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A FREE BOUNDARY PROBLEM WITH UNILATERAL CONSTRAINTS DESCRIBING THE EVOLUTION OF A TUMOUR CORD UNDER THE INFLUENCE OF CELL KILLING AGENTS

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Abstract

Abstract. A system of tumour cords is schematized by an array of identical cords each one having approximately a rotational symmetry around its central blood vessel. A mathematical model for the evolution of the cord is presented taking into account the following facts: the influence of a limiting nutrient on the proliferation rate and death rate of the cells, the volume reduction rate of the necrotic material due to fluid loss from the cord, the influence of chemotherapy or radiation treatment. Both the steady state and the evolution problem are considered, showing existence and uniqueness of the solution. A peculiar feature of the evolution model is that the boundary conditions for the nutrient concentration on the interface between viable cord and necrotic region may change during the response to treatment, according to the fact that new cells enter the necrotic region or not.

Key words: Tumour growth, cancer treatment, free boundary problems for PDE's.

1. Introduction and model formulation

In some human and experimental tumours, tumour cells appear to be arranged in cylindrical structures around central blood vessels, generally surrounded by necrosis. These structures are named tumour cords [17,13,16]. Oxygen and/or nutrient deprivation in cells remote from the central vessel are likely to play a decisive role in the decrease of cell proliferation rate within the cord and in the occurrence of necrosis. Mathematical models, describing the spatial distribution of proliferating cells and quiescent cells in a tumour cord at the stationary state, have been recently proposed [3,5]. The authors represented the proliferating cells as an age-dependent cell population or by discrete maturity compartments, and considered the case in which the fraction of newborn cells that become quiescent and/or the progression rate through cell cycle are assigned functions of the distance from the blood vessel. In [18] the existence and uniqueness of the steady-state age density of the cell population within the cord has been shown. The growth of an isolated tumour cord within the normal tissue, when nutrient is supplied by the central vessel and by a distributed peripheral source that mimics surrounding vessels, has been analyzed in [4]. The model equations described the diffusion and consumption of the nutrient, together with the dynamics of growth of the cord and the formation of necrosis.

In the present paper we propose a mathematical model that describes, using the continuum approach, the behaviour of a fully developed system of tumour cords under the influence of a therapeutic treatment. The existence of a unique stationary state in the absence of therapy will be shown, as well as the existence and uniqueness of the solution of the evolutive problem that arises following the perturbation of the stationary state. This problem is characterized by the presence of free boundaries, the most important being the ones that confine the necrotic zone: the external boundary is always a no-flux material surface, whereas the internal boundary may be slower than the cells or become a material surface, depending on the evolution of the whole cord.

We concentrate on one cord in the core of the system, supposing that:
(i) we have symmetry around the axis of the central blood vessel of the cord,
(ii) all the quantities describing the cord structure and the concentrations of the various chemical species are independent of the coordinate along the axis,
(iii) there is a cylindrical boundary around the cord where there is no radial exchange of matter (cells, necrotic material and diffusible chemicals) with the environment.
Such a geometry of the outer boundary, although idealized, can be considered a reasonable approximation by viewing the cord inside an array of parallel, identical cords.

As in previous works on the growth of spherical tumours [12,1,7, 10,11] and in [4,6], we consider for simplicity just one species of "nutrient" with concentration σ. Here we keep the simplified picture in which the system is considered a continuum where it is possible to define concentrations of the various diffusing substances in a global sense, *i.e.* without distinguishing the physical and chemical processes occurring within the cells and in the interstitial fluids. A finer description including the evolution of chemicals in cellular and extracellular spaces is by far more complicated (although it is certainly worth being investigated). Cells are assumed to die if σ reaches the death threshold σ_N. Moreover, we assume a certain degree of spontaneous death within the cord, according to a death rate $\mu(\sigma)$. Accordingly, within the cord we have viable cells, dead cells and extracellular fluids, the respective volume fractions ν_V, ν_N and ν_E adding to one.

Cells proliferate at the maximum rate χ_0 when $\sigma \geq \sigma_P > \sigma_N$ and ν_E is beyond some threshold $\bar{\nu}_E$. We introduce another threshold $\sigma_Q \in (\sigma_N, \sigma_P)$ below which the progression of cells across

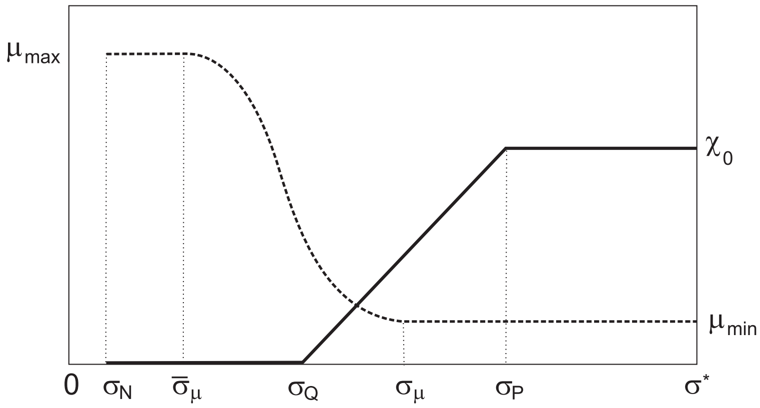

Fig. 1. An example of possible graphs of χ (solid line) and μ (dashed line) as functions of σ. For the meaning of the parameters see the text.

the cycle is arrested and all cells become quiescent, maintaining however the capacity to resume the proliferation. The inclusion of quiescence is important because the response to treatment of quiescent cells is generally different from that of proliferating cells. The properties of the proliferation rate $\chi(\sigma)$ and of the death rate $\mu(\sigma)$ are stated as follows (see Fig. 1):

- $\chi(\sigma)$, $\mu(\sigma)$ continuous and piecewise C^1 functions in $[\sigma_N, \sigma^\star]$, with bounded first derivatives and with $\sigma^\star > \sigma_P$ (H1)
- $\chi(\sigma) = \chi_0$ for $\sigma \geq \sigma_P$, and $\chi(\sigma) = 0$ for $\sigma \leq \sigma_Q$ (H2)
- $\chi'(\sigma) > 0$ for $\sigma \in (\sigma_Q, \sigma_P)$ (H3)
- $\mu(\sigma) = \mu_{min} \geq 0$ for $\sigma \geq \sigma_\mu$, with $\sigma_\mu \leq \sigma_P$ (H4)
- $\mu'(\sigma) \leq 0$; if $\sigma_\mu > \sigma_N$, $\mu'(\sigma) < 0$ only in an interval $(\bar{\sigma}_\mu, \sigma_\mu)$, with $\sigma_\mu > \bar{\sigma}_\mu \geq \sigma_N$ (H5)
- $\chi_0 > \mu_{min}$. (H6)

Some generalizations are possible, but (H1)-(H6) are physically natural and simplify the exposition. Owing to (i)-(ii) we may consider that the volume fractions and the concentrations of the chemical species depend on the time t and on the radial coordinate r, measured from the axis of the central blood vessel (of radius r_0). In the system we distinguish the following regions (from inner to outer): P (fully proliferating zone), $\sigma(r,t) \geq \sigma_P$; T (transition zone), $\sigma_P > \sigma(r,t) > \sigma_Q$; Q (quiescent zone), $\sigma_Q \geq \sigma(r,t) > \sigma_N$; N (necrotic zone), $\nu_V = 0$. The necrotic zone is present in the usual experimental cases with $\sigma(r,t) = \sigma_N$ and, as a matter of fact, σ never goes below σ_N if $\sigma(r_0, t)$ remains above σ_N. However, we shall see that in some conditions σ may exceed σ_N in the necrotic zone.

Concerning the dead cells, we assume that they decay to a liquid material at constant rate:

- $\mu_N > 0$ in P∪T∪Q, $\tilde{\mu}_N > 0$ in N. (H7)

Such different values reflect the different modes of cell death, *i.e.* apoptosis within the cord versus necrosis when σ reaches the death threshold. We shall also consider in section 2 the case in which the region N is absent.

We denote by $\mathbf{u}$ the velocity field of the cellular component (here assumed to be the same for both living and dead cells) and by $\mathbf{v}$ the velocity of the extracellular fluid. Assuming equal densities for viable cells, dead cells and extracellular fluid, the increment of cellular volume during proliferation is due to the incorporation of an equal volume of extracellular material.

Thus, the governing equations for the three volume fractions in P∪T∪Q are:

$$\frac{\partial \nu_V}{\partial t} + \nabla \cdot (\mathbf{u}\, \nu_V) = \chi(\sigma)\nu_V - [\mu(\sigma) + \mu_C(c,\sigma) + \mu_R(\sigma,t)]\, \nu_V \,, \tag{1.1}$$

$$\frac{\partial \nu_N}{\partial t} + \nabla \cdot (\mathbf{u}\, \nu_N) = [\mu(\sigma) + \mu_C(c,\sigma) + \mu_R(\sigma,t)]\, \nu_V - \mu_N \nu_N \,, \tag{1.2}$$

$$\frac{\partial \nu_E}{\partial t} + \nabla \cdot (\mathbf{v}\, \nu_E) = -\chi(\sigma)\nu_V + \mu_N \nu_N \,, \tag{1.3}$$

as long as $\nu_E > \bar{\nu}_E$ (otherwise the proliferation rate must be reduced by a factor tending to zero when $\nu_E \to 0$). In equations (1.1)-(1.3), c is the concentration of a cytotoxic chemical, and $\mu_C(c,\sigma)$ is the chemically induced death rate. The dependence of μ_C on σ allows us to represent a different sensitivity to treatment of cycling cells with respect to quiescent cells. The last term in (1.1) describes the cell killing rate by radiation: the dependence of μ_R on t takes into account the schedule of radiation treatment and the delayed effects following the delivery of a single dose.

In the region N, since $\nu_V = 0$, the balance equations reduce to

$$\frac{\partial \nu_N}{\partial t} + \nabla \cdot (\mathbf{u}\, \nu_N) = -\tilde{\mu}_N \nu_N \,, \tag{1.4}$$

$$\frac{\partial \nu_E}{\partial t} + \nabla \cdot (\mathbf{v}\, \nu_E) = \tilde{\mu}_N \nu_N \,. \tag{1.5}$$

Summing up (1.1)-(1.3) and (1.4)-(1.5), and imposing $\nu_V + \nu_N + \nu_E = 1$, we find

$$\nabla \cdot [\mathbf{u}(\nu_V + \nu_N) + \mathbf{v}\nu_E] = 0 \,, \tag{1.6}$$

that expresses total mass conservation.

To model the transport of the nutrient, we suppose, as previously mentioned, that its concentration within the cells is the same as the concentration in the extracellular fluid and that its diffusivity is uniform throughout the system. This proves to be the case for fast diffusing substances like oxygen. In such a way we can write the mass balance equation as follows:

$$\frac{\partial \sigma}{\partial t} - D\Delta\sigma + \nabla \cdot (\sigma[\mathbf{u}(\nu_V + \nu_N) + \mathbf{v}\nu_E]) = -\varphi(\sigma)\nu_V \,, \tag{1.7}$$

where $\varphi(\sigma)$ is the consumption rate of viable cells and D is the diffusion coefficient; $\varphi(\sigma)$ is assumed to be a function of Michaelis-Menten type (possibly different in P and in Q with a smooth interpolation in T). Thus:

• $\varphi(\sigma)$ is a bounded, twice continuously differentiable increasing function for $\sigma \geq \sigma_N$, and $\varphi(\sigma_N) > 0$. (H8)

In order to express the velocity fields in equations (1.1)–(1.7), one should describe the dynamics of the mixture of cells and extracellular fluids, writing the momentum balance and including the interactions among the components, as pointed out in [2]. To avoid new assumptions necessary to express the stress tensor and to take full advantage of the simplified geometry, we decided instead to remain in a purely kinematic framework, introducing the further approximation ν_E =constant (although ν_E is likely to take different values in P∪T∪Q and in the region N, and to change during the evolution of the system – in particular, it may become transiently large during treatments inducing cell death). Thus we set:

$$\nu_E = 1 - \nu^\star, \quad \nu^\star = \text{constant}\,.$$

This amounts to saying that both living and dead cells, despite their volume loss, keep a uniform spatial arrangement. As a result of this simplification, from (1.1), (1.2) and (1.4) we can deduce the following equation for the velocity field $\mathbf{u}$:

$$\nabla \cdot \mathbf{u} = \begin{cases} \chi(\sigma)\dfrac{\nu_V}{\nu^\star} - \mu_N(1 - \dfrac{\nu_V}{\nu^\star}) & \text{in P} \cup \text{T} \cup \text{Q} \\ -\tilde{\mu}_N \quad \text{in N.} \end{cases} \tag{1.8}$$

From now on, we will set

$$\frac{\nu_V}{\nu^\star} = \nu\,, \quad \nu \in [0,1]\,. \tag{1.9}$$

Moreover we assume that $\mathbf{u}$ has a negligible component along the axis of the cord (this simplification is justifiable away from the ends of the cord). Thus, denoting by $u(r,t)$ the radial component of $\mathbf{u}$, we can write

$$\operatorname{div} u = \frac{1}{r}\frac{\partial}{\partial r}(ru) = \begin{cases} (\chi(\sigma) + \mu_N)\nu - \mu_N & \text{in P} \cup \text{T} \cup \text{Q} \\ -\tilde{\mu}_N \quad \text{in N.} \end{cases} \tag{1.10}$$

Inserting (1.10) in $\operatorname{div}(\nu u) = \nu \operatorname{div} u + u\partial\nu/\partial r$, we finally get for ν in P∪T∪Q the following equation

$$\frac{\partial \nu}{\partial t} + u\frac{\partial \nu}{\partial r} + \nu\big[\mu + \mu_C + \mu_R - (\chi + \mu_N)(1-\nu)\big] = 0\,, \tag{1.11}$$

and, integrating (1.10) with the condition $u(r_0,t)=0$, we find in P∪T∪Q

$$ru = \int_{r_0}^{r} r'[(\chi(\sigma) + \mu_N)\nu - \mu_N]\,dr'\,. \tag{1.12}$$

Let $r = \rho_N(t)$ be the interface between the Q and N regions. Since necrotic material cannot be converted back to living cells, the following condition must be satisfied:

$$u(\rho_N,t) \geq \dot{\rho}_N\,, \tag{1.13}$$

$u(\rho_N,t) - \dot{\rho}_N$ being the feeding rate per unit surface of the necrotic zone. Condition (1.13) has a central role in the model.

