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**A. Bertuzzi, A. Fasano, A. Gandolfi**

**A MATHEMATICAL MODEL FOR THE GROWTH  
OF TUMOR CORDS INCORPORATING THE  
DYNAMICS OF A NUTRIENT**

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**Alessandro Bertuzzi** – Istituto di Analisi dei Sistemi ed Informatica del CNR, viale Manzoni  
30 - 00185 Roma, Italy. Email : [bertuzzi@iasi.rm.cnr.it](mailto:bertuzzi@iasi.rm.cnr.it).

**Antonio Fasano** – Dipartimento di Matematica “U. Dini”, Università di Firenze, viale Mor-  
gagni 67/A - 50134 Firenze, Italy. Email : [fasano@math.unifi.it](mailto:fasano@math.unifi.it).

**Alberto Gandolfi** – Istituto di Analisi dei Sistemi ed Informatica del CNR, viale Manzoni 30  
- 00185 Roma, Italy. Email : [gandolfi@iasi.rm.cnr.it](mailto:gandolfi@iasi.rm.cnr.it).

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Collana dei Rapporti  
dell'Istituto di Analisi dei Sistemi ed Informatica, CNR  
viale Manzoni 30, 00185 ROMA, Italy

tel. ++39-06-77161

fax ++39-06-7716461

email: [iasi@iasi.rm.cnr.it](mailto:iasi@iasi.rm.cnr.it)

URL: <http://www.iasi.rm.cnr.it>

## **Abstract**

We analyze the growth of a tumor cord in cylindrical symmetry, when nutrient is supplied by the central vessel and by a distributed peripheral source. The model equations describe the diffusion and consumption of the nutrient, together with the dynamics of growth of the cord and the formation of necrosis in the tumor or in the surrounding normal tissue. The different possible patterns of evolution are studied. One of the main points addressed is the possibility that nutrient diffuses through regions in which necrosis occurs.

*Key words:* Tumor cords, tumor growth, nutrient diffusion, necrosis, free boundaries.



## 1. Introduction

In some human and experimental tumors, tumor cells appear to be arranged in cylindrical structures around central blood vessels, often surrounded by necrosis. These structures are named tumor cords [2,3,4]. Oxygen and/or nutrients deprivation in cells remote from the central vessel are likely to play a central role in the decrease of cell proliferation rate within the cord and in the occurrence of necrosis. A mathematical model for tumor cords, describing the spatial distribution of proliferating cells (represented as an age-dependent cell population) and quiescent cells, has been recently proposed [1]. The authors studied the steady-state solutions in the case in which the probability for a cell to become proliferating or quiescent is a given function of the distance from the blood vessel.

In the present paper we concentrate on tumor growth and nutrient dynamics, simplifying to a large extent the description of the cell population and dealing with just one species of nutrient. Nutrient here has to be intended as a chemical that is critical for cell viability, also including oxygen. The interplay between the growth of the tumor cord and the diffusion of the chemical supplied by local vasculature is studied in cylindrical symmetry and disregarding axial changes of variables. We consider a central source (the central vessel of radius  $r_0$ ) plus a peripheral distributed source that mimics the neighbouring vessels. The growth of the tumor tissue is assumed to start close to the central vessel and to occur in the region delimited by the two sources, where a nonproliferating tissue characterized by a consumption rate different from that of the tumor is also present (see Fig. 1). The nutrient concentration  $\sigma(r, t)$  ( $r$  being the radial distance from the axis of the central vessel) is prescribed as  $\sigma = \sigma^*$  for  $r = r_0$ . The distant blood vessels provide another level surface  $\sigma = \sigma^*$ , which is considered to be a material surface (i.e. moving at the same speed as the cells). This is of course an idealized situation, but with no crucial role in the model (we could consider flux conditions and make different assumptions on the behavior of the external boundary).

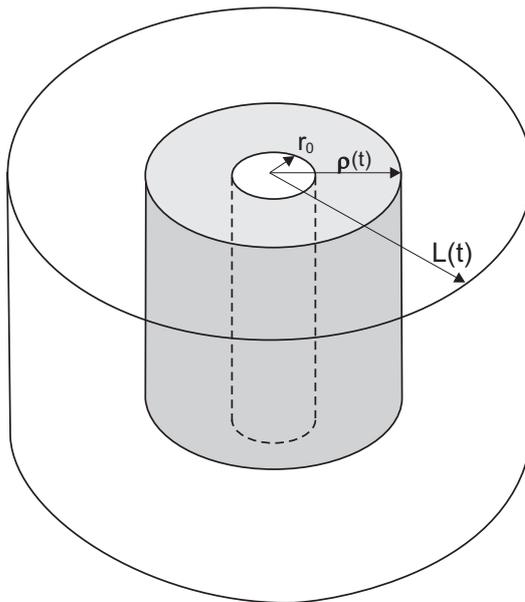


Fig. 1. Geometry of the tumor cord (gray) with the surrounding healthy tissue.

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We neglect the age structure in the tumor cell population and we consider the following regions:

Region **T**: the tumoral zone, made of cells proliferating at a constant rate;

Region **H**: made of normal (healthy) nonproliferating cells;

Region **N**: the necrotic zone, losing mass at a constant rate.

As we shall see, it will be necessary to consider two more regions, denoted as  $M_T$  and  $M_H$ , in which the dead cells coexist with the viable tumor cells and, respectively, with the viable normal cells.

In both regions, **T** and **H**, cell concentration is taken constant. We denote by  $\chi$  the specific expansion rate in **T**. During its growth, the tumor tissue displaces the region **H**, and in **H** we say that volume is conserved. We assume that cell death only occurs when nutrient concentration  $\sigma$  reaches the positive threshold value  $\sigma_d < \sigma^*$ . Let  $\mu$  be the specific contraction rate in **N**, due to cell disgregation and removal. If  $\mathbf{u}(r, t)$  denotes the velocity field in the system, the preceding assumptions read as follows:

$$\operatorname{div} \mathbf{u} = \begin{cases} \chi & \text{in T} \\ 0 & \text{in H} \\ -\mu & \text{in N.} \end{cases} \quad (1.1)$$

Assuming equal diffusivity  $D$  in the various regions, the concentration of the nutrient obeys the following law

$$\frac{\partial \sigma}{\partial t} + \operatorname{div}(-D\nabla \sigma + \sigma \mathbf{u}) = -\hat{\lambda}(\sigma), \quad (1.2)$$

with the consumption rate  $\hat{\lambda}$  taking different values in **T** and **H**. It is largely justified to consider the quasi-steady version of equation (1.2) and to neglect the convection. So we replace (1.2) by the o.d.e.'s

$$\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \sigma}{\partial r} \right) = \lambda_T \sigma \quad \text{in T} \quad (1.3)$$

$$\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \sigma}{\partial r} \right) = \lambda_H \sigma \quad \text{in H,} \quad (1.4)$$

with  $\lambda_T > \lambda_H > 0$ . For simplicity we have chosen a linear law for the consumption rate, but we can replace it by more general laws (e.g. of the Michaelis-Menten type).

