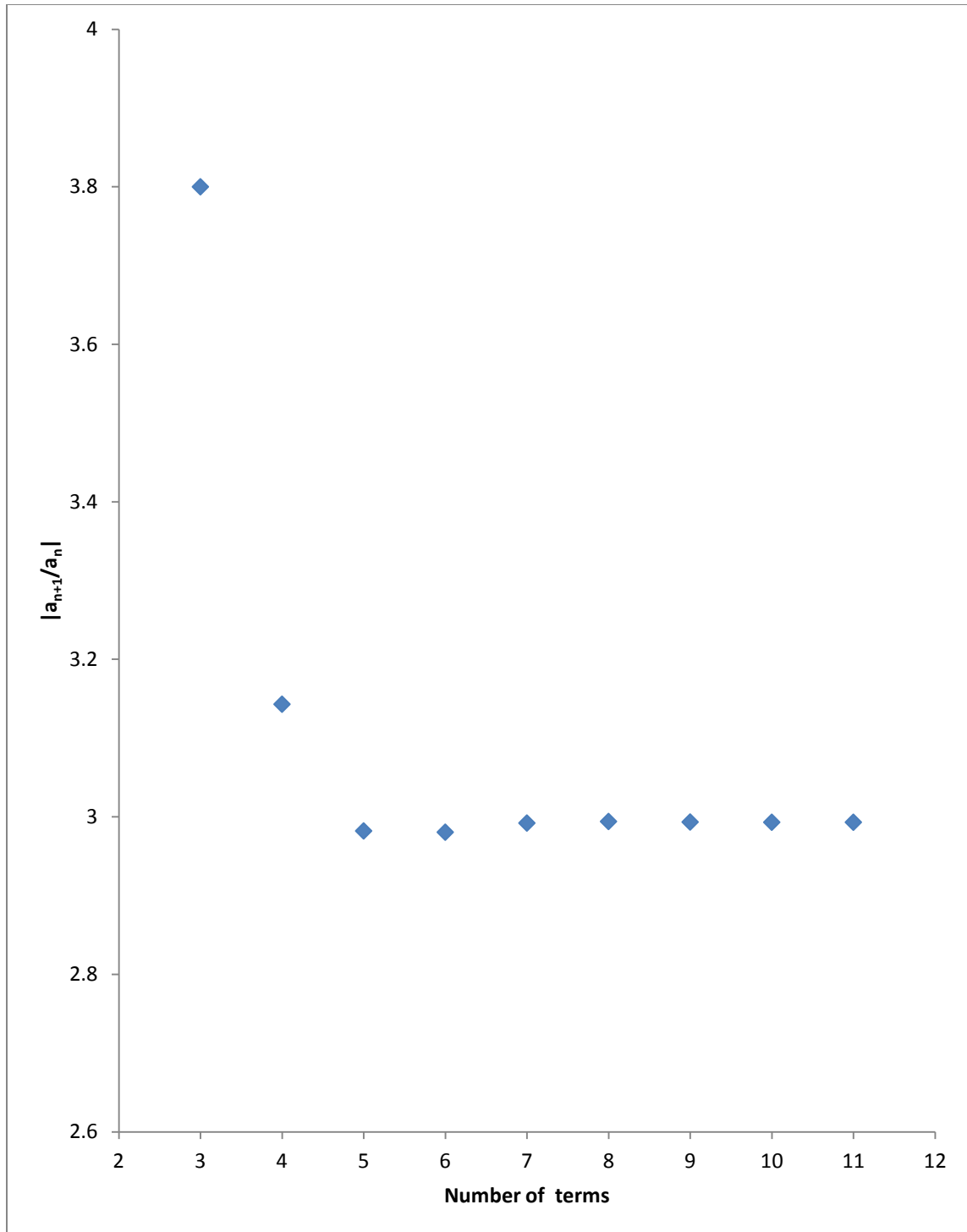


Figure 6.1. The ratio convergence test applied to the series coefficients (endothelial cell) for ADM and HPM as a function of the number of terms in series.

ADM and HPM provide analytical solution in terms of an infinite power series (see Eq. (6.38) for ADM and Eq. (6.47) for HPM). The series consists of both positive and negative terms, although not in a regular alternating fashion. The ratio test was applied to the absolute values of the series coefficient. This provides a sufficient condition for convergence of the series for a space interval ΔX in the form

$$\lim_{m \rightarrow \infty} \left| \frac{a_{m+1}}{a_m} \right| < \frac{1}{\Delta X} \quad (6.70)$$

However, the approach in this study was to replace Eq. (6.70) with

$$\lim_{m \rightarrow M} \left| \frac{a_{m+1}}{a_m} \right| < \frac{1}{\Delta X} \quad (6.71)$$

where M is a large constant. The behavior of the function $f(m) = |a_{m+1}/a_m|$ for increasing values of m was then observed as presented in Figure 6.1. It is clear from this figure that the ratio $f(m)$ decays as m increases, obviously indicating that the series is convergent.