Concerning the equation for σ, making use of (1.6) and of the assumption $\partial\sigma/\partial z = 0$ (z being the axial coordinate), that eliminates from (1.7) the axial component of $\mathbf{v}$, from equation (1.7) we derive

$$\frac{\partial \sigma}{\partial t} - D\Delta\sigma + \frac{\partial \sigma}{\partial r}[u\nu^\star + \bar{v}(1-\nu^\star)] = -\varphi(\sigma)\nu^\star\nu\,, \tag{1.14}$$

where by $\bar{v}(r,t)$ we denote the average along the axial direction of the radial component of the field $\mathbf{v}$ over the cord length. We may indirectly estimate the value of $\bar{v}$ at the vessel wall from the observation of a fluid loss rate from the vasculature ranging from 0.14 to 0.22 cm^3/h per gram of tissue in experimental tumours [7]. Assuming an overall surface of exchanging vasculature of 20 cm^2 per gram, we obtain $(1-\nu^\star)\bar{v} \simeq 70 \div 110$ μm/h, while a typical value for u is of the order of 1 μm/h. Since for oxygen we have $D \simeq 2 \cdot 10^{-5}$ cm^2/sec [17], we can compare the coefficients of $\partial\sigma/\partial r$ in (1.14), concluding that diffusion is largely dominating in cords whose radius is of the order of 100 μm. Moreover, in the typical time scale of cord evolution, the whole transport process can be considered quasi-stationary. Therefore (1.14) is effectively replaced by

$$\Delta\sigma = f(\sigma)\nu\,, \tag{1.15}$$

where $f(\sigma) = \varphi(\sigma)\nu^\star/D$. The interfaces $r = \rho_P(t)$, $r = \rho_Q(t)$ bounding T are defined implicitly as

$$\sigma(\rho_P(t), t) = \sigma_P\,, \quad \sigma(\rho_Q(t), t) = \sigma_Q\,. \tag{1.16}$$

At the inner boundary, *i.e.* at the vessel wall, we prescribe

$$\sigma(r_0, t) = \sigma^\star\,. \tag{1.17}$$

When the cells at the boundary $\rho_N(t)$ enter the necrotic zone, that is when

$$u(\rho_N, t) > \dot\rho_N\,, \tag{1.18}$$

the Q/N free boundary carries the conditions

$$\sigma(\rho_N(t), t) = \sigma_N \tag{1.19}$$

$$\left.\frac{\partial\sigma}{\partial r}\right|_{r=\rho_N(t)} = 0\,, \tag{1.20}$$

and so the interface is defined implicitly and is not a material surface. If condition (1.18) cannot be satisfied together with (1.19)-(1.20), as it may actually occur if absorption is decreasing because of the decrease of ν caused by the action of treatment, then the interface with the necrotic zone becomes a material surface and σ must be left free to raise above σ_N. In this case, the motion of the interface is described by the equation

$$\dot\rho_N = u(\rho_N, t)\,, \tag{1.21}$$

and the new constraint

$$\sigma(\rho_N, t) \geq \sigma_N \tag{1.22}$$

must be imposed, while (1.20) is unchanged. Of course, when (1.22) is violated, we must revert to the previous formulation. We remark that the possibility for the free boundary $r = \rho_N(t)$ to be non-material or material at different times is a particular feature of this model.

We must also define the exterior boundary, denoted as $B(t)$, where there is no exchange of matter. This boundary is defined as

$$\dot B = u(B, t) \tag{1.23}$$

originating from the initial condition

$$B(0) = B_0\,, \tag{1.24}$$

and is an additional free boundary in the problem.

The discussion about the initial condition for (1.11) and the selection of B_0 is rather delicate (note that equation (1.11) requires no boundary condition for $r = r_0$, where u vanishes). We denote by ν_0, σ_0 the steady state solution of the system of equations (1.11), (1.12), (1.15), (1.17), (1.19), (1.20), (1.23) (the latter interpreted as $u(B_0)=0$) in the absence of the chemical and of radiation ($\mu_C=\mu_R=0$). As we shall see, determining the triple (σ_0, ν_0, B_0) is by no means an easy task and we will devote Section 2 to it. To describe the response to a treatment starting at $t=0$ of a fully developed tumour cord, we assume

$$\nu(r,0) = \nu_0(r) \tag{1.25}$$

which implies

$$\sigma(r,0) = \sigma_0(r)\,. \tag{1.26}$$

The evolution problem must be complemented with the transport equation for c. Also for the cytotoxic chemical we do not distinguish the concentrations inside and outside the cells, and we assume uniform diffusivity. We can thus perform a discussion parallel to the one made for σ. However we must remark that: 1) the boundary conditions can be rapidly changing due to the pharmacokinetics of the drug, so that the process cannot be considered quasi-stationary; 2) the lower bound for the diffusion coefficient of the drug, D_C, which still allows us to neglect the convective terms, is about $5\cdot 10^{-8}$ cm^2/sec. For lower diffusivities the model should be considerably modified, because the field $\bar{v}$ becomes important. In this paper we keep the assumption $D_C > 5\cdot 10^{-8}$ cm^2/sec, which is satisfied, for instance, by drugs such as tirapazamine ($D_C=7.0\cdot 10^{-7}$ cm^2/sec [14]). Therefore we have for c the following diffusion-absorption equation:

$$\frac{\partial c}{\partial t} - D_C \Delta c = -\varphi_C(c,\sigma)\nu^\star \nu - \lambda c\,, \tag{1.27}$$

with

$$c(r_0,t) = c^\star(t)\,, \tag{1.28}$$

$$\left.\frac{\partial c}{\partial r}\right|_{r=B(t)} = 0\,, \tag{1.29}$$

$$c(r,0) = 0\,. \tag{1.30}$$

The various terms in (1.27) have the following meaning: $\varphi_C(c,\sigma)$ is a continuously differentiable function, positive for $c>0$ and vanishing for $c=0$, that represents the net cellular uptake and metabolism of the drug. Through the dependence of φ_C on σ it is possible to take into account the different drug uptake by cycling and quiescent cells, whereas the dependence on c takes into account the modality of uptake (for instance, the dependence on c may be of Michaelis-Menten type); the coefficient $\lambda \geq 0$ may be associated with a possible natural decay of c (if the substance is chemically unstable). The function $c^\star(t)$ in (1.28) will represent the pharmacokinetics of the drug in the tumour vasculature.

We summarize here the statement of the evolution problem.

Problem P: Find the field functions

- $\nu(r,t)$: differential equation (1.11) for $r_0 < r \leq \rho_N(t)$, initial condition (1.25), no boundary conditions, $\nu(r,t) \in [0,1]$,
- $u(r,t)$: integral equation (1.12) for $r_0 < r \leq \rho_N(t)$ and $\mathrm{div} u = -\tilde{\mu}_N$ for $\rho_N(t) < r < B(t)$, continuous across the interface,
- $\sigma(r,t)$: differential equation (1.15), condition on the fixed boundary (1.17), either free boundary conditions (1.19)-(1.20) under the constraint (1.18), or (1.20)-(1.21) if the latter is violated, with (1.22) becoming the new constraint,
- $c(r,t)$: differential equation (1.27), initial condition (1.30), boundary conditions (1,28)-(1.29),

and the interfaces
• $\rho_N(t)$: defined either implicitly through the Cauchy conditions (1.19)-(1.20) or as a material surface by (1.21),
• $B(t)$: differential equation (1.23), initial condition (1.24).
The interfaces $\rho_P(t)$, $\rho_Q(t)$ are defined as the level curves $\sigma=\sigma_P$, $\sigma=\sigma_Q$.

2. The stationary solution

In this section we investigate the stationary solution of the untreated system ($\mu_C = \mu_R = 0$), to be used as initial data for the evolution problem. For ease of notation we will drop in this section the subscript "0" used in (1.25),(1.26) to denote the stationary solution.

Although the typical experimental situation, to which we made specific reference in the formulation of the evolution problem, is characterized by the presence of a purely necrotic region, in the study of the steady state we also envisage the possibility that such a necrotic region may be absent. Both cases may occur, depending on the values of the various parameters involved.

The stationary problem with a necrotic region (Case I): Find the triple (σ, ν, u), $\nu(r) \in [0,1]$, and the boundaries ρ_N,B of the necrotic zone, with $B > \rho_N$, satisfying

$$\Delta\sigma = f(\sigma)\nu\,, \quad r_0 < r < \rho_N\,, \tag{2.1}$$

$$\sigma(r_0) = \sigma^\star\,, \tag{2.2}$$

$$\sigma(\rho_N) = \sigma_N\,, \tag{2.3}$$

$$\left.\frac{\partial\sigma}{\partial r}\right|_{r=\rho_N} = 0\,, \tag{2.4}$$

$$\frac{\partial\nu}{\partial r} + A\nu = 0\,, \quad r_0 < r < \rho_N\,, \tag{2.5}$$

$$A = \frac{1}{u}[\mu(\sigma) - (\chi(\sigma) + \mu_N)(1-\nu)] \tag{2.6}$$

with $\chi(\sigma)$ and $\mu(\sigma)$ previously defined,

$$ru = \begin{cases} \int_{r_0}^{r} r'[(\chi(\sigma) + \mu_N)\nu - \mu_N]\,dr'\,, & r_0 < r \le \rho_N \\ \rho_N u(\rho_N) - (\tilde{\mu}_N/2)(r^2 - \rho_N^2)\,, & \rho_N < r \le B\,, \end{cases} \tag{2.7}$$

$$u(B) = 0\,. \tag{2.8}$$

Of course, in the above formulation it is implicitly assumed that the parameters are such that $u(\rho_N) > 0$, so that $u > 0$ for $r_0 < r < B$.

The stationary problem without a necrotic region (Case II). The unknowns are (σ, ν, u) and the outer boundary B such that the following equations are satisfied: (2.1), (2.5), (2.6), the first equation in (2.7), all for $r_0 < r < B$, (2.2), (2.8) and

$$\sigma(B) \ge \sigma_N\,, \qquad \sigma > \sigma_N \;\text{ for } r_0 < r < B\,, \tag{2.3'}$$

$$\left.\frac{\partial\sigma}{\partial r}\right|_{r=B} = 0\,. \tag{2.4'}$$

We expect that the latter case occurs when μ_N is sufficiently large and μ is sufficiently large in Q.

We remark that the assumption (H8), *i.e.* $f(\sigma_N)>0$, is necessary in Case I (otherwise it can be seen that problem (2.1), (2.3), (2.4) for any finite ρ_N can only have the constant solution $\sigma\equiv\sigma_N$). Moreover, in both cases we may say a priori that $\sigma_r<0$ (in (r_0,ρ_N) or in (r_0,B), respectively) and that, as we shall see very soon, the right derivative of u at r_0 is equal to $\chi_0-\mu_{min}$, pointing out that $\chi_0>\mu_{min}$ is a necessary condition to have a positive velocity field. In the sequel, it will be convenient to distinguish the cases:

$$\mu_N > \mu_{max} \tag{2.9}$$

$$\mu_N \le \mu_{max}\,, \tag{2.10}$$

where μ_{max} is the maximal value of $\mu(\sigma)$ that exists finite in view of (H1). As we shall see, (2.9) allows to obtain a positive lower bound for ν in Case I.

We shall prove an existence and uniqueness theorem treating Case I and Case II simultaneously:

Theorem 2.1. *Under the previously stated assumptions (H1)-(H8), the stationary problem has one unique solution.*

The remarkable feature of (2.5)-(2.6) is that u vanishes for $r=r_0$, so (2.5) becomes degenerate and we cannot prescribe ν for $r=r_0$. We circumvent this difficulty by noting that when $\sigma>\sigma_P$ equations (2.5)-(2.6) are satisfied by $\nu=\nu_{max}$ with

$$\nu_{max} = 1 - \frac{\mu_{min}}{\chi_0+\mu_N}\,. \tag{2.11}$$

If $\mu_{min}=0$, $\nu_{max}=1$; otherwise $\nu_{max}\in(0,1)$ thanks to (H6). We can prove:

Lemma 2.1. *When $\chi(\sigma)=\chi_0$ and $\mu(\sigma)=\mu_{min}$, (2.11) is the only nontrivial bounded solution of (2.5), (2.6).*

Proof. We observe that if the limit of ν for $r\to r_0^+$ exists bounded and different from ν_{max} and zero, then the derivative of ν has a nonintegrable singularity near r_0, contradicting the existence of a bounded limit for ν. We can also exclude $\nu\to 0$ because $\partial\nu/\partial r$ and ν would have opposite sign in a neighbourhood of r_0, where it can be seen that $A>0$. If ν has no limit, we remark that it can oscillate only if all its maxima are equal to ν_{max} and all its minima equal to zero. However, if $\nu=\nu_{max}$ at any point separated from r_0 (A is then bounded), the only compatible solution of (2.5) is $\nu=\nu_{max}$. Therefore, we must only examine the case in which ν tends to ν_{max}. In that case, in the proximity of r_0, we have

$$u \simeq (\chi_0-\mu_{min})(r-r_0)$$

and, if we set $\nu=\nu_{max}-\tilde\nu$, then

$$A = -\frac{1}{u}(\chi_0+\mu_N)\tilde\nu\,.$$

From (2.5) we can see that, in the case we are considering, ν cannot exceed ν_{max}. By using the above first-order approximation for u, the behaviour of $\tilde\nu$ is described at the leading order in $r-r_0$ by the equation

$$\frac{\partial\tilde\nu}{\partial r} + \frac{\chi_0+\mu_N}{\chi_0-\mu_{min}}\,\frac{1}{r-r_0}\tilde\nu(\nu_{max}-\tilde\nu) = 0\,, \tag{2.12}$$

to which we impose the condition $\tilde{\nu} \to 0$ as $r \to r_0^+$ so to have the correct limit $\nu(r) \to \nu_{max}$ as $r \to r_0^+$. Separating the variables, we can integrate (2.12) backwards from a point $\bar{r}_0 > r_0$, where we suppose to know the value $\tilde{\nu}(\bar{r}_0) = \tilde{\nu}_0 < \nu_{max}$ with $\tilde{\nu}_0 > 0$. The result is

$$\frac{1}{\nu_{max}} \log \left| \frac{\tilde{\nu}(\nu_{max} - \tilde{\nu}_0)}{\tilde{\nu}_0(\nu_{max} - \tilde{\nu})} \right| = -\frac{\chi_0 + \mu_N}{\chi_0 - \mu_{min}} \log \frac{r - r_0}{\bar{r}_0 - r_0}, \tag{2.13}$$

and we see that for any $\tilde{\nu}_0 > 0$ we have a sign incompatibility in the limit $r \to r_0^+$. Hence, it must necessarily be $\tilde{\nu}_0 = 0$ and $\nu = \nu_{max}$. ∎

Thus we put $\nu \equiv \nu_{max}$ as long as $\sigma \geq \sigma_P$, *i.e.* for $r \in (r_0, \rho_P]$ and we work with the (nondegenerate) system (2.5),(2.6) for $r > \rho_P$, with the condition

$$\nu(\rho_P) = \nu_{max}. \tag{2.14}$$

A useful a priori result is the following:

Lemma 2.2. *In Case I the volume fraction ν is positive, continuously differentiable and nonincreasing in $(r_0, \rho_N]$. More precisely:*

a) if $\mu \equiv 0$ then $\nu \equiv 1$ in $P \cup T \cup Q$;

b) if $\mu = 0$ for $\sigma \geq \sigma_\mu$, with $\sigma_\mu \in (\sigma_N, \sigma_P]$ and $\mu > 0$ for $\sigma < \sigma_\mu$, then $\nu(r) = 1$ for $r_0 \leq r \leq \rho_\mu$, with ρ_μ defined by $\sigma(\rho_\mu) = \sigma_\mu$, and $\nu'(r) < 0$ for $\rho_\mu < r < \rho_N$;

c) if $\mu = \mu_{min} > 0$ for $\sigma \geq \sigma_\mu$, with $\sigma_\mu \in (\sigma_N, \sigma_P]$, then $\nu'(r) < 0$ for $\rho_P < r < \rho_N$.

Moreover, if $\mu_N > \mu_{max}$ then $\nu > \nu_{min}$, with

$$\nu_{min} = 1 - \frac{\mu_{max}}{\mu_N}. \tag{2.15}$$

In Case II, ν is positive, continuously differentiable and nonincreasing in (r_0, B). Either b) or c) hold after substituting B to ρ_N.

Proof. The continuity of $\nu'(r)$ is an immediate consequence of $\nu = \nu_{max}$ in $[r_0, \rho_P]$ and of (2.5)-(2.7). We start with Case I. First of all, we remark that, dealing a priori with a solution, we may use the properties $u(r) \geq \hat{u} > 0$ in (ρ_P, ρ_N) and $\sigma_r < 0$ in the same interval. Therefore, the property $\nu > 0$ comes directly from the formal integration of (2.5) for $r > \rho_P$ with the condition $\nu(\rho_P) = \nu_{max}$. In particular, $\nu(\rho_N) > 0$. Case a) is trivial: since $\chi + \mu_N > 0$, when $\mu \equiv 0$ the only solution of (2.5) with $\nu(\rho_P) = \nu_{max} = 1$ is $\nu \equiv 1$. We note that, when $\mu \equiv 0$, only a solution of type I is possible.