Despite all these simplifications the model is not trivial and, depending on the initial data and the values of model parameters, various cases may occur that will be analyzed separately. Let us start with examining the first stage of the process, characterized by the absence of the necrotic region.

## 2. First stage of development (no necrotic zone)

We assume that at time  $t = 0$  the cord has a radius  $\rho_0 > r_0$  and is surrounded by a layer of normal tissue of radius  $L_0 > \rho_0$ . The data must be compatible with the requirement that  $\sigma > \sigma_d$  everywhere (it is easy to show that it is indeed possible to select data satisfying this condition). Let  $L_H^2$  be equal to  $L_0^2 - \rho_0^2$ .

We want to analyze how the system evolves until the threshold  $\sigma_d$  is reached somewhere. During this time the regions T and H are separated by an interface  $r = \rho(t)$ , clearly a material surface, and the radius of the tumor cord evolves according to:

$$\dot{\rho} = u(\rho, t). \quad (2.1)$$

The function  $u(r, t)$  is easily obtained by integrating

$$\frac{\partial}{\partial r}(ru) = r\chi, \quad r_0 < r < \rho(t), \quad u(r_0, t) = 0, \quad (2.2)$$

so that  $u$  is independent of time and is given by

$$u(r) = \frac{\chi}{2r}(r^2 - r_0^2). \quad (2.3)$$

At this point we can integrate (2.1) with the initial condition  $\rho(0) = \rho_0$ , obtaining

$$\rho(t) = [r_0^2 + (\rho_0^2 - r_0^2)e^{\chi t}]^{1/2}. \quad (2.4)$$

The region H is pushed outwards in such a way that its volume is conserved, that is

$$ru(r, t) = \rho u(\rho), \quad \rho(t) < r < L(t) \quad (2.5)$$

and, in particular, the motion of the outer boundary is described by the equation

$$L^2(t) = \rho^2(t) + L_H^2. \quad (2.6)$$

**Remark 2.1.** In principle, one could let  $\chi$  depend on  $\sigma$ , thus coupling the expansion of the system to the diffusion-consumption process of the nutrient. Here we keep the scheme as simple as possible in order to emphasize the peculiar properties of the system.

Now we solve the problem for  $\sigma$ . We have to integrate the system of o.d.e.'s (1.3), (1.4) in a known domain for each  $t$ , with the boundary conditions

$$\sigma(r_0, t) = \sigma^*, \quad \sigma(L(t), t) = \sigma^*, \quad (2.7)$$

$$[\sigma] = \left[\frac{\partial \sigma}{\partial r}\right] = 0 \quad \text{at } r = \rho(t), \quad (2.8)$$

where  $[\ ]$  denotes the jump. We note that the presence of consumption and the fact that, according to (2.4),  $\rho(t)$  tends to infinity for  $t \rightarrow \infty$ , imply (as we shall see) that at some finite time  $t_{nec}$  the death threshold  $\sigma_d$  will be reached. In this section we study the solution in the interval  $(0, t_{nec})$ .

We show the following existence and uniqueness result.

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**Theorem 2.1.** *There exists one unique function  $\sigma$  which is smooth in  $r_0 < r < \rho(t)$ ,  $\rho(t) < r < L(t)$  and continuously differentiable in  $r_0 < r < L(t)$  satisfying (1.3), (1.4), (2.7) and (2.8).*

*Proof.* We use a shooting technique, which is constructive. First we solve a Cauchy problem in  $\mathbb{T}$ , integrating (1.3) for each  $t$  with the boundary conditions

$$\sigma(r_0, t) = \sigma^*, \quad \left. \frac{\partial \sigma}{\partial r} \right|_{r=r_0} = \Sigma^*(t) < 0, \quad (2.9)$$

where  $\Sigma^*(t)$  is a function to be determined. It is easy to see that this is the same as solving the Volterra integral equation

$$\sigma - \sigma^* = r_0 \Sigma^* \log \frac{r}{r_0} + \lambda_T \int_{r_0}^r z \sigma(z, t) \log \frac{r}{z} dz, \quad r_0 < r < \rho(t). \quad (2.10)$$

Moreover

$$\frac{\partial \sigma}{\partial r} = \frac{1}{r} \left[ r_0 \Sigma^* + \lambda_T \int_{r_0}^r z \sigma(z, t) dz \right], \quad r_0 < r < \rho(t). \quad (2.11)$$

Thus  $\sigma$  and  $\partial \sigma / \partial r$  are both strictly increasing functions of  $\Sigma^*$ , for fixed  $t$ .

We denote by  $\sigma_i(t)$ ,  $\Sigma_i(t)$  the interface values of  $\sigma$  and  $\partial \sigma / \partial r$ , respectively, so it is

$$\sigma_i - \sigma^* = r_0 \Sigma^* \log \frac{\rho}{r_0} + \lambda_T \int_{r_0}^{\rho} z \sigma(z, t) \log \frac{\rho}{z} dz, \quad (2.12)$$

$$\Sigma_i = \frac{1}{\rho} \left[ r_0 \Sigma^* + \lambda_T \int_{r_0}^{\rho} z \sigma(z, t) dz \right], \quad (2.13)$$

and we compute  $\sigma$  in  $\mathbb{H}$  by integrating (1.4) for  $r > \rho(t)$  with the Cauchy data (2.12) and (2.13), obtaining

$$\sigma - \sigma_i = \rho \Sigma_i \log \frac{r}{\rho} + \lambda_H \int_{\rho}^r z \sigma(z, t) \log \frac{r}{z} dz, \quad r > \rho(t). \quad (2.14)$$

$$\frac{\partial \sigma}{\partial r} = \frac{1}{r} \left[ \rho \Sigma_i + \lambda_H \int_{\rho}^r z \sigma(z, t) dz \right], \quad r > \rho(t). \quad (2.15)$$

Since  $\sigma$  in  $\mathbb{H}$  depends monotonically on  $\sigma_i$  and  $\Sigma_i$ , which are in turn increasing functions of  $\Sigma^*$ , we can say that  $\sigma$  in  $\mathbb{H}$  depends monotonically on  $\Sigma^*$ . For  $\Sigma^* = 0$  we have  $\sigma_i > \sigma^*$ ,  $\Sigma_i > 0$ , so that  $\sigma > \sigma^*$  for  $r > \rho(t)$ , while  $\sigma(L(t))$  decreases indefinitely as  $\Sigma^* \rightarrow -\infty$ . Hence, for each  $t$  there is a unique determination of  $\Sigma^*$  such that  $\sigma(L(t), t) = \sigma^*$ . ■

Now we prove the following basic qualitative properties of the solution  $\sigma(r, t)$ .