Figure 6.2 demonstrates that the initial response of the endothelial cells is essentially one of migration with proliferation of the cells.

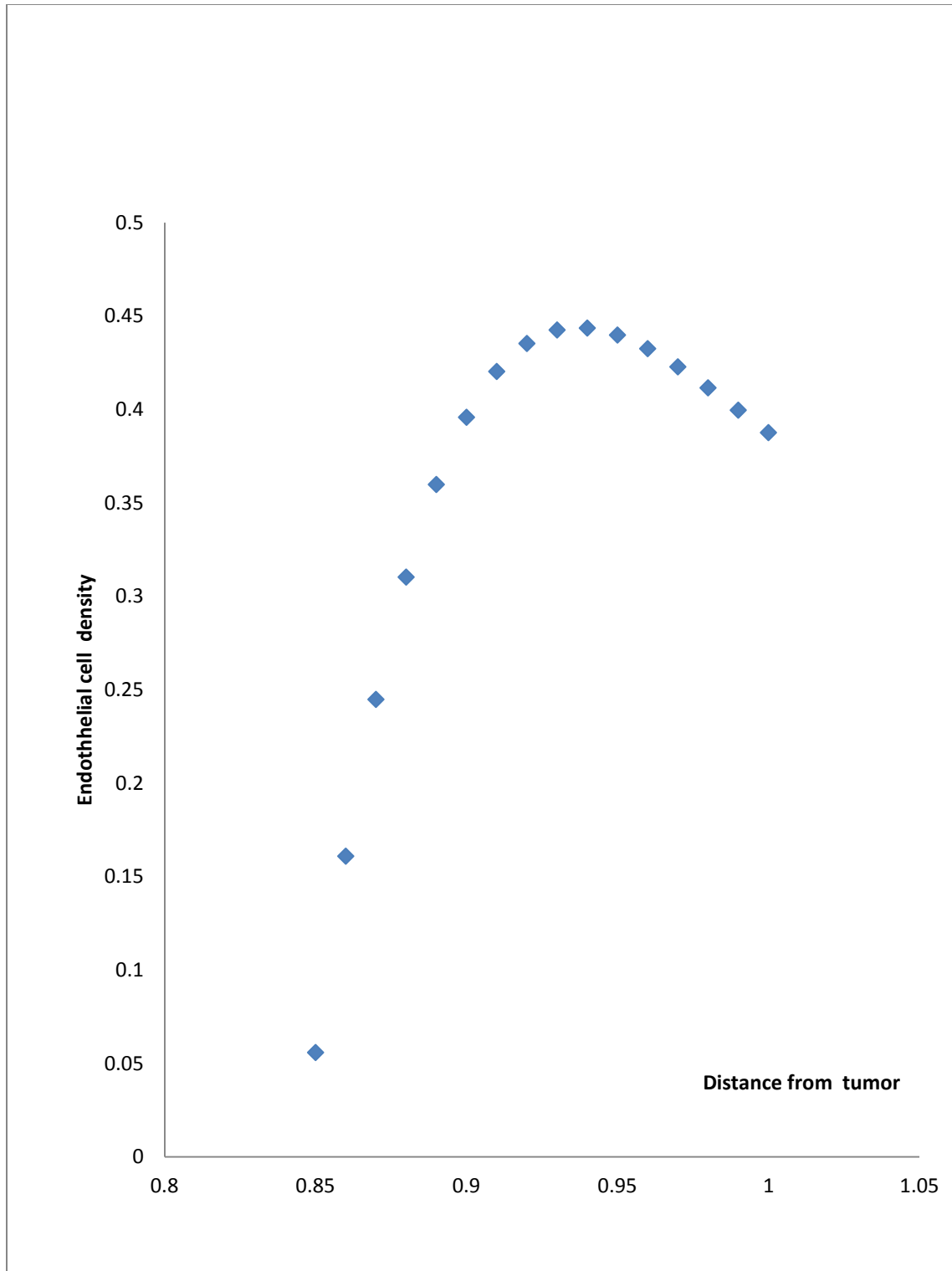


Figure 6.2. ADM and HPM solution of Equation (6.30). Profile of the endothelial cell density in the external host tissue at time $t = 0.1$.

6.7 Summary

In this chapter, we have presented a mathematical model for tumour angiogenesis based on ADM and HPM methods. The complete process of angiogenesis is a complicated one involving several distinct and not necessarily related events. To formulate a single mathematical model which would include all of these processes would be very difficult indeed. Here, we choose to focus our attention primarily on the endothelial cells concentration profile. We have modeled it in a simple but effective manner using ADM and HPM. Our results are in a good agreement with other models such as Stokes & Lauffenburger (1991) which being numerically solved. The nonlinear equation has been analyzed using ADM and HPM in which the nonlinear problems were treated in a manner similar to linear problems. Linearization, approximation and assumption are unnecessary during the analytic processes of both methods including faster convergence and higher accuracy. It may be used to solve the problems associated with the complex conditions.