In order to deal with b) and c), let us consider the function $\hat{\nu}(r)$ defined by the condition $A(r) = 0$, that is

$$\hat{\nu}(r) = 1 - \frac{\mu(\sigma(r))}{\chi(\sigma(r)) + \mu_N}. \tag{2.16}$$

Since $\mu_N > 0$, $\hat{\nu}(r)$ is defined also in Q. In case b) we have $\nu = \hat{\nu} = 1$ up to $r = \rho_\mu$. Computing

$$\hat{\nu}'(r) = \frac{\sigma_r}{\chi + \mu_N} \left[\frac{\mu \chi'}{\chi + \mu_N} - \mu' \right],$$

we see that $\hat{\nu}'(r) < 0$ in the union $\mathcal{I}$ of the intervals where $\mu \chi' > 0$ and/or $\mu' < 0$, which by assumption (H5) includes a right neighbourhood of ρ_μ and is connected. If $\sigma_\mu \in (\sigma_Q, \sigma_P]$ it is indeed $\mathcal{I} = (\rho_\mu, \max[\rho_Q, \bar{\rho}_\mu])$, $\bar{\rho}_\mu$ being such that $\sigma(\bar{\rho}_\mu) = \bar{\sigma}_\mu$, whereas if $\sigma_\mu \in (\sigma_N, \sigma_Q]$ it is

$\mathcal{I}=(\rho_\mu,\bar\rho_\mu)$. Now we prove that as long as $\hat\nu'<0$ we must have $\nu>\hat\nu$ and consequently $A>0$, implying $\nu'<0$. Suppose that for some $\bar r\in\mathcal{I}$ we have $\nu(\bar r)<\hat\nu(\bar r)$, implying $A(\bar r)<0$ and $\nu'(\bar r)>0$. As a consequence, there must be a point $r^\star\in(\rho_\mu,\bar r)$ in which ν has a local minimum and thus $A(r^\star)=0$ and $\nu(r^\star)<\hat\nu(r^\star)$, which is impossible. Also, we can exclude that ν equals $\hat\nu$ at some point $\bar r$ of $\mathcal{I}$, because at such a point $A=0$ and thus we are back to the previous contradiction in a left neighbourhood of $\bar r$. Therefore $\nu>\hat\nu$ and $\nu'<0$ in $\mathcal{I}$.

If $\bar\rho_\mu=\rho_N$ then $\nu'<0$ for $r\in(\rho_\mu,\rho_N)$. If not, in the interval $[\rho^\star,\rho_N)$, where $\rho^\star=\max[\rho_Q,\bar\rho_\mu]$, we have $\mu=\mu_{max}>0$ and $\hat\nu=1-\mu_{max}/\mu_N$. We investigate the behaviour of ν in the interval $[\rho^\star,\rho_N)$. If $\mu_N\le\mu_{max}$, it is $\hat\nu\le 0$ and necessarily $\nu>\hat\nu$ and $\nu'<0$ in $[\rho^\star,\rho_N)$. If $\mu_N>\mu_{max}$ it is $\hat\nu=\nu_{min}$ and, if $\nu(\rho^\star)>\nu_{min}$, we have $\nu>\nu_{min}$ and $\nu'<0$ in $(\rho^\star,\rho_N)$, because otherwise, integrating (2.5) backwards from a point where $\nu=\nu_{min}$, we conclude that $\nu(\rho^\star)=\nu_{min}$ against our assumption. Suppose now that $\nu(\rho^\star)=\nu_{min}$, which would imply $\nu=\nu_{min}$ in $[\rho^\star,\rho_N)$, and take the difference $\tilde\nu=\nu-\nu_{min}$. We have, for $r<\rho^\star$

$$A=\frac{1}{u}[\mu-(\chi+\mu_N)(1-\tilde\nu-\nu_{min})]=\frac{1}{u}[\mu-\mu_{max}+\mu_N\tilde\nu-\chi(\frac{\mu_{max}}{\mu_N}-\tilde\nu)]$$

and we can write the equation

$$\tilde\nu'+\frac{1}{u}[\mu-\mu_{max}+\mu_N\tilde\nu-\chi(\frac{\mu_{max}}{\mu_N}-\tilde\nu)](\tilde\nu+\nu_{min})=0$$

in the form

$$\tilde\nu'+\tilde A\tilde\nu=\delta$$

with

$$\begin{aligned}\tilde A&=\frac{1}{u}[\mu-\chi(\frac{\mu_{max}}{\mu_N}-\tilde\nu)-\mu_{max}+\mu_N\tilde\nu+(\chi+\mu_N)\nu_{min}]\\&=\frac{1}{u}[\mu-\chi(\frac{\mu_{max}}{\mu_N}-\tilde\nu-\nu_{min})-2\mu_{max}+\mu_N+\mu_N\tilde\nu]\end{aligned}$$

and

$$\delta=\frac{1}{u}(\mu_{max}-\mu+\chi\frac{\mu_{max}}{\mu_N})\nu_{min}\,.$$

For $\rho^\star-r>0$ sufficiently small, we have $\tilde A>0$, because $\tilde A(\rho^\star)>0$ since $\mu-\mu_{max}=\mu_N\tilde\nu=0$ for $r=\rho^\star$. Also, $\delta>0$ in the same interval. Therefore integrating the o.d.e. for $\tilde\nu$ backwards from $r=\rho^\star$ with the condition $\tilde\nu(\rho^\star)=0$, we obtain $\tilde\nu<0$, contradicting the already established result $\tilde\nu>0$ for $r<\rho^\star$.

In case c) the set $\mathcal{I}$ is not necessarily connected, but it includes at least the interval (ρ_P,ρ_Q), thus $\nu'<0$ in T. If μ is constant, then $\mathcal{I}$ coincides with T and, to extend the result $\nu'<0$ to Q, we may argue as in the case b). If there is a gap between region T and the set where $\mu'<0$ the same argument applies there, leading to the same conclusion.

In Case II, since $u(B)=0$, the formal integration of (2.5) gives $\nu>0$ for $r\in(r_0,B)$. We note preliminarly that in case b) it is $B>\rho_\mu$, because u is positive for $r_0<r\le\rho_\mu$. The same cannot be guaranteed in case c). Following the above arguments with the necessary slight modifications, the stated properties can be demonstrated. ∎

The proof of Theorem 2.1 is based on the following argument. First we consider the auxiliary problem in which, in place of conditions (2.3),(2.4), we prescribe

$$\left.\frac{\partial\sigma}{\partial r}\right|_{r=r_0}=\Sigma^\star<0 \tag{2.17}$$

and we look for (σ,ν,u) up to $r=\hat{\rho}$ which is the minimum among the points where u or σ_r vanish for the first time or where σ takes the value σ_N. In such a way σ is never increasing and $\sigma_{rr}>0$ as long as $\sigma_r<0$.

A basic property of the auxiliary problem is that, setting $\nu=\nu_{max}$, we can solve the system (2.1), (2.2), (2.17) for σ, reducing it to the nonlinear Volterra integral equation

$$\sigma = \sigma^\star + r_0\Sigma^\star \log\frac{r}{r_0} + \nu_{max}\int_{r_0}^{r} r' f(\sigma)\log\frac{r}{r'}\,dr' , \tag{2.18}$$

up to the point $\rho_P(\Sigma^\star)$ at which σ takes the value σ_P, which is defined if $\Sigma^\star$ is less than some negative constant. We also find that in the same interval (r_0,ρ_P)

$$\sigma_r = \Sigma^\star\frac{r_0}{r} + \nu_{max}\int_{r_0}^{r} f(\sigma)\frac{r'}{r}\,dr' , \tag{2.19}$$

and

$$u = \frac{1}{2}(\chi_0-\mu_{min})(r^2-r_0^2)\,. \tag{2.20}$$

Therefore, ν and u are independent of $\Sigma^\star$ as long as $\sigma\geq\sigma_P$, and differentiating (2.18) w.r.t. $\Sigma^\star$ we obtain a linear integral equation in $\partial\sigma/\partial\Sigma^\star$:

$$\frac{\partial\sigma}{\partial\Sigma^\star} = r_0\log\frac{r}{r_0} + \nu_{max}\int_{r_0}^{r} r' f'(\sigma)\frac{\partial\sigma}{\partial\Sigma^\star}\log\frac{r}{r'}\,dr' ,$$

showing that $\partial\sigma/\partial\Sigma^\star>0$. The fact that $\partial\sigma_r/\partial\Sigma^\star>0$ in the same interval is now an easy consequence of (2.19). It is also easy to conclude that $\rho_P(\Sigma^\star)$ is an increasing function.

Then, we shall go through the following steps:

1) We show that, for $r>\rho_P(\Sigma^\star)$ and $\Sigma^\star$ in a suitable interval, we can continue the solution (σ,ν,u) in a unique way up to $r=\hat{\rho}$.
2) We prove that σ, σ_r, ν, and u depend monotonically on $\Sigma^\star$ also for $r>\rho_P$.
3) We establish that there is a unique choice of $\Sigma^\star$ such that (2.3),(2.4) or (2.3′),(2.4′) are satisfied.

We start by looking for a priori bounds on $\Sigma^\star$.

Lemma 2.3. *The value of $\Sigma^\star$ making (2.3),(2.4) or (2.3′),(2.4′) satisfied lies in a suitable interval (Σ_1,Σ_2) which can be computed a priori.*

Proof. If we consider the Cauchy problem

$$\Delta\sigma = f(\sigma)\nu_{max} ,$$

$$\sigma(r_0)=\sigma^\star , \quad \left.\frac{\partial\sigma}{\partial r}\right|_{r=r_0} = \Sigma^\star ,$$

we immediately realize that both σ and σ_r depend monotonically on $\Sigma^\star$ and that we can choose $\Sigma^\star=\Sigma_2$ in such a way that $\partial\sigma/\partial r$ vanishes where σ takes the value σ_P. From (2.20) we note that $u(\rho_P)>0$. Therefore, if we want that (2.3),(2.4) or (2.3′),(2.4′) are fulfilled, we must necessarily have $\Sigma^\star<\Sigma_2$. We note that, for all $\Sigma^\star<\Sigma_2$, the function $\rho_P(\Sigma^\star)$ is uniquely defined in a monotone fashion.

Let us now establish a lower bound for $\Sigma^\star$. As we said, for any fixed $\Sigma^\star < \Sigma_2$, as long as $\sigma > \sigma_P$, the auxiliary problem is reduced to the integral equation (2.18). We also know that beyond ρ_P the volume fraction ν does not exceed ν_{max}. We compare the continuation of $\sigma(r)$ for $r > \rho_P$ with the function $\omega(r)$ satisfying

$$\Delta\omega = f(\sigma_P)\nu_{max}\,, \quad r > \rho_P\,, \tag{2.21}$$

$$\omega(\rho_P) = \sigma_P\,, \quad \omega_r(\rho_P) = \bar{\Sigma} < 0\,, \tag{2.22}$$

with $\bar{\Sigma}$ chosen in such a way that ω_r vanishes where $\omega = \sigma_N$. If $\sigma_r(\rho_P) \leq \bar{\Sigma}$, we see that $\omega > \sigma$, $\omega_r > \sigma_r$ and therefore σ_r is negative where $\sigma = \sigma_N$. If we denote by Σ_1 a Cauchy datum for $\sigma_r(r_0)$ which produces $\sigma_r(\rho_P) = \bar{\Sigma}$, then we should clearly have $\Sigma^\star > \Sigma_1$.

Proving the existence of Σ_1 is not difficult, but not trivial either. The function ω can be written explicitly for any $\rho_P > r_0$ and any $\bar{\Sigma} < 0$:

$$\omega = \sigma_P + \rho_P\bar{\Sigma}\log\frac{r}{\rho_P} + \frac{1}{2}S\Big(\frac{r^2-\rho_P^2}{2} - \rho_P^2\log\frac{r}{\rho_P}\Big)\,,$$

with $S = f(\sigma_P)\nu_{max}$, and

$$\omega_r = \bar{\Sigma}\frac{\rho_P}{r} + \frac{1}{2}S\big(r - \frac{\rho_P^2}{r}\big)\,.$$

Imposing that ω_r vanishes where $\omega = \sigma_N$, we obtain an algebraic system for the pair $(\bar{\rho}_N, \bar{\Sigma})$, $\bar{\rho}_N$ being the point such that $\omega(\bar{\rho}_N) = \sigma_N$. Putting $\bar{\rho}_N/\rho_P = y > 1$, such a system can be written in the following form:

$$\bar{\Sigma} = -\frac{1}{2}S\rho_P(y^2-1)\,, \tag{2.23}$$

$$\Phi(y) = \frac{2}{S\rho_P^2}(\sigma_P - \sigma_N)\,, \tag{2.24}$$

where

$$\Phi(y) = y^2\log y - \frac{y^2-1}{2} \tag{2.25}$$

is such that $\Phi'(y) = 2y\log y > 0$ for $y > 1$. Thus for $\rho_P \in (r_0, \rho_P(\Sigma_2))$ there is a one-to-one mapping between ρ_P and y, through which we can define the continuous function $\bar{\Sigma} = h(\rho_P)$ with range in a finite interval $\bar{\Sigma}_{min} \leq \bar{\Sigma} \leq \bar{\Sigma}_{max} < 0$. Going back to the question of determining Σ_1, we note that such a problem corresponds to the determination of a value of $\Sigma^\star$ with the property that the function $\Sigma_\star$, defined as $\Sigma_\star(\Sigma^\star) = \sigma_r(\rho_P(\Sigma^\star))$, takes precisely the value of $\bar{\Sigma}$ corresponding to $\rho_P(\Sigma^\star)$.

Since

$$\Sigma_\star = \Sigma^\star\frac{r_0}{\rho_P} + \frac{\nu_{max}}{\rho_P}\int_{r_0}^{\rho_P} f(\sigma)r\,dr < 0$$

for $\Sigma^\star \in (-\infty, \Sigma_2)$, we have

$$\frac{d\Sigma_\star}{d\Sigma^\star} = -\frac{1}{\rho_P}\frac{d\rho_P}{d\Sigma^\star}\Sigma_\star + \frac{r_0}{\rho_P} + \frac{\nu_{max}}{\rho_P}\int_{r_0}^{\rho_P} rf'(\sigma)\frac{\partial\sigma}{\partial\Sigma^\star}\,dr + S\frac{d\rho_P}{d\Sigma^\star} > 0\,,$$

and we conclude that $\Sigma_\star$ grows from $-\infty$ to 0 as $\Sigma^\star$ varies from $-\infty$ to Σ_2.

Hence, we can define a C^1 function $\rho_P = g(\Sigma_\star)$, monotonically increasing from r_0 to $\rho_P(\Sigma_2)$, over the interval $(-\infty, 0)$. On the other hand, as we have seen, we have the C^1 mapping $\bar{\Sigma} = h(\rho_P)$. Therefore, in the plane $(\bar{\Sigma}, \rho_P)$ the two graphs $\rho_P = g(\bar{\Sigma})$ and $\bar{\Sigma} = h(\rho_P)$ must have at least one intersection. To each intersection we associate a value of Σ_1 via the mapping $\rho_P \to \Sigma^\star$, and our final definition of Σ_1 is the largest in the set of the values above. ∎

Now we turn our attention to the existence of a solution to the auxiliary problem.

Lemma 2.4. *The auxiliary problem (2.1), (2.2), (2.17), (2.5), (2.6), (2.7) is uniquely solvable for any* $\Sigma^\star \in (\Sigma_1, \Sigma_2)$ *up to* $r = \hat{\rho}$.