**Theorem 2.2.** *Let  $\sigma(r, t) > \sigma_d$  be a solution of (1.3), (1.4), (2.7), (2.8) with  $\rho(t)$  given by (2.4) and  $L(t)$  by (2.6). Then*

- (i)  $\sigma < \sigma^*$  in  $(r_0, L)$  and  $\sigma$  has exactly one minimum,
- (ii)  $\sigma$  decreases in time and its minimum is bound to reach  $\sigma_d$  at a finite time  $t_{nec}$ .

*Proof.* (i) The equality  $\sigma < \sigma^*$  trivially follows from the maximum principle. Also, we can say that  $\partial \sigma / \partial r$  is negative at  $r = r_0$  and positive at  $r = L(t)$ , hence the existence of a minimum follows. Since there can be no relative maxima in  $(r_0, L(t))$ , the minimum is unique.

(ii) First, we show that if  $\rho$  increases then  $\Sigma^*$  decreases, thus implying that  $\sigma$  decreases everywhere. For a given  $\rho$ , fix the corresponding  $\Sigma^*(\rho)$  and compute the values of  $\sigma_i, \Sigma_i$ . Then replace  $\lambda_H$  with  $\lambda_T > \lambda_H$  in (2.14) and (2.15). In this way we see that the continuation  $\hat{\sigma}$  of the solution of (1.3) for  $r > \rho$  is such that  $\hat{\sigma} > \sigma$  and  $\partial\hat{\sigma}/\partial r > \partial\sigma/\partial r$ . Indeed the difference  $\delta = \hat{\sigma} - \sigma$  satisfies

$$\delta = \lambda_H \int_{\rho}^r z \delta \log \frac{r}{z} dz + (\lambda_T - \lambda_H) \int_{\rho}^r z \hat{\sigma} \log \frac{r}{z} dz. \quad (2.16)$$

Therefore, if we take  $\tilde{\rho} > \rho$  and we integrate (1.4) for  $r > \tilde{\rho}$  with the updated Cauchy data in  $r = \tilde{\rho}$ , we see that the new integral  $\tilde{\sigma}$  evaluated for  $r = L$ , i.e. the boundary corresponding to  $\rho$ , exceeds  $\sigma^*$ . Thus, in order to meet the condition  $\tilde{\sigma}(\tilde{L}) = \sigma^*$ ,  $\tilde{L} > L$  being the boundary corresponding to  $\tilde{\rho}$ , we must decrease  $\Sigma^*$ .

Then, suppose that for all  $t$  the minimum of  $\sigma$  stays above  $\sigma_d$ . The coordinate  $r_{min}$  at which  $\sigma$ , for a given  $\rho$ , takes its minimum cannot remain bounded when  $\rho \rightarrow \infty$ . Indeed also  $L \rightarrow \infty$  and, if  $r_{min}$  does not grow to infinity, then  $\sigma(L)$  cannot remain bounded. Now, either the minimum occurs in **T** (exceptionally at the interface) or it occurs in **H**, but in the latter case it is estimated from above by the continuation of the solution of (1.3) beyond  $r = \rho$ . Thus the minimum of (2.10) for  $r > r_0$  is an upper estimate of the minimum of our solution. In other words, we have the following possibilities: ( $\alpha$ )  $r_{min} < \rho$  (and tends to infinity as  $\rho \rightarrow \infty$ ); ( $\beta$ )  $r_{min} > \rho$ , then we consider the continuation  $\hat{\sigma}$  of  $\sigma$  given by (2.10) for  $r > \rho$ , and we denote by  $\hat{r}_{min}$  the coordinate of its minimum. Since  $\hat{r}_{min} > \rho$ , obviously  $\hat{r}_{min} \rightarrow \infty$  as  $\rho \rightarrow \infty$ . Moreover,  $\hat{\sigma}(\hat{r}_{min}) > \sigma(r_{min})$ . In any case, let us compute the minimum of (2.10). According to (2.11) the minimum occurs when

$$r_0 \Sigma^* = -\lambda_T \int_{r_0}^{\hat{r}_{min}} z \hat{\sigma} dz$$

(with  $\hat{\sigma} = \sigma$  and  $\hat{r}_{min} = r_{min}$  in case ( $\alpha$ )). Using this in (2.10) we get

$$\hat{\sigma}_{min} - \sigma^* = \lambda_T \int_{r_0}^{\hat{r}_{min}} z \hat{\sigma} \log \frac{r_0}{z} dz. \quad (2.17)$$

Since  $\hat{\sigma} \geq \sigma$  and we are supposing  $\sigma > \sigma_d$ , we get the estimate

$$\begin{aligned} \hat{\sigma}_{min} - \sigma^* &< \lambda_T \sigma_d \int_{r_0}^{\hat{r}_{min}} z \log \frac{r_0}{z} dz \\ &= -\lambda_T \sigma_d \frac{1}{2} \left[ \hat{r}_{min}^2 \log \frac{\hat{r}_{min}}{r_0} - \frac{1}{2} (\hat{r}_{min}^2 - r_0^2) \right]. \end{aligned} \quad (2.18)$$

Moreover we know that  $\hat{r}_{min} \rightarrow \infty$  if  $\rho \rightarrow \infty$ , leading to the contradiction  $\hat{\sigma}_{min} \rightarrow -\infty$ . ■

Depending on the values of  $\rho_0$  and  $L_0$ , and on the values of model parameters, the location of the minimum at time  $t = t_{nec}$  may be such that  $r_{min}(t_{nec}) < \rho(t_{nec})$  (Case I) or  $r_{min}(t_{nec}) \geq \rho(t_{nec})$  (Case II). In Case I the tumor zone **T** for  $t > t_{nec}$  is split into two regions, **T**<sub>1</sub> and **T**<sub>2</sub>. In the second case (with the exception of the equality sign, in which case the qualitative behavior is similar) the region **H** is going to be split into **H**<sub>1</sub> and **H**<sub>2</sub>.

For  $t > t_{nec}$  the model must include the presence of dead cells but, as we shall see, situations may arise in which the system cannot be described as the collection of regions made by just one type of cells (tumor, normal, dead). The real mathematical nature of the problem is that of a multiple free boundary problem for the diffusion-consumption equation for  $\sigma$  with a constraint on the velocity of one of the interfaces. Let us begin with the analysis of Case I.

### 3. Case I (the necrotic region splitting the tumor cord)

If at  $t = t_{nec}$  the threshold  $\sigma_d$  is reached at a point  $R = r_{min}(t_{nec})$  in the interior of T, then we expect to have for  $t > t_{nec}$  two tumor regions,  $T_1$  and  $T_2$ , separated by a necrotic zone N. Let us suppose that this happens, and let  $\rho_{nec}$  be the radius of the N– $T_2$  interface. Note that, to have a solution with a physical meaning, it must be  $\dot{\rho}_{nec} \geq u(\rho_{nec})$ , because the necrotic material cannot return to be viable. The difference  $\dot{\rho}_{nec} - u(\rho_{nec})$  represents the feeding rate of N per unit surface through the N– $T_2$  interface.