Proof. For each $\Sigma^\star \in (\Sigma_1, \Sigma_2)$, we find $\sigma(r)$ in $(r_0, \rho_P(\Sigma^\star))$, and beyond ρ_P, we consider the continuation $\omega(r)$ obtained by solving (2.21),(2.22), with $\bar{\Sigma} = \sigma_r(\rho_P^-)$. For any given function $\nu(r)$ taking values in $(0, \nu_{max}]$ the solution of $\Delta\sigma = f(\sigma)\nu$ with the same Cauchy data in ρ_P as for ω is such that $\sigma \le \omega$, $\sigma_r \le \omega_r$. In particular, σ is decreasing as long as ω is decreasing. Thus we have an estimate (ρ_P, r_1), r_1 being such that $\omega_r(r_1) = 0$, of the interval in which σ is decreasing. Also, we note that $u(\rho_P)$ can be computed as

$$u(\rho_P) = \frac{\chi_0 - \mu_{min}}{2\rho_P}(\rho_P^2 - r_0^2) \tag{2.26}$$

and that for $r > \rho_P$

$$u(r) > \frac{1}{r}\left[\frac{\chi_0 - \mu_{min}}{2}(\rho_P^2 - r_0^2) - \frac{\mu_N}{2}(r^2 - \rho_P^2)\right] = F(r)\,. \tag{2.27}$$

Thus for any $u_m \in (0, u(\rho_P))$ we can define r_2 such that $F(r_2) = u_m$.

At this point we try to set up a fixed point argument to prove existence in $(\rho_P, \bar{r})$, with $\bar{r} = \min(r_1, r_2)$. We introduce the set of functions

$$\mathcal{N} = \{\nu \in C([\rho_P, \bar{r}]) \,|\, \nu(\rho_P) = \nu_{max},\ \nu \text{ nonincreasing},\ \nu \in [0, \nu_{max}],$$
$$\operatorname{Lip} \nu \le \frac{\mu_{max}\nu_{max}}{u_m}\}\,,$$

which, if $\mu = 0$, reduces to the only element $\nu = 1$. For ν given in $\mathcal{N}$ we solve the problem

$$\Delta\sigma = f(\sigma)\nu\,, \quad \sigma(\rho_P) = \sigma_P\,, \quad \sigma_r(\rho_P^+) = \sigma_r(\rho_P^-)\,, \quad r > \rho_P \tag{2.28}$$

and we define $\tilde{\nu}(r)$ by solving the problem

$$\frac{\partial\tilde{\nu}}{\partial r} + \tilde{A}\tilde{\nu} = 0\,, \quad \tilde{\nu}(\rho_P) = \nu_{max}\,, \tag{2.29}$$

with

$$\tilde{A} = \frac{1}{u}[\mu(\sigma) - (\chi(\sigma) + \mu_N)(1 - \tilde{\nu})] \tag{2.30}$$

and

$$ru = \rho_P u(\rho_P) + \int_{\rho_P}^{r} r'[(\chi(\sigma) + \mu_N)\nu - \mu_N]\,dr'\,, \tag{2.31}$$

σ being the solution of (2.28) and ν the chosen element of $\mathcal{N}$. If $\mu = 0$, the trivial fixed point is $\nu = 1$. We know that in $(\rho_P, \bar{r})$ σ is decreasing and $u > u_m > 0$. Re-reading the proof of Lemma 2.2 we see that this is all we need to conclude that $\tilde{\nu}$ is non-increasing and with range in $(0, \nu_{max}]$. In addition, since $\tilde{A} \ge 0$, we can say that $\tilde{A} \le \mu_{max}/u_m$ and therefore $\tilde{\nu} \in \mathcal{N}$.

Take now ν_1, ν_2 $\in$ $\mathcal{N}$ and consider the corresponding functions $\tilde{\nu}_1$, $\tilde{\nu}_2$ as well as $\tilde{A}_1$, $\tilde{A}_2$, σ_1, σ_2, u_1, u_2. We put $\delta = \nu_1 - \nu_2$, $\tilde{\delta} = \tilde{\nu}_1 - \tilde{\nu}_2$. It is not difficult to show that $\tilde{\delta}$ satisfies

$$\frac{\partial\tilde{\delta}}{\partial r} + \left[\tilde{A}_1 + \frac{\tilde{\nu}_2}{u_2}(\chi_2 + \mu_N)\right]\tilde{\delta} = \frac{\tilde{\nu}_2}{u_2}\left[\overline{\chi}'(\sigma_1 - \sigma_2)(1 - \tilde{\nu}_1) + (u_1 - u_2)\tilde{A}_1 - \overline{\mu}'(\sigma_1 - \sigma_2)\right], \tag{2.32}$$

with $\overline{\chi}'$ and $\overline{\mu}'$ evaluated at values between σ_1 and σ_2 and $\tilde{\delta}(\rho_P)=0$, and that

$$u_1 - u_2 = -\frac{1}{r}\int_{\rho_P}^{r} r'[(\chi(\sigma_1)+\mu_N)\delta + \nu_2\overline{\chi}'(\sigma_1-\sigma_2)]\,dr'\,. \tag{2.33}$$

As to the difference $\sigma_1 - \sigma_2$, we have

$$\Delta(\sigma_1-\sigma_2) = [f(\sigma_1)-f(\sigma_2)]\nu_1 + f(\sigma_2)\delta \tag{2.34}$$

with zero Cauchy data at $r=\rho_P$. Thus

$$\sigma_1-\sigma_2 = \int_{\rho_P}^{r} r'\log\frac{r}{r'}[\overline{f}'(\sigma_1-\sigma_2)\nu_1 + f(\sigma_2)\delta]\,dr'\,. \tag{2.35}$$

So we can use Gronwall's inequality to obtain the following estimate

$$\sup_{(\rho_P,r)}|\sigma_1-\sigma_2| \le C_1(r)\int_{\rho_P}^{r}\delta(r')\,dr'\,, \tag{2.36}$$

where $C_1(r)$ is a known increasing function of r, vanishing for $r=\rho_P$. Hence, a similar inequality holds for $|u_1-u_2|$

$$\sup_{(\rho_P,r)}|u_1-u_2| \le C_2(r)\int_{\rho_P}^{r}\delta(r')\,dr'\,. \tag{2.37}$$

Writing down the explicit expression of $\tilde{\delta}$, we obtain

$$|\tilde{\delta}(r)| \le \int_{\rho_P}^{r} C_3(r')\int_{\rho_P}^{r'}\delta(r'')\,dr''\,dr'\,. \tag{2.38}$$

Therefore we conclude that the mapping $\nu \to \tilde{\nu}$ is continuous in the sup-norm and contractive for r close enough to ρ_P. By standard arguments this provides existence and uniqueness up to $\bar{r}$.

In order to conclude the proof of the lemma we apply the same procedure for $r>\bar{r}$, redefining ω as the solution of

$$\Delta\omega = f(\sigma(\bar{r}))\nu(\bar{r})\,,\quad \omega(\bar{r}^+) = \sigma(\bar{r}^-)\,,\quad \omega_r(\bar{r}^+) = \sigma_r(\bar{r}^-)\,, \tag{2.39}$$

thus shifting r_1 to the right, and redefining the function $F(r)$ as

$$F(r) = \frac{1}{r}\left[\bar{r}u(\bar{r}) - \frac{\mu_N}{2}(r^2-\bar{r}^2)\right],$$

which provides a new value of r_2 through $F(r_2)=u_m$, $u_m\in(0,u(\bar{r}))$. Finally, if we observe that we can take u_m arbitrarily close to zero, we conclude that repeating this procedure we obtain precisely the desired result. ∎

We remark that the function $\nu(r)$ obtained as solution of the auxiliary problem is positive and nonincreasing in $(r_0,\hat{\rho})$. Moreover, if $\mu_{min}>0$, it is $\nu'<0$ in $(\rho_P,\hat{\rho})$, whereas if $\mu_{min}=0$ it is $\nu'<0$ in $(\rho_\mu,\hat{\rho})$ for the values of $\Sigma^\star$ such that $\sigma(\hat{\rho})<\sigma_\mu$. These properties can be checked following the argument of Lemma 2.2.

The monotonicity result (step 2) is now stated by the following lemma.

Lemma 2.5. *The functions σ, ν and u solving the auxiliary problem depend monotonically on $\Sigma^\star$. Indeed, $\partial\sigma/\partial\Sigma^\star > 0$, $\partial\sigma_r/\partial\Sigma^\star > 0$, $\partial\nu/\partial\Sigma^\star \geq 0$ ($\partial\nu/\partial\Sigma^\star > 0$ in the interval in which ν is decreasing) and $\partial u/\partial\Sigma^\star \geq 0$.*

Proof. The auxiliary problem is equivalently rewritten as

$$\sigma = \sigma^\star + r_0 \Sigma^\star \log\frac{r}{r_0} + \int_{r_0}^{r} r' f(\sigma)\nu \log\frac{r}{r'}\, dr' , \quad r_0 \leq r \leq \hat{\rho}(\Sigma^\star) \tag{2.40}$$

$$\nu = \nu_{max} \exp\left(- \int_{\rho_P}^{r} A\, dr' \right) , \quad r > \rho_P , \quad \rho_P \leq r \leq \hat{\rho}(\Sigma^\star) \tag{2.41}$$

together with the expression (2.7) for u. We recall that A contains u, σ and ν, so that (2.41) is just a formal way of representing ν. Let us differentiate (2.40), (2.7) and (2.41) with respect to $\Sigma^\star$. We obtain

$$\frac{\partial\sigma}{\partial\Sigma^\star} = r_0 \log\frac{r}{r_0} + \int_{r_0}^{r} r' \left[f'(\sigma)\frac{\partial\sigma}{\partial\Sigma^\star}\nu + f(\sigma)\frac{\partial\nu}{\partial\Sigma^\star} \right] \log\frac{r}{r'}\, dr' , \tag{2.42}$$

$$r\frac{\partial u}{\partial\Sigma^\star} = \int_{r_0}^{r} r' \left[\chi' \frac{\partial\sigma}{\partial\Sigma^\star}\nu + (\chi + \mu_N)\frac{\partial\nu}{\partial\Sigma^\star} \right] dr' , \tag{2.43}$$

$$\frac{\partial\nu}{\partial\Sigma^\star} = -\nu \int_{\rho_P}^{r} \frac{\partial A}{\partial\Sigma^\star}\, dr' , \tag{2.44}$$

where we have used $A(\rho_P) = 0$. We note that for $r_0 \leq r \leq \rho_P(\Sigma^\star)$ the r.h.s. of (2.43) is identically zero ($\chi' = 0$, $\nu = \nu_{\max}$), in agreement with $ru = \frac{1}{2}(\chi_0 - \mu_{min})(r^2 - r_0^2)$, independent of $\Sigma^\star$.

Next we compute

$$\frac{\partial A}{\partial\Sigma^\star} = -\frac{A}{u}\frac{\partial u}{\partial\Sigma^\star} - \frac{1}{u}\left[\chi'\frac{\partial\sigma}{\partial\Sigma^\star}(1-\nu) - (\chi + \mu_N)\frac{\partial\nu}{\partial\Sigma^\star} - \mu'\frac{\partial\sigma}{\partial\Sigma^\star} \right] \tag{2.45}$$

in which we may eliminate $\partial u/\partial\Sigma^\star$ making use of (2.43). It is also important to recall that the problem for σ is uncoupled up to $r = \rho_P$ (because $\nu = \nu_{max}$) and that $\partial\sigma/\partial\Sigma^\star > 0$ in that interval, as it is easily deduced from (2.42) itself and as already mentioned. Thus the monotone dependence result has in fact to be shown for $r > \rho_P(\Sigma^\star)$ (ρ_P is an increasing function of $\Sigma^\star$). For this reason we rewrite (2.42) in the form

$$\frac{\partial\sigma}{\partial\Sigma^\star} = \left.\frac{\partial\sigma}{\partial\Sigma^\star}\right|_{r=\rho_P(\Sigma^\star)} + r_0 \log\frac{r}{\rho_P} + \int_{\rho_P}^{r} r' \log\frac{r}{r'} f'\nu\frac{\partial\sigma}{\partial\Sigma^\star}\, dr'$$
$$+ \int_{\rho_P}^{r} r' \log\frac{r}{r'} f \frac{\partial\nu}{\partial\Sigma^\star}\, dr' , \quad r > \rho_P \tag{2.46}$$

while (2.44) becomes, after some algebra,

$$\frac{1}{\nu}\frac{\partial\nu}{\partial\Sigma^\star} = \int_{\rho_P}^{r} \left[\left(r' F(r', r)\nu + \frac{1}{u}(1-\nu) \right)\chi' - \frac{\mu'}{u} \right] \frac{\partial\sigma}{\partial\Sigma^\star}\, dr'$$
$$+ \int_{\rho_P}^{r} \left[r' F(r', r) - \frac{1}{u} \right] (\chi + \mu_N)\frac{\partial\nu}{\partial\Sigma^\star}\, dr' , \quad r > \rho_P \tag{2.47}$$

with

$$F(r',r) = \int_{r'}^{r} \frac{1}{r''}\frac{A}{u}\,dr'' , \quad r > r' . \tag{2.48}$$

As we said, the term $\partial\sigma/\partial\Sigma^\star|_{r=\rho_P(\Sigma^\star)}$ in (2.46) is strictly positive, while $\partial\nu/\partial\Sigma^\star$ is zero at the same point. We have obtained a system of linear Volterra integral equations for the pair $\partial\sigma/\partial\Sigma^\star$, $\partial\nu/\partial\Sigma^\star$ and we restrict r to stay far from the possible singularity of $1/u$. We distinguish the same three cases a), b) and c) as in the proof of Lemma 2.2. Case a): $\mu\equiv 0$ implies $\partial\nu/\partial\Sigma^\star\equiv 0$ implying also $\partial\sigma/\partial\Sigma^\star > 0$. Case b): $\partial\nu/\partial\Sigma^\star = 0$ up to $r=\rho_\mu$ and we may rewrite (2.47) replacing ρ_P by ρ_μ. Note that the problem for σ is uncoupled in (r_0,ρ_μ), where we can easily see that $\partial\sigma/\partial\Sigma^\star > 0$. We consider the modified version of (2.47) for $r>\rho_\mu$ and sufficiently close to ρ_μ, so that $\partial\sigma/\partial\Sigma^\star > 0$. If $(1-\nu)\chi' - \mu' = -\mu' > 0$ for $r=\rho_\mu^+$, then $\int_{\rho_\mu}^r (1/u)[(1-\nu)\chi' - \mu'](\partial\sigma/\partial\Sigma^\star)\,dr' > 0$ is the only term of order $r-\rho_\mu$, all the remaining ones being at least $O[(r-\rho_\mu)^2]$. Thus $\partial\nu/\partial\Sigma^\star > 0$ for a sufficiently small interval on the right of ρ_μ.

If $\mu' = 0$ at $r=\rho_\mu^+$ we rewrite (2.47) in the form

$$Y(r) = \Theta(r) + \Xi(r) - \int_{\rho_\mu}^{r} \frac{1}{u}\nu(\chi+\mu_N)Y\,dr' , \tag{2.49}$$

having defined

$$Y(r) = \frac{1}{\nu}\frac{\partial\nu}{\partial\Sigma^\star}$$

$$\Theta(r) = \int_{\rho_\mu}^{r} \frac{1}{u}[(1-\nu)\chi' - \mu']\frac{\partial\sigma}{\partial\Sigma^\star}\,dr'$$

$$\Xi(r) = \int_{\rho_\mu}^{r} r'F(r',r)\nu\left[\frac{\partial\sigma}{\partial\Sigma^\star} + (\chi+\mu_N)Y\right]dr' .$$

We note that $\Theta(r) > 0$, at least as long as $\partial\sigma/\partial\Sigma^\star > 0$, and we can make $\Xi(r) > 0$ for r not too far from ρ_μ (note that $A > 0$ for $r > \rho_\mu$, see Lemma 2.2, implying $F > 0$, and that $Y(\rho_\mu) = 0$). Hence (2.49) can be written

$$Y(r) + \int_{\rho_\mu}^{r} a(r')Y(r')\,dr' = Z(r) \tag{2.50}$$

with $Z = \Theta + \Xi > 0$, $a = (1/u)\nu(\chi+\mu_N) \geq 0$. From (2.50) it is not difficult to conclude that Y has the same sign as Z in a neighbourhood of ρ_μ. In case c), either $(1-\nu)\chi' - \mu'$ is positive for $r=\rho_P$, or it is positive in a right neighbourhood of it, and we can repeat the argument above. Clearly $\partial\sigma/\partial\Sigma^\star$ remains positive if $\partial\nu/\partial\Sigma^\star > 0$, and even in a larger interval beyond the possible sign inversion of $\partial\nu/\partial\Sigma^\star$.

Let us now suppose that $\partial\nu/\partial\Sigma^\star$ vanishes for the first time in some $r=\hat{r}$ after it has become positive. Consider first the case c) with $\hat{r}\in(\rho_P,\rho_Q]$. From (2.47) we have

$$\int_{\rho_P}^{\hat{r}} \left[\left(r'F(r',\hat{r})\nu + \frac{1}{u}(1-\nu)\right)\chi' - \frac{\mu'}{u}\right]\frac{\partial\sigma}{\partial\Sigma^\star}\,dr'$$

$$+ \int_{\rho_P}^{\hat{r}} \left[r'F(r',\hat{r}) - \frac{1}{u}\right](\chi+\mu_N)\frac{\partial\nu}{\partial\Sigma^\star}\,dr' = 0$$

and for $r>\hat{r}$ we can write

$$\frac{1}{\nu}\frac{\partial\nu}{\partial\Sigma^\star}=\int_{\rho_P}^{\hat{r}} r'\Phi(r,\hat{r})\nu\chi'\frac{\partial\sigma}{\partial\Sigma^\star}\,dr'+\int_{\rho_P}^{\hat{r}} r'\Phi(r,\hat{r})(\chi+\mu_N)\frac{\partial\nu}{\partial\Sigma^\star}\,dr'$$

$$+\int_{\hat{r}}^{r}\left[\left(r'F(r',r)\nu+\frac{1}{u}(1-\nu)\right)\chi'-\frac{\mu'}{u}\right]\frac{\partial\sigma}{\partial\Sigma^\star}\,dr'+\int_{\hat{r}}^{r}\left[r'F(r',r)-\frac{1}{u}\right](\chi+\mu_N)\frac{\partial\nu}{\partial\Sigma^\star}\,dr'\,,\quad(2.51)$$

with

$$\Phi(r,\hat{r})=F(r',r)-F(r',\hat{r})=\int_{\hat{r}}^{r}\frac{1}{r''}\frac{A}{u}\,dr''>0\,.$$

The first three terms are positive. Since $\chi'>0$ in some interval and $\Phi(r,\hat{r})=O(r-\hat{r})$ (remember that A is strictly positive near $\hat{r}$) we can say that the first and the third terms are $O(r-\hat{r})$, thus dominating the last term, whose sign is uncertain. In other words, we have proved that $\partial(\partial\log\nu/\partial\Sigma^\star)/\partial r$ is positive in $\hat{r}$, contradicting the fact that $\partial\nu/\partial\Sigma^\star$ has attained a minimum there in $[\rho_P,\hat{r}]$. If we are still in case c), but $\hat{r}>\rho_Q$, (2.51) simplifies to

$$\frac{1}{\nu}\frac{\partial\nu}{\partial\Sigma^\star}=\int_{\rho_P}^{\rho_Q} r'\Phi(r,\hat{r})\nu\chi'\frac{\partial\sigma}{\partial\Sigma^\star}\,dr'+\int_{\rho_P}^{\hat{r}} r'\Phi(r,\hat{r})(\chi+\mu_N)\frac{\partial\nu}{\partial\Sigma^\star}\,dr'$$

$$+\int_{\hat{r}}^{r}\left[r'F(r',r)-\frac{1}{u}\right]\mu_N\frac{\partial\nu}{\partial\Sigma^\star}\,dr'-\int_{\hat{r}}^{r}\frac{\mu'}{u}\frac{\partial\sigma}{\partial\Sigma^\star}\,dr'\,,\qquad(2.52)$$

and we reach a similar conclusion.

Passing to case b), we can argue in the same way if $\rho_\mu\in(\rho_P,\rho_Q)$. If instead $\rho_\mu\geq\rho_Q$, we have to modify (2.51) to

$$\frac{1}{\nu}\frac{\partial\nu}{\partial\Sigma^\star}=\int_{\rho_\mu}^{\hat{r}} r'\Phi(r,\hat{r})\mu_N\frac{\partial\nu}{\partial\Sigma^\star}\,dr'$$

$$+\int_{\hat{r}}^{r}\left[r'F(r',r)-\frac{1}{u}\right]\mu_N\frac{\partial\nu}{\partial\Sigma^\star}\,dr'-\int_{\hat{r}}^{r}\frac{\mu'}{u}\frac{\partial\sigma}{\partial\Sigma^\star}\,dr'\,,$$

and we infer the desired conclusion since $\mu_N>0$.

Once we have seen that $\partial\sigma/\partial\Sigma^\star>0$, $\partial\nu/\partial\Sigma^\star>0$, it is immediate to check that $\partial\sigma_r/\partial\Sigma^\star>0$ by differentiating

$$r\frac{\partial\sigma}{\partial r}=r_0\Sigma^\star+\int_{r_0}^{r} r'f(\sigma)\nu\,dr'$$

w.r.t. $\Sigma^\star$. ∎

Now we can complete the proof of Theorem 2.1, on the basis of the monotonicity results obtained in the previous lemma.

Proof. Proof of Thm. 2.1. In view of Lemma 2.4, we have obtained a one-parameter family of solutions of the auxiliary problem, including all possible solutions of the original problem. The reason why a solution of that family is not a solution of the original problem is related to its behaviour at the terminal radial coordinate $\hat{\rho}$. Namely, we may distinguish the following three disjoint classes of solutions of the auxiliary problem not solving the original problem:

(α) $\sigma_r(\hat{\rho})=0$, $\sigma(\hat{\rho})>\sigma_N$, $u(\hat{\rho})>0$;

(β) $\sigma_r(\hat{\rho})<0$, $\sigma(\hat{\rho})=\sigma_N$, $u(\hat{\rho})>0$;

(γ) $\sigma_r(\hat{\rho})<0$, $u(\hat{\rho})=0$.

The class (α) is certainly not empty, because it contains all the solutions with $\Sigma^\star$ sufficiently close to Σ_2. One of the classes (β) or (γ) may be empty. The set (α) may confine with (β) or with (γ). In the former case (α) and (β) are generally separated by a solution of the type of Case I. In the latter case (α) and (γ) are separated by a solution of Case II. Classes (β) and (γ) may both exist, but a boundary element, corresponding to some $\Sigma^\star = \Sigma_{\beta\gamma}$, generally belongs to (γ) and therefore is not a solution. However, there can be the exceptional case in which such a boundary element is precisely the limit solution of Case II characterized by $\sigma_r(\rho_N) = 0$, $\sigma(\rho_N) = \sigma_N$, $u(\rho_N) = 0$, and also confining with class (α). We can approach the solution of our problem from above or from below, making $\Sigma^\star$ decrease from Σ_2 or increase from Σ_1, respectively. Let us study each of such procedures. We recall that σ is strictly increasing with $\Sigma^\star$ and that $\partial\nu/\partial\Sigma^\star \geq 0$ is not identically zero in $(r_0, \hat\rho)$, except for the trivial case $\mu \equiv 0$. This implies that $\partial u/\partial\Sigma^\star$ (always nonnegative) is also not identically zero and in particular it is strictly positive near the end point $\hat\rho$ (see (2.43)).

1) $\Sigma^\star$ *decreasing from* Σ_2. Obviously we are moving through the set (α). Taking into account that $\sigma_r(\hat\rho) = 0$ and $\sigma(\hat\rho)$ is strictly decreasing as long as $u(\hat\rho) > 0$, two cases are possible: either $u(\hat\rho)$ remains positive until $\sigma(\hat\rho)$ reaches σ_N or $u(\hat\rho)$ vanishes before (or possibly when $\sigma(\hat\rho)$ reaches σ_N). In the first case, for the corresponding value of $\Sigma^\star$ a solution of type I is found, otherwise we have obtained a solution of type II.

2) $\Sigma^\star$ *increasing from* Σ_1. For $\Sigma^\star$ close to Σ_1 we may have solutions in class (β) or in class (γ). Suppose we start with class (β). Increasing $\Sigma^\star$, either $u(\hat\rho)$ remains positive and then we reach exactly the same solution of type I approached from above, or $u(\hat\rho)$ vanishes for some $\Sigma^\star$ meaning that we are shifting to class (γ), unless $\sigma_r(\hat\rho)$ also vanishes, so that we have recovered the limit solution of type II having $\sigma_r(\hat\rho) = 0$, $\sigma(\hat\rho) = \sigma_N$, $u(\hat\rho) = 0$. Moving within (γ) (possibly from $\Sigma^\star = \Sigma_1$), an increase of $\Sigma^\star$ produces a positive velocity and the point $\hat\rho$ is shifted to the right. The procedure stops when we reach a $\hat\rho$ such that not only $u(\hat\rho) = 0$, but also $\sigma_r(\hat\rho) = 0$, so that (2.3′),(2.4′) are satisfied.

As a result of the discussion above, we can say that the interval (Σ_1, Σ_2) is partitioned in one of the following ways:

$$(\Sigma_1, \Sigma_{\beta\gamma}) \cup [\Sigma_{\beta\gamma}, \Sigma_{sol}^{II}) \cup \{\Sigma_{sol}^{II}\} \cup (\Sigma_{sol}^{II}, \Sigma_2) \equiv I_\beta \cup I_\gamma \cup \{\Sigma_{sol}^{II}\} \cup I_\alpha \tag{2.53}$$

$$(\Sigma_1, \Sigma_{sol}^{I}) \cup \{\Sigma_{sol}^{I}\} \cup (\Sigma_{sol}^{I}, \Sigma_2) \equiv I_\beta \cup \{\Sigma_{sol}^{I}\} \cup I_\alpha\,. \tag{2.54}$$

In (2.53) the intervals I_β, I_γ, I_α correspond to solutions in the respective classes and Σ_{sol}^{II} is the value of $\Sigma^\star$ providing a solution of type II. The interval I_β is possibly empty. In (2.54) Σ_{sol}^{I} is the value of $\Sigma^\star$ providing a solution of type I. It is quite evident that the monotone structure of the family of solutions has implied the uniqueness of the solution to the original free boundary problem. ∎

All we need to complete the description of the solution of Case I is to calculate the velocity field in the region N:

$$ru - \rho_N u(\rho_N) = -\frac{1}{2}\tilde\mu_N (r^2 - \rho_N^2)\,, \tag{2.55}$$

which gives the coordinate B of the resting point

$$B^2 = \rho_N^2 + \frac{2}{\tilde\mu_N}\rho_N u(\rho_N)\,. \tag{2.56}$$

3. Existence and uniqueness for the evolution problem

We suppose that at $t=0$ the system is in equilibrium and a purely necrotic region is present (Case I). In addition to (H1)-(H8), we make the following assumptions:

• $\mu_C(c,\sigma)$ is a nonnegative, twice continuously differentiable, bounded function, increasing with respect to c and vanishing for $c=0$ (H9)

• $\mu_R(\sigma,t)$, $t\geq 0$, is a nonnegative, twice continuously differentiable, bounded function, with $\mu_R(\sigma,0)=0$ (H10)

• $c^\star(t)$, $t\geq 0$, is nonnegative, continuously differentiable and bounded with $c^\star(0)=0$. (H11)

The aim of this section is to prove the existence and uniqueness of the solution of *Problem P* stated at the end of section 1. To this purpose, we approximate the solution of the evolution problem using a step-by-step procedure. For a given time interval $[0,T]$ we take a partition in n equal parts: to simplify notation, we will omit the index "n" in the variables of the approximation of order n. For technical reasons, we need to extend the definition of the consumption coefficient $\varphi(\sigma)$ for values of σ less than σ_N:

• $\varphi(\sigma)$ is extended for $0\leq\sigma<\sigma_N$ in such a way it possesses the same regularity stated in (H8), and it remains strictly positive. (H12)

Let us now describe our approximation scheme, starting from the first interval $[0,\theta]$, with $\theta=T/n$. All the quantites referring to the steady state are denoted with the subscript "0" as in section 1.

1. Compute the curves $\gamma(\hat r): r=\eta(\hat r,t)$ integrating

$$\dot\eta = u_0(\eta)\,, \qquad \eta(\hat r,0)=\hat r\,, \quad \hat r\in[r_0,B_0]\,. \tag{3.1}$$

Note that $\eta(B_0,t)=B_0$, that is, the external boundary $B(t)$ is equal to B_0 in $[0,\theta]$. The characteristic lines do not intersect because (3.1) has a unique solution forward and backward (u_0 is indeed Lipschitz continuous), and the equation $r=\eta(\hat r,t)$ defines $\hat r=\zeta(r,t)$ uniquely. Moreover, $\partial\eta/\partial\hat r>0$ and, more precisely, from $\partial(\partial\eta/\partial\hat r)/\partial t=u_0'(\eta)(\partial\eta/\partial\hat r)$, $\partial\eta/\partial\hat r|_{t=0}=1$, we can say that $\partial\eta/\partial\hat r=\exp[\int_0^t u_0'(\eta(\hat r,\tau))\,d\tau]$, giving a positive lower (and upper) bound for $\partial\eta/\partial\hat r$. Also, we write $0=(\partial\eta/\partial\hat r)(\partial\zeta/\partial t)+\partial\eta/\partial t$, giving $\partial\zeta/\partial t=-u_0/(\partial\eta/\partial\hat r)$, which is obviously a-priori bounded. Similarly we have $1=(\partial\eta/\partial\hat r)(\partial\zeta/\partial r)$, implying $\partial\zeta/\partial r=(\partial\eta/\partial\hat r)^{-1}$, positive and a-priori bounded. Moreover, the derivatives $\partial\zeta/\partial r$, $\partial\zeta/\partial t$ are continuous.

2. In the domain $[r_0,B_0]\times[0,\theta]$ solve the problem for c

$$\frac{\partial c}{\partial t} - D_C\Delta c = -\lambda c\,, \tag{3.2}$$

$$c(r_0,t)=c^\star(t)\,, \tag{3.3}$$

$$c_r(B_0,t)=0\,, \tag{3.4}$$

$$c(r,0)=0\,. \tag{3.5}$$

The consumption term $\varphi_C(c,\sigma)$ is omitted in (3.2) because in the first step we put $c\equiv c(r,0)=0$ in it. This problem is standard, and it is well known that $0\leq c\leq\sup_{[0,\theta]}c^\star(t)$ and that $|c_r|$ can be estimated in terms of $\sup_{[0,\theta]}|\dot c^\star(t)|$.

3. Integrate the equation

$$D_u\nu = -\nu\big[\mu(\sigma_0) + \mu_R(\sigma_0, t) + \mu_C(c, \sigma_0) - (\chi(\sigma_0) + \mu_N)(1 - \bar{\nu}^0)\big] \equiv -\nu H(t, c, \sigma_0, \bar{\nu}^0) \tag{3.6}$$

along the curves $\gamma(\hat{r})$, where D_u is the derivative along the characteristic lines (in this interval $D_u = \partial/\partial t + u_0\, \partial/\partial r$), and we have denoted $\bar{\nu}^0(r,t) = \nu_0(\zeta(r,t))$. The initial datum is $\nu(\hat{r}, 0) = \nu_0(\hat{r})$, $\hat{r} \in (r_0, \rho_{N0}]$, and $\nu(\hat{r}, 0) = 0$, $\hat{r} \in (\rho_{N0}, B_0]$, ρ_{N0} being the stationary value of ρ_N.