The region  $T_1$  is stationary and its interface  $r = R$  with N does not move. The cellular velocity

$$u(R) = \frac{\chi}{2} \frac{R^2 - r_0^2}{R} \quad (3.1)$$

is also the feeding rate of N per unit surface across the interface  $T_1$ –N. The velocity field in N is easily computed as

$$ru(r) = \frac{\chi}{2}(R^2 - r_0^2) - \frac{\mu}{2}(r^2 - R^2), \quad (3.2)$$

and we have

$$\rho_{nec}u(\rho_{nec}) = \frac{\chi}{2}(R^2 - r_0^2) - \frac{\mu}{2}(\rho_{nec}^2 - R^2). \quad (3.3)$$

The  $T_2$ –H interface  $r = \rho(t)$  is still a material surface moving with the cellular velocity. In  $T_2$  the velocity field must be found by integrating the equation

$$\frac{\partial}{\partial r}(ru) = \chi r, \quad \rho_{nec}(t) < r < \rho(t) \quad (3.4)$$

with the continuity condition for  $r = \rho_{nec}(t)$ , obtaining

$$ru(r) = \frac{\chi}{2}(R^2 - r_0^2) - \frac{\mu}{2}(\rho_{nec}^2 - R^2) + \frac{\chi}{2}(r^2 - \rho_{nec}^2). \quad (3.5)$$

Putting  $r = \rho(t)$  in (3.5) we obtain the motion equation of the  $T_2$ –H interface

$$\rho\dot{\rho} = \frac{\chi}{2}(R^2 - r_0^2) - \frac{\mu}{2}(\rho_{nec}^2 - R^2) + \frac{\chi}{2}(\rho^2 - \rho_{nec}^2). \quad (3.6)$$

Of course  $\rho(t_{nec})$  is known and if we define  $P = \rho^2/2$  and  $\xi = g(\rho_{nec}) = (\chi + \mu)(\rho_{nec}^2 - R^2)/2$  we can reformulate (3.6) in the linear form

$$\dot{P} = \chi(P - \frac{1}{2}r_0^2) - \xi, \quad P(t_{nec}) = \frac{1}{2}\rho^2(t_{nec}). \quad (3.7)$$

If the N– $T_2$  interface were material, i.e.  $\dot{\rho}_{nec} = u(\rho_{nec})$ ,  $\rho_{nec}(t)$  would be given by the o.d.e. (3.3) with the initial condition  $\rho_{nec}(t_{nec}) = R$ , and then  $\rho(t)$  could be computed from (3.7). Since in N there is no consumption, the continuous differentiability of  $\sigma$  imposes  $\sigma = \sigma_d$  in N and  $\partial\sigma/\partial r = 0$  at  $r = \rho_{nec}(t)$ . If we compute  $\sigma(L(t))$  with the Cauchy data  $\sigma = \sigma_d$  and  $\partial\sigma/\partial r = 0$  at  $r = \rho_{nec}(t)$ , and with  $\rho_{nec}(t)$  and  $\rho(t)$  as given under the hypothesis of  $\dot{\rho}_{nec} = u(\rho_{nec})$ , we can verify that it is not possible to meet the condition  $\sigma(L) = \sigma^*$  for all  $t > t_{nec}$ . Therefore, to have a necrotic zone between  $T_1$  and  $T_2$ , the N– $T_2$  interface must not be a material surface and

$$\dot{\rho}_{nec} > u(\rho_{nec}(t)). \quad (3.8)$$

A suitable  $\rho_{nec}(t)$  should allow  $\sigma$  to satisfy the Cauchy data at  $r = \rho_{nec}$  and the boundary condition at  $r = L$ . In order to define  $\rho_{nec}(t)$  we construct the mapping

$$\bar{\rho} = f(\gamma) \quad (3.9)$$

in the following way. Take  $\gamma \geq R$  and  $\bar{\rho} \geq \gamma$ , and define  $\bar{L}$  so that  $\bar{L}^2 - \bar{\rho}^2 = L_H^2$ . Then solve the system (1.3), (1.4) for  $\gamma < r < \bar{L}$ , with the no-jump condition (2.8) at  $r = \bar{\rho}$  and the Cauchy data  $\sigma = \sigma_d$  and  $\partial\sigma/\partial r = 0$  for  $r = \gamma$ , obtaining some value  $\sigma(\bar{L}) = \phi(\gamma, \bar{\rho})$ . Clearly, for fixed  $\gamma$ ,  $\sigma(\bar{L})$  increases unboundedly with  $\bar{\rho}$ , so we will be able to find a unique value of  $\bar{\rho}$  such that  $\sigma(\bar{L}) = \sigma^*$ , provided that  $\phi(\gamma, \gamma) < \sigma^*$ . It can be recognized that the function  $\phi(\gamma, \gamma)$  is decreasing with  $\gamma$  (we recall that it can be expressed in terms of modified Bessel functions). Moreover, at  $t = t_{nec}$  it is  $\phi(R, \rho(t_{nec})) = \sigma^*$  with  $\rho(t_{nec}) > R$ . Thus  $\phi(R, R) < \sigma^*$ , and then  $\phi(\gamma, \gamma) < \sigma^*$  for any  $\gamma > R$ . We note that  $f$  has the domain  $[R, \infty)$  and that  $f(\gamma) > \gamma$  for every  $\gamma > R$ . The function  $f(\gamma)$  is invertible because  $\phi(\gamma, \bar{\rho})$ , for fixed  $\bar{\rho}$ , is a monotone function of  $\gamma$ . Thus  $\rho_{nec}$  must satisfy  $\rho(t) = f(\rho_{nec}(t))$  and is determined by  $\rho$ .