If we set $\mathcal{H}(\hat{r}, t) = H|_{r=\eta(\hat{r},t)}$, we have

$$\nu(r,t) = \nu_0(\zeta(r,t)) \exp\left(- \int_0^t \mathcal{H}(\zeta(r,t), \tau)\, d\tau \right). \tag{3.7}$$

Since ν_0 is strictly positive for $\hat{r} \in (r_0, \rho_{N0}]$ and $\mathcal{H}$ is bounded, also $\nu(r,t)$ is strictly positive for $r \le \eta(\rho_{N0}, t)$. From expression (3.7) we may calculate $\partial\nu/\partial r$ and $\partial\nu/\partial t$:

$$\frac{\partial \nu}{\partial r} = \nu \frac{\partial \zeta}{\partial r} \left(\frac{\nu_0'}{\nu_0} - \int_0^t \frac{\partial \mathcal{H}}{\partial \hat{r}}\, d\tau \right), \tag{3.8}$$

$$\frac{\partial \nu}{\partial t} = -\nu H + \nu \frac{\partial \zeta}{\partial t} \left(\frac{\nu_0'}{\nu_0} - \int_0^t \frac{\partial \mathcal{H}}{\partial \hat{r}}\, d\tau \right). \tag{3.9}$$

We remark that the right hand sides of (3.8)-(3.9) contain σ_0, ν_0, c and their first derivatives w.r.t. r.

4. Find $\sigma(r,t)$ and $\tilde{\rho}_N(t)$ such that

$$\Delta\sigma = f(\sigma)\nu\,, \quad r_0 < r < \tilde{\rho}_N(t)\,, \tag{3.10}$$

$$\sigma(r_0, t) = \sigma^\star\,, \tag{3.11}$$

$$\sigma(\tilde{\rho}_N, t) = \sigma_N\,, \tag{3.12}$$

$$\sigma_r(\tilde{\rho}_N, t) = 0\,. \tag{3.13}$$

Equations (3.10)-(3.13) are equivalent to

$$\sigma - \sigma_N = \int_r^{\tilde{\rho}_N(t)} r' \log \frac{r'}{r} f(\sigma)\nu\, dr'\,, \tag{3.14}$$

and

$$\sigma^\star - \sigma_N = \int_{r_0}^{\tilde{\rho}_N(t)} r \log \frac{r}{r_0} f(\sigma)\nu\, dr\,. \tag{3.15}$$

We want to show that the pair $(\sigma, \tilde{\rho}_N)$ can be found with $\tilde{\rho}_N(0) = \rho_{N0}$ and $\tilde{\rho}_N(t) < \eta(\rho_{N0}, t)$ in some interval $(0, \hat{t})$, $\hat{t} \le \theta$. It is easily seen that (3.10)-(3.13) have a unique solution $(\sigma, \tilde{\rho}_N)$ provided that ν does not approach zero. In order to fulfil this condition, for the moment we give ν a positive continuous extension for $r > \eta(\rho_{N0}, t)$ setting $\nu(r,t) = \nu(\eta(\rho_{N0}, t), t)$. Then we recall that $\nu \to \nu_0$ (provided that ν_0 is extended in the same way) and $\partial\nu/\partial t \to 0$ as $t \to 0$ in view of assumptions (1.30) and (H9)-(H11), and because of (3.9), (2.5)-(2.6). We may also establish the continuity of $\partial\sigma/\partial t$, noting that it satisfies the equation $\Delta(\partial\sigma/\partial t) = f'(\sigma)(\partial\sigma/\partial t)\nu + f(\sigma)(\partial\nu/\partial t)$,

$r_0 < r < \tilde\rho_N(t)$, with zero boundary values at $r = r_0$, $r = \tilde\rho_N(t)$. In particular, since $\partial\nu/\partial t$ vanishes for $t = 0$, so does $\partial\sigma/\partial t$. Now we compute $\dot{\tilde\rho}_N$ by differentiation of (3.15), obtaining

$$\dot{\tilde\rho}_N \; \tilde\rho_N [f(\sigma)\nu]\Big|_{r=\tilde\rho_N(t)} \log \frac{\tilde\rho_N}{r_0} = -\int_{r_0}^{\tilde\rho_N} r \log \frac{r}{r_0} \frac{\partial}{\partial t}[f(\sigma)\nu]\, dr\,. \tag{3.16}$$

Owing to the remarks above, (3.16) implies $\dot{\tilde\rho}_N\ (0) = 0 < u_0(\rho_{N0})$. Therefore, in some time interval $[0, \hat t]$, $\hat t \le \theta$, the pair $(\sigma, \tilde\rho_N)$ is actually the solution of (3.14)-(3.15) where no use is made of the extension of ν (in other words, ν is precisely the function calculated in step 3). Moreover, (3.16) shows the continuity of $\dot{\tilde\rho}_N$.

Starting from $t = 0$, as long as $u_0(\tilde\rho_N) \ge \dot{\tilde\rho}_N$, we set $\rho_N(t) = \tilde\rho_N(t)$ and accept the solution σ given by (3.14) up to the time $\bar t$ such that either a right neighbourhood of $\bar t$ exists in which $u_0(\tilde\rho_N) < \dot{\tilde\rho}_N$, or in any right neighbourhood of $\bar t$ the difference $u_0(\tilde\rho_N) - \dot{\tilde\rho}_N$ undergoes infinite sign changes. In the first case, for $t > \bar t$ we force ρ_N to coincide with the characteristic line tangent to $r = \tilde\rho_N(t)$ at $t = \bar t$, that is we set $\dot\rho_N = u_0(\rho_N)$. In this case ρ_N becomes known and we redefine σ by solving the problem (3.10)-(3.11) and (3.13) (with $\tilde\rho_N$ changed to ρ_N). We have:

$$\sigma - \sigma(\rho_N(t), t) = \int_r^{\rho_N(t)} r' \log \frac{r'}{r} f(\sigma)\nu\, dr'\,, \tag{3.17}$$

$$\sigma^\star - \sigma(\rho_N(t), t) = \int_{r_0}^{\rho_N(t)} r \log \frac{r}{r_0} f(\sigma)\nu\, dr\,, \tag{3.18}$$

and it can be easily seen that $\sigma(\rho_N(t), t) > \sigma_N$ in an open right neighbourhood of $\bar t$. In the second case, we must reconstruct artificially the possibility of computing the continuation of the approximate solution over a finite time interval. To this end, we select a velocity u_{tol} as a small fraction of $u_0(\rho_P)$, given by (2.26), and we consider the time interval in which $u_0(\tilde\rho_N) > \dot{\tilde\rho}_N - u_{tol}/n$. Here we choose one of the zeroes of the difference $u_0(\tilde\rho_N) - \dot{\tilde\rho}_N$ beyond which such a quantity becomes negative. At that time instant we switch to the condition $\dot\rho_N = u_0(\rho_N)$, replacing (3.14)-(3.15) with (3.17)-(3.18).

Of course, we have to switch back to $\rho_N(t) = \tilde\rho_N(t)$ from the possible time $\tilde t$ after which (3.18) can be satisfied only with $\sigma(\rho_N(t), t) < \sigma_N$, and we will have again $u_0(\tilde\rho_N) > \dot{\tilde\rho}_N$ in an open right neighborhood of $\tilde t$ with a possible discontinuity of $\dot\rho_N$ at $t = \tilde t$. If after $\tilde t$ the difference $\sigma(\rho_N, t) - \sigma_N$ has infinitely many sign changes in any right neighbourhood, after selecting $\sigma_{tol} < \sigma_N$, we consider the time interval in which $\sigma(\rho_N, t) > \sigma_N - \sigma_{tol}/n$, switching to $\rho_N(t) = \tilde\rho_N(t)$ at one of the zeroes of $\sigma(\rho_N, t) - \sigma_N$ beyond which $\sigma(\rho_N, t) - \sigma_N < 0$.

We remark that if $\hat t < \theta$, or $\hat t = \theta$ and $\rho_N(\hat t) = \eta(\rho_{N0}, \theta)$, the time $\bar t < \hat t$ previously defined will exist. Indeed, in this case we may identify $\hat t$ as the time instant such that

$$\sigma^\star - \sigma_N = \int_{r_0}^{\eta(\rho_{N0}, \hat t)} r \log \frac{r}{r_0} f(\sigma)\nu\, dr\,.$$

Therefore, for $t \in (0, \hat t)$, we have $\eta(\rho_{N0}, t) > \tilde\rho_N(t)$ and $\eta(\rho_{N0}, 0) = \tilde\rho_N(0)$, $\eta(\rho_{N0}, \hat t) = \tilde\rho_N(\hat t)$. In this situation the curve $r = \tilde\rho_N(t)$ becomes tangent to one of the characteristic lines $\eta(\hat r, t)$ for some $\hat r < \rho_{N0}$ at some time smaller than $\hat t$. Since the curve $r = \tilde\rho_N(t)$ cannot lay on this

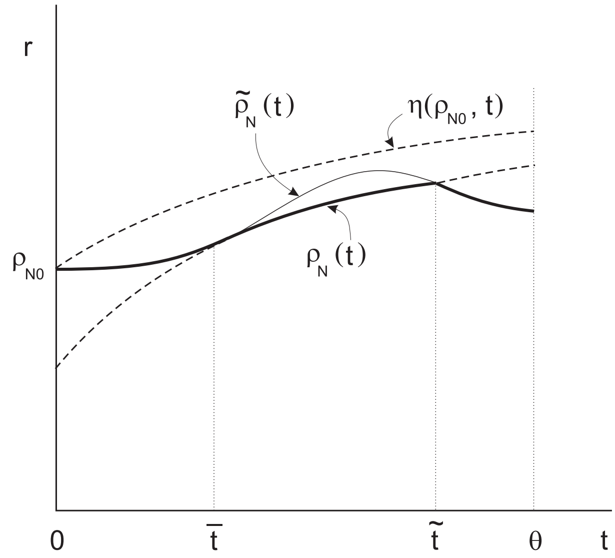

Fig. 2. An example of the construction of $\rho_N(t)$ (thick line) in the first time step. The characteristic lines are indicated by dashed lines and $\tilde{\rho}_N(t)$ by a thin continuous line. In this example $\hat{t}=\theta$.

characteristic line up to $\hat{t}$, it will leave the characteristic line at some $\bar{t}<\hat{t}$. However, $\bar{t}$ may exist even if $\hat{t}=\theta$ and $\rho_N(\hat{t})<\eta(\rho_{N0},\theta)$. Figure 2 shows an example of the construction of $\rho_N(t)$.
5. We set ν equal to zero and $\sigma(r,t)=\sigma(\rho_N(t),t)$ for $r>\rho_N(t)$, and this is the final form of ν and σ in the step. Moreover, we continue $c(r,t)$ for $r>B$ by setting $c(r,t)=c(B(t),t)$.
6. With the new values of σ, ν we compute the new velocity field on the basis of (1.10)

$$ru = \begin{cases} \int_{r_0}^{r} r'[(\chi(\sigma)+\mu_N)\nu - \mu_N]\,dr', & r_0 < r \le \rho_N(t) \\ \rho_N u(\rho_N) - (\tilde{\mu}_N/2)(r^2-\rho_N^2), & r > \rho_N(t) \end{cases} \tag{3.19}$$

where we have extended the definition of u beyond $r=B(t)$ because we may need it in the sequel.

We are now ready to go to the second time step $(\theta, 2\theta]$, in which we have:
1. Continuation of the characteristic lines $r=\eta(\hat{r},t)$. Starting with the value $\eta(\hat{r},\theta)$ we integrate

$$\dot{\eta}(t) = u(\eta(t), t-\theta), \quad t \in (\theta, 2\theta)\,. \tag{3.20}$$

From the continuation of the characteristic line $r=\eta(\hat{r},t)$, the function $\hat{r}=\zeta(r,t)$ is also defined for $t\in(\theta,2\theta]$. Likewise we continue the external boundary as

$$\dot{B}(t) = u(B(t), t-\theta)\,, \quad B(\theta^+) = B(\theta^-)\,. \tag{3.21}$$

2. Computation of c

$$\frac{\partial c}{\partial t} - D_C \Delta c = -\varphi_C(c^\theta, \sigma^\theta)\bar{\nu}^\theta - \lambda c\,, \tag{3.22}$$

$$c(r_0, t) = c^\star(t)\,, \tag{3.23}$$

$$c_r(B(t), t) = 0\,, \tag{3.24}$$

$$c(r, \theta^+) = c(r, \theta^-)\,, \quad r \in (r_0, B(\theta)]\,, \tag{3.25}$$

Here and in the sequel, we denote $c^\theta(r,t) = c(r,t-\theta)$, $\sigma^\theta(r,t) = \sigma(r,t-\theta)$, and $\bar\nu^\theta(r,t) = \nu(\eta(\zeta(r,t),t-\theta),t-\theta)$. Note that $\bar\nu^\theta(r,t)>0$ if $r\le\eta(\zeta(\rho_N(\theta),\theta),t)$, otherwise $\bar\nu^\theta=0$. Therefore, the consumption term in (3.22) is discontinuous. The solution exists in the space $W_q^{2,1}$ for q arbitrarily large, and is in fact in the Hölder space $H^{1+\alpha,(1+\alpha)/2}$ for any $\alpha\in(0,1)$ (see [15, ch. 4]).
3. Computation of ν

$$D_u\nu = -\nu H(t,c,\sigma^\theta,\bar\nu^\theta)\,, \tag{3.26}$$

the initial values for ν being provided by continuity through $t=\theta$. Thus, equation (3.7) can be extended to the interval $(\theta,2\theta]$.
4. Computation of σ and ρ_N as described in the corresponding point of the first step, the velocity field being now $u(r,t-\theta)$. In the comparison between $u(\tilde\rho_N(t),t-\theta)$ and $\dot{\tilde\rho}_N(t)$, the expression of $\dot{\tilde\rho}_N(t)$ at the general step is still given by (3.16). Note that the existence of $\rho_N(t)$, such that $u(\rho_N,t-\theta)>\dot\rho_N(t)$ in a right neighbourhood of $t=\theta$, is now not guaranteed.
5. The function ν is set equal to zero and $\sigma\equiv\sigma(\rho_N(t),t)$ for $r>\rho_N(t)$. The function $c(r,t)$ is also continued as in the first step.
6. Computation of u by means of (3.19).
Precisely the same scheme can be iterated up to $t=T$. In the following, when we refer to $\partial\nu/\partial t$, we mean that it is calculated in the positivity set of ν. In particular, the sup-norm $\|\partial\nu/\partial t\|$ is likewise referred to the support of ν.

Remark 3.1. In the approximating solutions, according to the above described procedure, it is not difficult to see that the function $B(t)$ together with all the characteristic lines is $C^1[0,T]$, whereas the interface $\rho_N(t)$ is not in general continuously differentiable at the switching points. The function $\nu(r,t)$ is C^1 for $r\in[r_0,\rho_N]$ and for $r\in(\rho_N,\infty)$, $t\in[0,T]$. The functions $\sigma(r,t)$, $u(r,t)$ and $c(r,t)$ are continuous in $[r_0,\infty)\times[0,T]$. Moreover, as we shall see, the function c belongs to $H^{1+\alpha,(1+\alpha)/2}$, $\alpha\in(0,1)$. The functions $u(r,t)$ and $\rho_N(t)$ satisfy $u(\rho_N(t),t-\theta)-\dot\rho_N(t)> -u_{tol}/n$ (with $t-\theta$ set to zero for $t<\theta$), so they will not necessarily satisfy inequality (1.13). Also, it can happen that $\sigma<\sigma_N$ and $\nu>0$ at the same (r,t) point; the approximating solutions may therefore be "non-physical".

Our aim is now to show that the sequence of approximating solutions so generated defines sets of functions that, when restricted to suitable compact domains, are compact in the sup-norm. First, we can establish the following properties:

Lemma 3.1. *In the family of approximating solutions, the functions ν for $r\in(r_0,\rho_N(t)]$ and $t\in[0,T]$ satisfy the inequalities*

$$0 < N_1 \le \nu(r,t) \le N_2\,, \tag{3.27}$$

where

$$N_1 = \inf_{r\in(r_0,\rho_{N0}]} \nu_0(r)\mathrm{e}^{-\|H\|T}, \qquad N_2 = \sup_{r\in(r_0,\rho_{N0}]} \nu_0(r)\mathrm{e}^{\|H\|T} \tag{3.28}$$

and $\|H\|$ denotes the sup of $|H|$.