We may use  $f$  to define  $F$  such that  $\rho = f(g^{-1}(\xi)) = F(\xi)$ . Since also  $F(\xi)$  is invertible, setting  $\xi = F^{-1}(\rho) = \Xi(P)$  and going back to (3.7), we can write a nonlinear o.d.e. for  $P$

$$\dot{P} = \chi(P - \frac{1}{2}r_0^2) - \Xi(P), \quad P(t_{nec}) = \frac{1}{2}\rho^2(t_{nec}). \quad (3.10)$$

Equation (3.10) is uniquely solvable, provided that  $\Xi(P)$  is Lipschitz continuous. In order to check this, it is sufficient to show that

$$f'(\rho_{nec}) \geq \alpha > 0 \quad (3.11)$$

for some  $\alpha$ . For  $\gamma \in [R, \infty)$ , consider the function  $\sigma_\gamma(r)$  satisfying (1.3), (1.4) for  $\gamma < r < L$ , and (2.8) with a fixed  $\rho$  and the Cauchy data  $\sigma_\gamma = \sigma_d$ ,  $\partial\sigma_\gamma/\partial r = 0$  at  $r = \gamma$ . In order to have (3.11) it is sufficient that, for  $r = \rho > \gamma + \epsilon$  ( $\epsilon > 0$  sufficiently small), the derivative  $\partial\sigma_\gamma/\partial\gamma$  at  $r = \rho$  remains separated from zero. As a matter of fact this means that if we move  $\gamma$  at a finite speed, then we have to move  $\rho = f(\gamma)$  at a finite speed too in order to satisfy  $\sigma_\gamma(L) = \sigma^*$ . Now, as long as we are integrating (1.3), we can write for  $r \leq \rho$

$$\sigma_\gamma(r) - \sigma_d = \lambda_T \int_\gamma^r z \sigma_\gamma(z) \log \frac{r}{z} dz \quad (3.12)$$

and therefore

$$\frac{\partial\sigma_\gamma}{\partial\gamma} = -\lambda_T \gamma \sigma_d \log \frac{r}{\gamma} + \lambda_T \int_\gamma^r z \frac{\partial\sigma_\gamma}{\partial\gamma} \log \frac{r}{z} dz \quad (3.13)$$

which implies, since  $\partial\sigma_\gamma/\partial\gamma < 0$ , that  $\partial\sigma_\gamma/\partial\gamma < -\lambda_T \gamma \sigma_d \log[1 + (\epsilon/\gamma)]$ , that is precisely what we need (from (3.13) we can also get a lower bound via Gronwall's lemma).

At this point  $\rho(t)$  and  $\rho_{nec}(t) = f^{-1}(\rho(t))$  are known. The condition (3.8) is guaranteed by continuity in a time interval  $(t_{nec}, \bar{t})$  if at  $t = t_{nec}$

$$\dot{f}^{-1}(\rho(t))|_{t=t_{nec}} > u(f^{-1}(\rho(t_{nec}))) = u(R). \quad (3.14)$$

We can summarize the above discussion in the following statement:

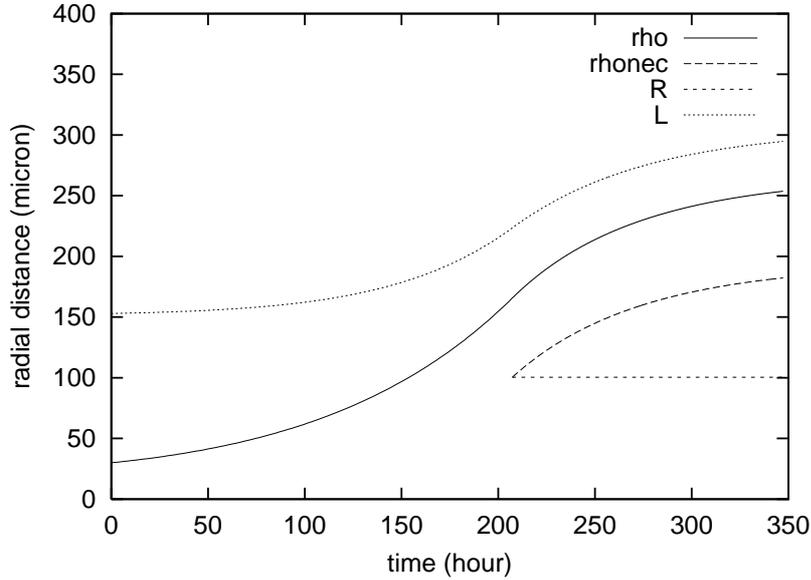


Fig. 2. Evolution of  $\rho$ ,  $\rho_{nec}$ , and  $L$  in case I. Model parameters:  $r_0 = 20 \mu\text{m}$ ,  $\rho_0 = 30 \mu\text{m}$ ,  $L_H = 150 \mu\text{m}$ ,  $\chi = 0.0193 \text{ h}^{-1}$ ,  $\mu = 0.03 \text{ h}^{-1}$ ,  $\lambda_T = 0.00148 \mu\text{m}^{-2}$ ,  $\lambda_H = 0.25\lambda_T$ ,  $\sigma^* = 40 \text{ mmHg}$ ,  $\sigma_d = 2 \text{ mmHg}$ .

**Theorem 3.1.** *If condition (3.14) holds, there exists a unique solution of the problem describing the evolution of the system  $T_1-N-T_2-H$ , having the  $C^1$  interfaces  $R$ ,  $\rho_{nec}$ ,  $\rho$ ,  $L$ , for  $t > t_{nec}$  and until violation of condition (3.8) occurs.*

**Remark 3.1.** Although a formal proof is not available, numerical simulations suggested that, when (3.14) holds, the condition (3.8) is satisfied for any  $t > t_{nec}$ .

If the condition (3.8) is not violated at any time  $t > t_{nec}$ , the system reaches the equilibrium state with the limit interfaces,  $\rho_{nec}^{(\infty)}$  and  $\rho^{(\infty)}$ , characterized by the equations

$$\rho^{(\infty)} = f(\rho_{nec}^{(\infty)}) \quad (3.15)$$

$$\chi(\rho^{(\infty)2} - r_0^2) = (\chi + \mu)(\rho_{nec}^{(\infty)2} - R^2), \quad (3.16)$$

the latter condition expressing  $\dot{\rho} = 0$ . We note that, if Case I occurs, (3.15) and (3.16) have a solution  $\rho^{(\infty)} > \rho_{nec}^{(\infty)} > R$ , provided that  $\mu > 0$ . The curves defined by (3.15) and (3.16) have indeed an intersection for  $\rho_{nec} > R$ , since it can be seen that they start from  $\rho(t_{nec})$  and  $r_0$ , respectively, and have asymptotes with slopes equal to 1 and greater than 1.

Figure 2 shows a numerical simulation of the evolution of the characteristic boundaries in Case I when the necrotic region arises after  $t_{nec}$ . The values of model parameters were reasonably chosen making reference to oxygen as the diffusing species.

#### 4. The onset of the mixed region

It may happen that at  $t = t_{nec}$  it is  $\dot{f}^{-1}(\rho(t))|_{t=t_{nec}} < u(R)$ . This is the situation in which a necrotic region, if present, could not advance over  $T_2$ , the interface with  $T_2$  should be a material surface and the value of  $\sigma$  on this interface should rise above the threshold to meet the outer boundary condition. The region  $T_2+H$  is indeed too thin to consume all the supplied nutrient. As a result, nutrient should start diffusing through the region between  $T_1$  and  $T_2$  and in this zone the concentration should be logarithmic (with  $\partial^2\sigma/\partial r^2 < 0$ ), due to the absence of consumption. Therefore, the only way to make the system compatible with the existence of a minimum for  $\sigma$  is that the region between  $T_1$  and  $T_2$  possesses some residual consumption capability. A simple interpretation of this new zone is that of a mixed region,  $M_T$ , in which we have a fraction  $\nu$  of living cells. The conjecture expressed in Remark 3.1 implies that the mixed region, if it arises, can have onset only at  $t_{nec}$ . Only this case will be discussed.

**Remark 4.1.** It is important to observe that the necessity of introducing  $M_T$  is by no means related to any of the simplifying assumptions made so far. Considering the inertia term in the diffusion equation would not remove the impossibility of having a minimum of  $\sigma$  at the boundary of  $N$ , nor we can expect any help from the neglected convective term (which in  $N$  would rather favour the existence of local maxima). It is equally easy to realize that the onset of  $M_T$  is not linked to the particular condition chosen at the external boundaries, which could be replaced for instance by imposing that the entering flux is proportional to  $\sigma^* - \sigma$ . To eliminate the region  $M_T$ , the boundary condition at  $r = L$  should be modified so to decrease the nutrient supply rate in a way which is perfectly balanced with the motion of the boundary, a choice looking quite artificial.

Obviously the quantity  $\nu$  is unknown, and we may argue whether it depends on  $r$  as well as on  $t$ . For simplicity, we formulate the model for  $M_T$  in the following way: (i) The  $M_T-T_2$  interface at  $r = \rho_m$  is a material surface; (ii) the fraction  $\nu(t)$  of living cells is uniform in  $M_T$ ; (iii)  $\nu(t)$  determines the specific volume rate of change according to

$$\operatorname{div} \mathbf{u} = -(1 - \nu)\mu + \nu\chi. \quad (4.1)$$

Now let us proceed to the existence proof in the presence of  $M_T$ . First we establish a relationship between  $\rho_m(t)$  and  $\nu(t)$ , exploiting (i):

$$\dot{\rho}_m = u(\rho_m). \quad (4.2)$$

Clearly in  $M_T$  we have (recall (3.1))

$$ru(r, t) = \frac{\chi}{2}(R^2 - r_0^2) - \frac{1}{2}[(1 - \nu(t))\mu - \nu(t)\chi](r^2 - R^2), \quad R < r \leq \rho_m \quad (4.3)$$

so that (4.2) becomes

$$\rho_m \dot{\rho}_m = \frac{\chi}{2}(R^2 - r_0^2) + \frac{1}{2}[-\mu + (\chi + \mu)\nu(t)](\rho_m^2 - R^2), \quad (4.4)$$

which can be read as a linear equation in  $P_m = \rho_m^2/2$

$$\dot{P}_m + [\mu - (\chi + \mu)\nu(t)]P_m = \frac{\chi}{2}(R^2 - r_0^2) - \frac{1}{2}[-\mu + (\chi + \mu)\nu(t)]R^2, \quad (4.5)$$

with the initial condition  $P_m(t_{nec}) = R^2/2$ . Next we remark that in the present case  $\rho_m$ ,  $\rho$  and  $L$  are all material interfaces and that the velocity field for  $r > \rho_m$  can be found in terms of  $\rho_m$ :

$$ru(r, t) = \rho_m u(\rho_m) + \frac{\chi}{2}(r^2 - \rho_m^2), \quad \rho_m < r \leq \rho \quad (4.6)$$

$$ru(r, t) = \rho u(\rho), \quad \rho < r \leq L. \quad (4.7)$$

Using (4.6), (4.7) we can compute the boundaries  $\rho(t)$  and  $L(t)$ . We proceed as follows. By putting  $r = \rho$  in (4.6), we write

$$\dot{P} - \chi P = \dot{P}_m - \chi P_m. \quad (4.8)$$

Defining  $Q = P - P_m$ , we get

$$\dot{Q} - \chi Q = 0, \quad Q(t_{nec}) = \frac{1}{2}\rho^2(t_{nec}) - \frac{1}{2}R^2 \quad (4.9)$$

and consequently

$$P(t) = P_m(t) + Q(t_{nec})e^{\chi(t-t_{nec})}, \quad t > t_{nec}. \quad (4.10)$$

Finally, we just have  $L(t)$  from (2.6). Thus we see that  $\rho(t)$  and  $L(t)$  are expressed in terms of  $\rho_m(t)$ , and do not explicitly involve  $\nu(t)$ .

Now, for each fixed  $t > t_{nec}$ , let us suppose we know  $\rho_m$ , and hence also  $\rho$  and  $L$  via (4.10) and (2.6), and consider the problem

$$\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \sigma}{\partial r} \right) = \lambda(r) \sigma, \quad R < r < L, \quad (4.11)$$

where  $\lambda(r)$  is equal to  $\nu \lambda_T$  for  $R < r < \rho_m$ , to  $\lambda_T$  for  $\rho_m < r < \rho$  and to  $\lambda_H$  for  $\rho < r < L$ , and with  $\sigma = \sigma_d$  and  $\partial \sigma / \partial r = 0$  at  $r = R$ ,  $\sigma$  being continuously differentiable on the whole interval  $(R, L)$ . We calculate  $\sigma(L)$  and we look for  $\nu$  such that  $\sigma(L) = \sigma^*$ . Noting that  $\rho$  and  $L$  depend on  $\rho_m$  and  $t$ , we obtain the mapping

$$\nu = h(\rho_m, t) = H(P_m, t) \quad (4.12)$$

which allows us to rewrite (4.5) as an o.d.e. for the function  $P_m$ . Such an equation is more conveniently reformulated in the unknown  $y = P_m - R^2/2$  and we can see that the function  $H$  is such that we find a unique  $C^1$  solution  $y(t)$  satisfying  $y(t_{nec}) = 0$ .

Therefore, the only thing that remains to be defined is the admissible range for  $\rho_m$  for each  $t$ . By this we mean the range of values that, for some  $\nu \in [0, 1]$ , allow to meet the condition  $\sigma(L) = \sigma^*$  at time  $t$ . It can be verified that for  $t > t_{nec}$  and close enough to  $t_{nec}$ , for any increasing  $C^1$  function  $\rho_m(t)$  having  $\dot{\rho}_m(t_{nec}) = u(R)$  we have  $\sigma(L) > \sigma^*$  if  $\nu = 1$  and  $\sigma(L) < \sigma^*$  if  $\nu = 0$  (in view of the condition  $f^{-1}(\rho(t))|_{t=t_{nec}} < u(R)$ ), that is the admissible range is not empty. Thus we can state the following

**Theorem 4.1.** *As long as  $\rho_m(t)$  lies in the admissible range, we can determine the  $C^1$  functions  $\nu$ ,  $\rho_m$ ,  $\rho$ ,  $L$  (and  $\sigma$ ) in a unique way.*

**Remark 4.2.** In the present situation the mass of the region  $T_2$  is steadily increasing and there cannot be an asymptotic equilibrium solution. The system would come to the point in which  $\sigma$  cannot take the value  $\sigma^*$  at  $r = L$ , not even for  $\nu = 0$ . In that case the necrotic zone resumes advancing over  $T_2$ , with a non-material interface, while the mixed zone is converted into a purely necrotic zone ( $\rho_m(t)$  has indeed reached the boundary of the admissible range, at which  $\nu = 0$ ). In other words, we go back to the previous situation.