Proof. Having defined the characteristic line $r=\eta(\hat r,t)$ in the whole interval $[0,T]$, we can define the function $\hat r=\zeta(r,t)$ for $r\in(r_0,B(t)]$ and $t\in[0,T]$. Thus, we can extend (3.7) for $r\in(r_0,\rho_N(t)]$, $t\in[0,T]$, namely

$$\nu(r,t) = \nu_0(\zeta(r,t))\exp\left(-\int_0^t \mathcal{H}(\zeta(r,t),\tau)\,d\tau\right), \tag{3.29}$$

where $\zeta(r,t) \in (r_0, \rho_{N0}]$. From (3.29), the inequalities (3.27) follow immediately considering that $\|H\| \leq \max[\max\mu + \max\mu_R + \max\mu_C, \chi_0 + \mu_N]$. ∎

Lemma 3.2. *In the family of approximating solutions, $\rho_N(t)$ satisfies the inequalities*

$$r_0 < R_1 < \rho_N(t) < R_2\,, \tag{3.30}$$

where

$$R_1 = \left[r_0^2 + (\hat{R}_1^2 - r_0^2)\mathrm{e}^{-\mu_{Nmax}T}\right]^{1/2}, \tag{3.31}$$

with $\mu_{Nmax} = \max[\mu_N, \tilde{\mu}_N]$, $\hat{R}_1$ being the unique solution larger than r_0 of the equation

$$x^2 \log\frac{x}{r_0} - \frac{1}{2}(x^2 - r_0^2) = 2\frac{\sigma^\star - \sigma_N}{f(\sigma^\star)N_2}\,, \tag{3.32}$$

and R_2 the unique solution larger than r_0 of the equation

$$x^2 \log\frac{x}{r_0} - \frac{1}{2}(x^2 - r_0^2) = 2\frac{\sigma^\star}{f(\sigma_N)N_1}\,. \tag{3.33}$$

Moreover

$$B(t) > \rho_N(t)\,. \tag{3.34}$$

Proof. Let $\mathcal{T}_1$ be the set of values of $t \in [0,T]$ such that $\sigma(\rho_N(t),t) = \sigma_N$. For $t \in \mathcal{T}_1$, we have from (3.14)

$$\begin{aligned}\sigma^\star - \sigma_N &\leq f(\sigma^\star)N_2 \int_{r_0}^{\rho_N(t)} r \log\frac{r}{r_0}\,dr \\ &= f(\sigma^\star)N_2\left[\frac{1}{2}\rho_N^2 \log\frac{\rho_N}{r_0} - \frac{1}{4}(\rho_N^2 - r_0^2)\right],\end{aligned} \tag{3.35}$$

so that $\rho_N(t) \geq \hat{R}_1 > R_1 > r_0$. Recalling the construction of ρ_N, at the time points of $\mathcal{T}_2 = [0,T] - \mathcal{T}_1$ (if not empty) the curve $r = \rho_N(t)$ is tangent to a characteristic line. Let us now consider a generic characteristic line $r = \eta(t)$ passing through (r', t'). For $t \geq t'$, $\eta(t)$ satisfies

$$\dot{\eta} = u(\eta(t), t - \theta)\,, \quad \eta(t') = r'\,, \tag{3.36}$$

($t - \theta$ set to zero when $t < \theta$). From (3.19) we have

$$ru(r, t - \theta) > -\frac{\mu_{Nmax}}{2}(r^2 - r_0^2) \tag{3.37}$$

and thus

$$\eta\dot{\eta} > -\frac{\mu_{Nmax}}{2}(\eta^2 - r_0^2)\,, \tag{3.38}$$

that implies

$$\eta(t)^2 - r_0^2 > (r'^2 - r_0^2)\mathrm{e}^{-\mu_{Nmax}(t-t')}\,. \tag{3.39}$$

If $\mathcal{T}_2$ is not empty, for $t \in \mathcal{T}_2$ let $\mathcal{T}_{1t}$ be the subset of $\mathcal{T}_1$ such that $t > \tau$ for each $\tau \in \mathcal{T}_{1t}$, and let $s_t = \sup\mathcal{T}_{1t}$. The characteristic line to which $(\rho_N(t), t)$ belongs will pass through $(\rho_N(s_t), s_t)$, so from (3.39) we have

$$\rho_N(t)^2 - r_0^2 > (\rho_N(s_t)^2 - r_0^2)\mathrm{e}^{-\mu_{Nmax}(t-s_t)}\,. \tag{3.40}$$

Since $\rho_N(s_t) \geq \hat{R}_1$, it follows that $\rho_N(t) > R_1$. Turning now to the upper bound, we have for each $t \in [0,T]$

$$\sigma^\star - \sigma(\rho_N(t),t) \geq f(\sigma_N)N_1 \int_{r_0}^{\rho_N(t)} r \log \frac{r}{r_0}\, dr$$

$$= f(\sigma_N)N_1 \big[\frac{1}{2}\rho_N^2 \log \frac{\rho_N}{r_0} - \frac{1}{4}(\rho_N^2 - r_0^2)\big]\,, \tag{3.41}$$

so that $\rho_N(t)$ is smaller than the solution larger than r_0 of

$$\frac{1}{2}x^2 \log \frac{x}{r_0} - \frac{1}{4}(x^2 - r_0^2) = \max_{t\in[0,T]} \frac{\sigma^\star - \sigma(\rho_N(t),t)}{f(\sigma_N)N_1}\,, \tag{3.42}$$

which is smaller than the solution R_2 of (3.33).

To prove that $B(t) > \rho_N(t)$, it is enough to recognize that for each $t \in [0,T]$ there exists $\hat{r}_t \in (r_0, \rho_{N0}]$ such that $\rho_N(t) = \eta(\hat{r}_t, t)$. Taking into account that $B_0 > r_0$ and that the characteristic lines do not intersect each other, the property (3.34) follows. ∎

Moreover, we have:

Lemma 3.3. *In the family of approximating solutions, the functions ρ_N, B and $\dot{B}$ are uniformly bounded and uniformly Lipschitz continuous. The functions σ, u are uniformly bounded and uniformly Lipschitz continuous in $[r_0, M_B]\times[0,T]$, M_B denoting a uniform upper bound of B. The function ν has the same property in $r_0 \leq r \leq \rho_N(t)$, $t\in[0,T]$. The function c is estimated uniformly in $H^{1+\alpha,(1+\alpha)/2}$ for $(r,t)\in[r_0,M_B]\times[0,T]$ and $\alpha\in(0,1)$. In addition, in any domain whose closure has a positive distance from the boundary $r=r_0$ and from the interface $r=\rho_N(t)$, we have uniform estimates of the norm of c in the space $H^{2+\alpha,1+\alpha/2}$.*

Proof. Concerning ν and ρ_N, the uniform boundedness is given by Lemmas 3.1 and 3.2, respectively. Moreover $c(r,t)$ takes values between 0 and $\sup_{[0,T]} c^\star(t)$, owing to the maximum principle. Again from the maximum principle, we can say that $0<\sigma\leq\sigma^\star$. Recalling (3.19) and taking into account the uniform boundedness of ν and ρ_N, the uniform boundedness of u, B and $\dot{B}$ easily follows. Since H is uniformly bounded, and remembering (3.27), we immediately see that $D_u\nu$ is also uniformly bounded.

In order to prove that ν is uniformly Lipschitz in $r_0 \leq r \leq \rho_N(t)$, $t \in [0,T]$, we note that equations (3.8)-(3.9) are also valid in the whole domain, with σ^θ, $\bar{\nu}^\theta$ suitably replacing σ_0, $\bar{\nu}^0$ in the expression of $\mathcal{H}$. First we use (3.8), noting that $\partial\mathcal{H}/\partial\hat{r}$ involves the derivatives $\partial\sigma^\theta/\partial r$, $\partial c/\partial r$ and $\partial\bar{\nu}^\theta/\partial r$ multiplied by $\partial\eta/\partial\hat{r}$, which can be easily estimated for each t as done in the first step. The derivatives $\partial\zeta/\partial r$, $\partial\zeta/\partial t$ are as well bounded as explained in the first step. Thus, from (3.8), we can derive a Gronwall-type inequality for the quantity $\sup_{[0,t]} |\partial\nu/\partial r|_{\gamma(\hat{r})}$, leading to an estimate of $\sup|\partial\nu/\partial r|$ in terms of ν_0, ν_0' and the sup of $|\partial\sigma^\theta/\partial r|$ and $|\partial c/\partial r|$. Uniform bounds on σ^θ, $|\partial\sigma^\theta/\partial r|$, $|\partial^2\sigma^\theta/\partial r^2|$ are trivial. A bound on $|\partial c/\partial r|$ can be found as follows. Take the transformation

$$\tilde{r} - r_0 = \frac{R - r_0}{B(t) - r_0}(r - r_0)\,, \tag{3.43}$$

carrying the domain $r_0 < r < B(t)$, $0<t<T$ into a fixed domain $r_0 < \tilde{r} < R$, $0<t<T$. Defining $\tilde{c}(\tilde{r},t) = c(r(\tilde{r}),t)$, the operator $\mathcal{L}c = \partial c/\partial t - D_C \Delta c$ becomes

$$\tilde{\mathcal{L}}\tilde{c} = \frac{\partial\tilde{c}}{\partial t} - \frac{\partial\tilde{c}}{\partial\tilde{r}}\left[\frac{\dot{B}}{B - r_0}(\tilde{r} - r_0) + D_C\frac{R - r_0}{B - r_0}\left((\tilde{r} - r_0)\frac{B - r_0}{R - r_0} + r_0\right)^{-1}\right]$$

$$-D_C\left(\frac{R-r_0}{B-r_0}\right)^2\frac{\partial^2\tilde{c}}{\partial\tilde{r}^2}\,, \tag{3.44}$$

and the problem for c defined by (3.22)-(3.25) can be rewritten for $\tilde{c}$. On the basis of the fact that c, σ, ν are bounded and that $\dot{B}/(B-r_0)$, $(R-r_0)/(B-r_0)$, $(B-r_0)/(R-r_0)$ are a-priori bounded ($B-r_0$ has indeed a positive lower bound, see Lemma 3.2), we can apply well-known results (see Th. 9.1 and Remark at the end of section 9 in [15, Ch. 4]) guaranteeing uniform estimates for the norms of $\tilde{c}$ (and hence of c) at least in the spaces $W_q^{2,1}$ (for any $q>1$) and $H^{1+\alpha,(1+\alpha)/2}$ (for any $\alpha\in(0,1)$). In particular we have now the uniform bound for $|\partial c/\partial r|$, needed to obtain a uniform bound for $|\partial\nu/\partial r|$. Once we have this, we get a uniform bound for $|\partial\nu/\partial t|$ just using Eq. (3.9).

The less trivial step is now to establish uniform bounds on $|\partial\sigma/\partial t|$ and $|\dot{\rho}_N|$, needed to complete the proof of compactness. Let $z(r,t)=\partial\sigma/\partial t$. Differentiating $\Delta\sigma=f(\sigma)\nu$ w.r.t. time, we obtain

$$\frac{\partial^2 z}{\partial r^2}+\frac{1}{r}\frac{\partial z}{\partial r}=f'(\sigma)z\nu+f(\sigma)\frac{\partial\nu}{\partial t}\,. \tag{3.45}$$

At a possible maximum of z in (r_0,ρ_N), it must be $\partial z/\partial r=0$, $\partial^2 z/\partial r^2\le 0$, so that from (3.45) it follows

$$f'(\sigma)z\nu\le -f(\sigma)\frac{\partial\nu}{\partial t}\,.$$

Denoting by $\bar{z}_{max}$ the value of z at such local maximum, and being $f_{max}=\max_\sigma f(\sigma)$ and $f'_{min}=\min_\sigma f'(\sigma)$, the inequality above gives

$$\bar{z}_{max}\le -\frac{f(\sigma)}{f'(\sigma)}\frac{1}{\nu}\frac{\partial\nu}{\partial t}\le\frac{f_{max}}{f'_{min}}\frac{1}{N_1}\left\|\frac{\partial\nu}{\partial t}\right\|. \tag{3.46}$$

At a possible minimum of z in (r_0,ρ_N), it must be

$$\bar{z}_{min}\ge -\frac{f(\sigma)}{f'(\sigma)}\frac{1}{\nu}\frac{\partial\nu}{\partial t}\ge -\frac{f_{max}}{f'_{min}}\frac{1}{N_1}\left\|\frac{\partial\nu}{\partial t}\right\|, \tag{3.47}$$

where $\bar{z}_{min}$ is the value of z at such local minimum.

In the case in which $\sigma(\rho_N(t),t)=\sigma_N$, since $z=0$ for $r=r_0$ and $r=\rho_N(t)$, we can conclude

$$\left|\frac{\partial\sigma}{\partial t}\right|\le\frac{f_{max}}{f'_{min}}\frac{1}{N_1}\left\|\frac{\partial\nu}{\partial t}\right\|. \tag{3.48}$$

Thus, from (3.16) written for $\rho_N(t)$, we get a uniform bound for $|\dot{\rho}_N|$.

In the case in which ρ_N is a material surface, *i.e.* $\dot{\rho}_N=u(\rho_N,t\text{–}\theta)$, the desired estimate for $|\dot{\rho}_N|$ is provided by the uniform boundedness of u. Moreover, since $\partial\sigma/\partial r|_{r=\rho_N(t)}=0$, differentiating w.r.t. time we obtain

$$\left.\frac{\partial^2\sigma}{\partial r^2}\right|_{r=\rho_N(t)}\dot{\rho}_N+\left.\frac{\partial^2\sigma}{\partial r\partial t}\right|_{r=\rho_N(t)}=0\,. \tag{3.49}$$

Also, we know that

$$\left.\frac{\partial^2\sigma}{\partial r^2}\right|_{r=\rho_N(t)}=\left.[f(\sigma)\nu]\right|_{r=\rho_N(t)}\equiv g(t)\,, \tag{3.50}$$

which is positive and bounded. Therefore, in each step, we can construct the solution of the problem

$$\Delta z = \frac{\partial}{\partial t}[f(\sigma)\nu]\,, \tag{3.51}$$

with boundary data

$$z(r_0) = 0\,, \qquad \left.\frac{\partial z}{\partial r}\right|_{r=\rho_N} = -g\dot{\rho}_N\,. \tag{3.52}$$

The solution will satisfy

$$z = -\dot{\rho}_N\rho_N g \log\frac{r}{r_0} - \int_{r_0}^{r}\frac{1}{r'}\left(\int_{r'}^{\rho_N} r''\frac{\partial}{\partial t}[f(\sigma)\nu]\,dr''\right)dr'$$

$$= -\dot{\rho}_N\rho_N g \log\frac{r}{r_0} - \int_{r_0}^{\rho_N} r'\log\frac{\min[r',r]}{r_0}\frac{\partial}{\partial t}[f(\sigma)\nu]\,dr'\,. \tag{3.53}$$

Let us suppose that $\dot{\rho}_N < 0$. Then, from (3.50) and (3.52), $\partial z/\partial r|_{r=\rho_N} > 0$ and z may have an absolute maximum at $r = \rho_N$. If $z_{max} = z(\rho_N)$, from (3.53) and taking into account (3.47) we obtain

$$z_{max} \le -\dot{\rho}_N\rho_N g \log\frac{\rho_N}{r_0} + f_{max}\left\|\frac{\partial\nu}{\partial t}\right\|\int_{r_0}^{\rho_N} r'\log\frac{r'}{r_0}\,dr'$$

$$+f'_{max}\frac{f_{max}}{f'_{min}}\frac{N_2}{N_1}\left\|\frac{\partial\nu}{\partial t}\right\|\int_{r_0}^{\rho_N} r'\log\frac{r'}{r_0}\,dr'\,, \tag{3.54}$$

that, together with (3.46)-(3.47), guarantees the uniform boundedness of $|\partial\sigma/\partial t|$. If $\dot{\rho}_N > 0$, $\partial z/\partial r|_{r=\rho_N} < 0$ and z may have an absolute minimum at $r = \rho_N$. If $z_{min} = z(\rho_N)$, we can obtain similarly

$$z_{min} \ge -\dot{\rho}_N\rho_N g \log\frac{\rho_N}{r_0} - f_{max}\left\|\frac{\partial\nu}{\partial t}\right\|\int_{r_0}^{\rho_N} r'\log\frac{r'}{r_0}\,dr'$$

$$-f'_{max}\frac{f_{max}}{f'_{min}}\frac{N_2}{N_1}\left\|\frac{\partial\nu}{\partial t}\right\|\int_{r_0}^{\rho_N} r'\log\frac{r'}{r_0}\,dr'\,, \tag{3.55}$$

leading to the parallel conclusion about the lower bound. If $\dot{\rho}_N = 0$, z may have either a maximum or a minimum at $r = \rho_N$. In such cases (3.54) or (3.55) apply, still confirming the boundedness of $|\partial\sigma/\partial t|$.