## 5. Case II (the necrotic region splitting the region H)

We are now assuming that for  $t = t_{nec}$  the minimum  $\sigma = \sigma_d$  is reached at a location  $r_{min}(t_{nec}) = \rho_1 > \rho(t_{nec})$ . The radius  $\rho_1$  is characterized by the fact that the solution of (1.4) with Cauchy data  $\sigma = \sigma_d$  and  $\partial\sigma/\partial r = 0$  at  $r = \rho_1$  takes the value  $\sigma^*$  for  $r = L(t_{nec}) = (\rho^2(t_{nec}) + L_H^2)^{1/2}$ . The determination of  $\rho_1$  is unique (see section 2).

For  $t > t_{nec}$  and not too large, there will be two regions of normal tissue:  $H_1$  for  $\rho(t) < r < \rho_{min}(t)$ , and  $H_2$  for  $\rho_m(t) < r < L(t)$ . At  $t = t_{nec}$ , it is  $\rho_{min} = \rho_m = \rho_1$ . The interface  $r = \rho(t)$  separates T from  $H_1$  and is a material surface that evolves according to (2.1), (2.3) and is therefore the same as (2.4). The velocity field  $u(r, t)$  in  $H_1$  is described once again by (2.5). Owing to the fact that  $\lambda_T > \lambda_H$ , the coordinate  $\rho_{min}(t)$  of the minimum decreases ( $\rho_{min}$  would remain constant if  $\lambda_T = \lambda_H$ ), up to the time  $t_0$  such that  $\rho(t_0) = \rho_{min}(t_0) = R$ , marking the disappearance of  $H_1$ . After  $t_0$  the tumor region remains stationary. The cells leaving  $H_1$  at  $\rho_{min}(t)$  (as long as  $\rho_{min}(t) > \rho(t)$ ) enter a region that has to contain a fraction of dead cells. Once more, the intermediate region  $\rho_{min}(t) < r < \rho_m(t)$  is necrotic or mixed depending on whether  $\dot{\rho}_m(t) > u(\rho_m)$  or not. In the latter case  $\rho_m$  becomes a material surface (i.e.  $\dot{\rho}_m(t) = u(\rho_m)$ ) and the intermediate region is of the mixed type.

Assuming for the moment that  $H_1$  and  $H_2$  are separated by a mixed region  $M_H$ , we have to determine the pair of functions  $(\rho_m, \nu)$ . We recall that the function  $\rho_{min}(t)$  can be found easily, as well as  $\rho(t)$  still given by (2.4), and that from (2.5) and (2.3)

$$u(\rho_{min}) = \frac{\chi}{2\rho_{min}}(\rho_0^2 - r_0^2)e^{\chi t} \quad (5.1)$$

(note that the relative velocity  $u(\rho_{min}) - \dot{\rho}_{min}$  is the feeding rate per unit surface of  $M_H$  by  $H_1$ ). Now, in place of (4.1), we should write in  $M_H$   $\text{div } \mathbf{u} = -(1 - \nu)\mu$  and consequently

$$\frac{\partial}{\partial r}(ru) = -r(1 - \nu)\mu \quad (5.2)$$

which implies, in particular,

$$\rho_m \dot{\rho}_m = \frac{\chi}{2}(\rho_0^2 - r_0^2)e^{\chi t} - (1 - \nu)\frac{\mu}{2}(\rho_m^2 - \rho_{min}^2). \quad (5.3)$$

In addition, we have a mapping similar to (4.13)

$$\nu = h(\rho_m, t), \quad (5.4)$$

namely: given  $t$  and  $\rho_m$  (in a permitted interval), there is a unique choice of  $\nu$  in  $[0, 1]$  such that, solving

$$\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \sigma}{\partial r} \right) = \nu \lambda_H \sigma \quad (5.5)$$

in  $(\rho_{min}(t), \rho_m)$  with the Cauchy data  $\sigma = \sigma_d$  and  $\partial\sigma/\partial r = 0$  at  $r = \rho_{min}(t)$ , and continuing the solution beyond  $\rho_m$ , the value  $\sigma = \sigma^*$  is taken precisely at  $r = (\rho_m^2 + L^2(t_{nec}) - \rho_1^2)^{1/2}$ . The system (5.3), (5.4) must be solved for  $t > t_{nec}$  with the condition  $\rho_m(t_{nec}) = \rho_1$ . The study of (5.3), (5.4) is parallel to the corresponding system in the previous section. Of course, the solution exists as long as  $\rho_m$  remains in the admissible set (as in section 4).

The conclusion we have reached so far can be expressed as follows: the onset and growth of a mixed region separating  $H_1$ ,  $H_2$  is a solution compatible with the evolution of the physical

system. Such a solution can be continued in the interval  $[t_{nec}, t_0]$  up to the time when  $\rho_m$  possibly leaves the admissible range. In order to convert this statement into an existence and uniqueness theorem we have to rule out the alternative possibility, namely that a purely necrotic region N may appear when  $H_1, H_2$  separate. Moreover, we have to investigate the case that eventually  $\rho_m$  is no longer contained in the admissible range for the mapping  $\nu = h(\rho_m, t)$ , implying that  $M_H$  reverts to N at a later time.

To allow the development of a necrotic region  $\rho_{min} < r < \rho_{nec}$  (the radius of the inner boundary of  $H_2$  is now denoted by  $\rho_{nec}$ ), it is required that  $\dot{\rho}_{nec} > u(\rho_{nec})$ , i.e. mass has to be lost in  $H_2$ . A necessary condition for mass reduction is that  $\rho_{nec} < \rho_1$ , since only in that case the solution of (1.4) with  $\sigma = \sigma_d$  and  $\partial\sigma/\partial r = 0$  at  $r = \rho_{nec}$  can reach the value  $\sigma^*$  at a distance  $G(\rho_{nec})$  such that  $G^2(\rho_{nec}) - \rho_{nec}^2 < L^2(t_{nec}) - \rho_1^2$ . Thus the necrotic region can appear only at a time  $\bar{t}$  such that  $\rho_{nec}(\bar{t}) = \rho_1$  (which is not, as we shall see, the time  $t_{nec}$ ). The time  $\bar{t}$  is indeed the time at which  $\rho_m$  leaves the admissible range.

The evolution equation for  $\rho_{nec}$  can be written considering that

$$L\dot{L} = \rho_{nec}u(\rho_{nec}) \quad (5.6)$$

and by replacing  $L$  by  $G(\rho_{nec})$  in (5.6). We have

$$G(\rho_{nec})G'(\rho_{nec})\dot{\rho}_{nec} = \rho_{nec}u(\rho_{nec}), \quad \rho_{nec}(\bar{t}) = \rho_1, \quad (5.7)$$

where the right-hand-side is

$$\rho_{nec}u(\rho_{nec}) = \rho_{min}u(\rho_{min}) - \frac{\mu}{2}(\rho_{nec}^2 - \rho_{min}^2). \quad (5.8)$$

Since  $G' > 0$ , from (5.7) we see that if we are going to have mass loss for  $t > \bar{t}$  we need  $\dot{\rho}_{nec}(t) \leq 0$ , i.e.  $u(\rho_{nec}) \leq 0$ , that is certainly not true for  $t = t_{nec}$ . Therefore we conclude the following: (i) no necrotic region can appear soon after  $t_{nec}$ ; (ii) a necrotic region will be formed only if  $\rho_m$  reaches a maximum and then shrinks back to  $\rho_1$  (thus the cellular velocity is also negative). In the latter case, that occurs if the value of  $\mu$  is large enough, the asymptotic limit is reached when  $u(\rho_{nec}) = \dot{\rho}_{nec} = 0$ . Thus we can summarize the above results as follows:

**Theorem 5.1.** *In case II, soon after  $t = t_{nec}$  a mixed region  $M_H$  grows between regions  $H_1, H_2$ . The region  $H_1$  is bound to disappear at a finite time  $t_0$ , after which the tumor region T becomes stationary. In the time interval  $[t_{nec}, t_0]$  the region  $M_H$  may expand or, if the value of  $\mu$  is large enough, its outer boundary may invert its motion and possibly reach the value  $\rho_1$  at which it is  $\sigma = \sigma_d$  and  $\partial\sigma/\partial r = 0$ . At this time,  $M_H$  becomes totally necrotic and the region N evolves to an asymptotic limit.*

For  $t > t_0$ , the region between T and  $H_2$  is fed by tumor cells and, if the mixed region has not become totally necrotic, a region of type  $M_T$  should appear along with the existing  $M_H$  region. The study can be performed by further specifying the properties of  $M_T$  and  $M_H$ , for instance by assuming that the fraction of living cells  $\nu$  is uniform in  $M_T + M_H$ . In this case it can be seen that the mixed region may reach an asymptotic limit in which  $M_T$  replaces  $M_H$ , or may become necrotic when its outer boundary shrinks to  $\rho_1$ . We do not provide here a detailed description of this evolution. Figure 3 shows an example of the evolution of the system in Case II when the mixed region reverts to be purely necrotic before time  $t_0$ .

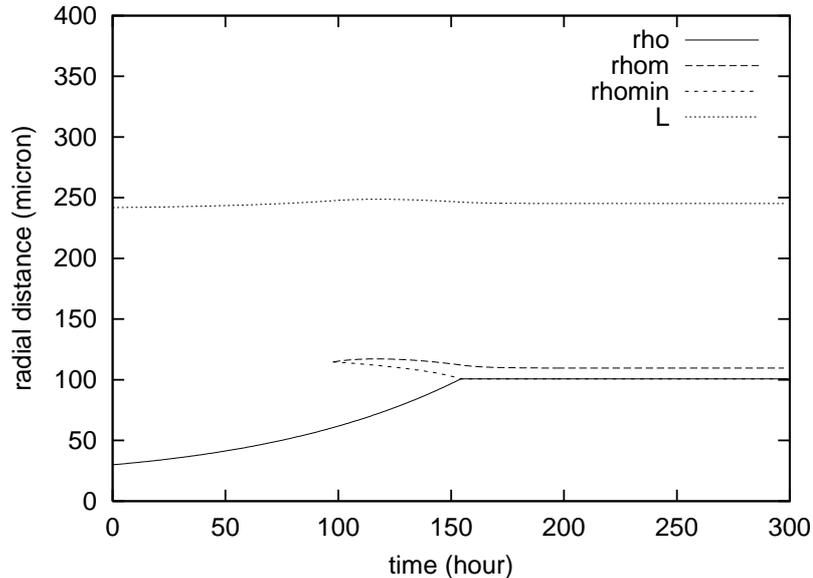


Fig. 3. Evolution of  $\rho$ ,  $\rho_{min}$ ,  $\rho_m$  and  $L$  in case II. Model parameters as in Fig. 2 except:  $L_H = 240 \mu\text{m}$ ,  $\mu = 0.1 \text{ h}^{-1}$ ,  $\lambda_H = 0.6\lambda_T$ .

## 6. Concluding remarks

We have presented a model for the evolution of tumor cords which, despite of the many simplifying assumptions, describes some general features of such systems. The model predicts that necrosis may occur within the tumor tissue, and in this case the final spatial pattern is composed by a central cord of tumor cells around the vessel and an annular region of tumor tissue, with a totally necrotic zone in between. Although this precise pattern has not been observed, it is reminiscent of the tumor tissue organization in cords and islands, separated by necrosis or stroma, that is found in histological specimens. For different parameter values, a region in which dead and viable cells coexist occurs in the healthy tissue, and this region (possibly become totally necrotic) will eventually separate the tumor cord from the healthy region.

A more realistic model, still keeping the symmetry around the central blood vessel, should include the following effects: i) a spontaneous (or therapeutically induced) death rate in the regions T and H; ii) an activity threshold for the cells, below which we have apoptosis for normal cells and no replication for tumor cells. Removing the assumption about symmetry produces a considerably difficult problem even in the naive approach we have used here.

In the present system, in some situations, we had to consider mixed regions in which dead cells coexist with viable cells, to make the motions of material interfaces compatible with nutrient diffusion. It is expected that a similar difficulty can arise in other kinds of tumor models, thus we believe that it might be a basic question (still not satisfactorily solved) in the general framework of tumor growth modelling.

**References**

1. A. Bertuzzi and A. Gandolfi, Cell kinetics in a tumour cord, *J. theor. Biol.* 204(2000), 587-599.
2. J. Holash, P.C. Maisonpierre, D. Compton, P. Boland, C.R. Alexander, D. Zagzag, G.D. Yankopoulos and S.J. Wiegand, Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF, *Science* 284(1999), 1994-1998.
3. J.V. Moore, P.S. Hasleton and C.H. Bookley, Tumour cords in 52 bronchial and cervical squamous cell carcinomas: inferences for their cellular kinetics and radiobiology, *Br. J. Cancer* 51(1985), 407-413.
4. I.F. Tannock, The relation between cell proliferation and the vascular system in a transplanted mouse mammary tumour, *Br. J. Cancer* 22(1968), 258-273.