From the above estimates, it also follows that $u(r,t)$ is uniformly Lipschitz continuous. Finally, concerning $\tilde{c}$, we can say that we have uniform inner Schauder estimates on both sides of the discontinuity curve of the consumption term (see [15, Ch. 4]). As a matter of fact, the Lipschitz continuity of $\dot{B}(t)$ allows us to extend such estimate to the outer boundary $r = B(t)$. Therefore, uniform estimates for c in the norm $H^{2+\alpha,1+\alpha/2}$ are available in all the domains whose closure does not touch $r = r_0$, nor the interface $r = \rho_N(t)$. ∎

Now we can prove the following theorem:

Theorem 3.1. *Under the assumptions (H1)–(H12) for $\chi(\sigma)$, $\mu(\sigma)$, $\mu_C(c,\sigma)$, $\mu_R(\sigma,t)$, $f(\sigma)$, Problem P has a solution $(\nu,\sigma,u,\rho_N,B,c)$ in an arbitrarily large time interval.*

Proof. Let us indicate here by the subscript "n" the approximations of order n. The existence proof is rather simple thanks to Lemma 3.3, which provides enough compactness of the family of approximating solutions. Indeed, we can select a subsequence of indices, say $\{n_k\}$, for which we have uniform convergence of $\rho_{N_{n_k}}, B_{n_k}$ to ρ_N, B, and of the functions ν_{n_k} to ν in $r_0 \le r \le \rho_N(t)$ and of σ_{n_k}, c_{n_k} to σ, c in $r_0 \le r \le B(t)$, $t \in [0,T]$. We notice that the convergence of the approximations ν_{n_k} has to be intended as

$$\lim_{k\to\infty} \sup_{(r,t)\in D_{n_k}\cap D} |\nu_{n_k}(r,t) - \nu(r,t)| = 0 \,,$$

where $D_n = \{(r,t) \,:\, r \in [r_0, \rho_{N_n}(t)], t \in [0,T]\}$ and $D = \{(r,t) \,:\, r \in [r_0, \rho_N(t)], t \in [0,T]\}$. In turn, through (3.19), this implies the uniform convergence of the corresponding sequence u_{n_k} (and $\partial u_{n_k}/\partial r$). Although the constraints (1.13) and (1.22) in the approximating scheme are not used as written, but with a time shift, and moreover they can be applied with the respective tolerance u_{tol}/n and σ_{tol}/n, it is clear that the correct inequalities are obtained in the limit. Similarly we have the uniform convergence of the characteristic lines and we can pass to the limit in equation (3.29). At the same time we can pass to the limit in equations (3.14)-(3.15) (with $\tilde{\rho}_N(t) = \rho_N(t)$) or (3.17)-(3.18), showing that the limit functions satisfy the same equations, so that in particular the limit ρ_N preserves the properties characterizing the boundary of the necrotic region. Thus we see that the limit functions ν, σ, u satisfy the governing equations of the model in their integral form. From the integral form we can go back to the original differential statement of the problem just performing the derivatives and checking that all the governing differential equations are satisfied, as well as the initial and boundary conditions. Concerning c, the Schauder's estimates allow us to pass to the limit directly in the parabolic differential equation separately in P∪T∪Q and in N, while the differential equation is satisfied in the whole domain in the sense of $W_q^{2,1}$. Therefore, any convergent subsequence in the family of approximating solutions provides a solution to the original problem. ∎

The approximating procedure previously described becomes constructive if we can say that the whole sequence is convergent. In turn, this is guaranteed if we prove uniqueness. First we prove the following property of the solution:

Lemma 3.4. *The solution ν, for $r \in (r_0, \rho_N(t)]$, satisfies the inequalities*

$$0 < N_1 \le \nu(r,t) \le 1 \,, \quad t \in [0,T] \,, \tag{3.56}$$

where N_1 is defined by (3.28).

Proof. We observe preliminarly that, as done for the approximating solutions, we can also define for the real solution the function $\hat{r} = \zeta(r,t)$ for $r \in (r_0, \rho_N(t)]$ and $t \in [0,T]$, such that $r = \eta(\zeta(r,t),t)$, $\eta(\hat{r},t)$ being the characteristic line starting from $\hat{r}$. In particular, we can interpret (1.11) as $D_u\nu = -\nu H(t,c,\sigma,\nu)$ on the characteristic lines, and we can see that $D_u\nu < 0$ at all points where $\nu > 1$. Since $\nu_0 \le 1$ everywhere, this implies that ν cannot take values greater that one. Since the lower bound N_1 holds for all the approximations of ν, it will also hold for their limit. ∎

In order to proceed further, we need the following additional assumption:

$$\|f'\| \left[R_2^2 \log \frac{R_2}{r_0} - \frac{1}{2}(R_2^2 - r_0^2) \right] < 1 \,. \tag{3.57}$$

Now we can state:

Theorem 3.2. *Under the assumptions (H1)–(H12) and (3.57), Problem P has one unique solution.*

Proof. We have already noticed that for a certain time interval starting from $t=0$ the difference $u(\rho_N,t)-\dot\rho_N(t)$ is positive for all possible solutions (the argument is the same we applied for the approximate solutions during the first time step). Therefore we start comparing two solutions of this type.

Let us consider two possible solutions of type (1.18)-(1.19) in a time interval $(0,\hat t\,)$, $\hat t \le T$, and let us denote by $\delta\nu$, δu, $\delta\sigma$, $\delta\rho_N$, δc, δB the differences of the respective quantities. Using the labels $1,2$ for the two solutions (so that $\delta\nu(r,t)=\nu_1(r,t)-\nu_2(r,t)$, and so on) and setting $\rho_{min}(t)=\min[\rho_{N_1}(t),\rho_{N_2}(t)]$, $\rho_{max}(t)=\max[\rho_{N_1}(t),\rho_{N_2}(t)]$, we have the following equation (where μ_1, μ_{R_1}, μ_{C_1}, χ_1 mean that the quantities are evaluated for solution 1, and the overbar means that the derivative is computed at a suitable point between the values of the independent variables for solutions 1,2):

$$D_{u_1}\delta\nu + [\mu_1+\mu_{R_1}+\mu_{C_1}-(\chi_1+\mu_N)+(\chi_1+\mu_N)(\nu_1+\nu_2)]\,\delta\nu+\frac{\partial\nu_2}{\partial r}\delta u$$
$$+\nu_2\left[\overline{\frac{\partial\mu}{\partial\sigma}}+\overline{\frac{\partial\mu_R}{\partial\sigma}}+\overline{\frac{\partial\mu_C}{\partial\sigma}}-\overline{\chi}'(1-\nu_2)\right]\delta\sigma+\nu_2\overline{\frac{\partial\mu_C}{\partial c}}\delta c=0\,, \tag{3.58}$$

with zero initial conditions and with $\delta\nu$ continued in (ρ_{min},ρ_{max}) as $(-1)^{j+1}\nu_j$, with $j=1$ if $\rho_{N_1}\ge\rho_{N_2}$ and $j=2$ otherwise. Of course $\delta\nu=0$ in the intersection of the two necrotic regions N_1, N_2. Moreover we have:

$$r\delta u=\begin{cases}\int_{r_0}^{r} r'\left[\delta\nu(\chi_1+\mu_N)+\nu_2\overline{\chi}'\delta\sigma\right]dr'\,, & r\in[r_0,\rho_{min}]\\ \int_{r_0}^{\rho_{min}} r\left[\delta\nu(\chi_1+\mu_N)+\nu_2\overline{\chi}'\delta\sigma\right]dr+(-1)^{j+1}\int_{\rho_{min}}^{r} r'\left[\nu_j(\chi_j+\mu_N)-\mu_N\right]dr' & \\ +(-1)^{j+1}\frac{\tilde\mu_N}{2}(r^2-\rho_{min}^2)\,, & r\in(\rho_{min},\rho_{max}]\,.\end{cases} \tag{3.59}$$

Taking into account that for σ_i, $i=1,2$, we have

$$\sigma_i(r,t)-\sigma_N=\int_r^{\rho_{N_i}(t)} r'\log\frac{r'}{r}f(\sigma_i)\nu_i\,dr'\,, \tag{3.60}$$

$$\sigma^\star-\sigma_N=\int_{r_0}^{\rho_{N_i}(t)} r\log\frac{r}{r_0}f(\sigma_i)\nu_i\,dr\,, \tag{3.61}$$

we obtain from (3.61)

$$(-1)^j\int_{\rho_{min}}^{\rho_{max}} r\log\frac{r}{r_0}f(\sigma_j)\nu_j\,dr=\int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}[f(\sigma_1)\nu_1-f(\sigma_2)\nu_2]\,dr\,. \tag{3.62}$$

From (3.60), for $r\in(r_0,\rho_{min}]$, we have

$$\delta\sigma=(-1)^{j+1}\int_{\rho_{min}}^{\rho_{max}} r'\log\frac{r'}{r}f(\sigma_j)\nu_j\,dr'+\int_r^{\rho_{min}} r'\log\frac{r'}{r}[f(\sigma_1)\nu_1-f(\sigma_2)\nu_2]\,dr'\,, \tag{3.63}$$

whereas, for $r\in(\rho_{min},\rho_{max}]$,

$$\delta\sigma=(-1)^{j+1}\int_r^{\rho_{max}} r'\log\frac{r'}{r}f(\sigma_j)\nu_j\,dr'\,. \tag{3.64}$$

Because there exists a positive lower bound of the product $f\nu$, a lower estimate of the l.h.s. of (3.62) can be written in the form $(f\nu)_{min}\,\rho_{min}\log(\rho_{min}/r_0)|\delta\rho_N|$. Since a lower estimate for ρ_N is trivially obtained from (3.61) (as in Lemma 3.2), from (3.62) we get the inequality

$$|\delta\rho_N| \le K_1 \int_{r_0}^{\rho_{min}} r\big(\|f\|\,|\delta\nu| + \|f'\|\,|\delta\sigma|\big)\log\frac{r}{r_0}\,dr \tag{3.65}$$

where K_1 is a known constant. From (3.63)-(3.64), we see that for $r\in(r_0,\rho_{max}]$

$$|\delta\sigma| \le \int_{\rho_{min}}^{\rho_{max}} r\log\frac{r}{r_0} f(\sigma_j)\nu_j\,dr + \int_{r}^{\rho_{min}} r'\log\frac{r'}{r}|f(\sigma_1)\nu_1 - f(\sigma_2)\nu_2|\,dr'\,.$$

Taking into account (3.62) and that $\nu\le 1$ (see Lemma 3.4), we obtain

$$\begin{aligned}|\delta\sigma| &\le \int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}|f(\sigma_1)\nu_1 - f(\sigma_2)\nu_2|\,dr + \int_{r}^{\rho_{min}} r'\log\frac{r'}{r}|f(\sigma_1)\nu_1 - f(\sigma_2)\nu_2|\,dr' \\ &\le \|f'\|\left(\int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}|\delta\sigma|\,dr + \int_{r}^{\rho_{min}} r'\log\frac{r'}{r}|\delta\sigma|\,dr'\right) \\ &\quad+\|f\|\left(\int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}|\delta\nu|\,dr + \int_{r}^{\rho_{min}} r'\log\frac{r'}{r}|\delta\nu|\,dr'\right) \\ &\le 2\|f'\|\int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}|\delta\sigma|\,dr + 2\|f\|\int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}|\delta\nu|\,dr\,. \end{aligned} \tag{3.66}$$

Provided that

$$2\|f'\|\int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}\,dr = \|f'\|\left[\rho_{min}^2\log\frac{\rho_{min}}{r_0} - \frac{1}{2}(\rho_{min}^2 - r_0^2)\right] < 1\,, \tag{3.67}$$

which is guaranteed by assumption (3.57), from (3.66) we obtain

$$\|\delta\sigma\|_t \le K_2\|\delta\nu\|_t\,, \tag{3.68}$$

where $\|\cdot\|_t$ means the sup with respect to r and with respect to time in $[0,t]$. Continuing our analysis of the set of equations for the differences, we come to the equation for δc to be satisfied in $r_0<r<B_{min}(t)$, $0<t<\hat{t}$, B_{min} denoting $\min[B_1,B_2]$:

$$\frac{\partial\delta c}{\partial t} - D_C\Delta\delta c = -\varphi_{C_1}\delta\nu - \left(\overline{\frac{\partial\varphi_C}{\partial c}}\right)\nu_2\delta c - \left(\overline{\frac{\partial\varphi_C}{\partial\sigma}}\right)\nu_2\delta\sigma - \lambda\delta c\,, \tag{3.69}$$

$$\delta c(r_0,t) = 0\,, \tag{3.70}$$

$$\delta c(r,0) = 0\,. \tag{3.71}$$

If $\hat{t}$ is sufficiently small to guarantee that the differences $B_i-\rho_{N_j}$, $i=1,2$, $j=1,2$, remain strictly positive, we have also

$$\left.\frac{\partial\delta c}{\partial r}\right|_{r=B_{min}(t)} = (-1)^{k+1}\left.\frac{\partial^2 c_k}{\partial r^2}\right|_{r=\bar{r}(t)}|\delta B|\,, \tag{3.72}$$

where $\bar{r}(t)$ is a suitable point between the boundaries $B_1(t), B_2(t)$, and $k=1$ if $B_1 \geq B_2$ and $k=2$ otherwise. The coefficient of $|\delta B|$ in (3.72) is a-priori bounded since c_1,c_2 possess the same properties stated for the approximating functions in Lemma 3.3.

Now we are able to write the following chain of inequalities, starting with

$$\|\delta\nu\|_t \leq \int_0^t \left(k_1\|\delta u\|_\tau + k_2\|\delta\sigma\|_\tau + k_3\|\delta c\|_\tau\right) d\tau \tag{3.73}$$

that can be obtained from (3.58). From (3.59) we see that $\|\delta u\|_\tau$ can be estimated in terms of $\|\delta\rho_N\|_\tau$,$\|\delta\sigma\|_\tau$, $\|\delta\nu\|_\tau$ and, ultimately, because of (3.65) and (3.68), in terms of $\|\delta\nu\|_\tau$, so that (3.73) implies

$$\|\delta\nu\|_t \leq \int_0^t \left(k_3\|\delta c\|_\tau + k_4\|\delta\nu\|_\tau\right) d\tau\,. \tag{3.74}$$

Going back to problem (3.69)-(3.72), for which an estimate of $\partial^2 c_k/\partial r^2$ is available in the region between B_{min} and $B_{max} = \max[B_1, B_2]$, taking into account that $|\delta B| \leq \int_0^t \|\delta u\|_\tau\, d\tau$, and exploiting the estimates already used for $\delta\sigma$ and δu, we obtain by classical means the inequality

$$\|\delta c\|_t \leq \int_0^t \left(k_5\|\delta\nu\|_\tau + k_6\|\delta c\|_\tau\right) d\tau \tag{3.75}$$

which, together with (3.74), immediately yields $\|\delta c\|_t = \|\delta\nu\|_t = 0$. At this point we may conclude that the solution is unique in a suitably small time interval, and by extension up to a possible time point $\bar{t}$ such that in any right neighbourhood (1.18)-(1.19) cannot hold.

Let us suppose, for the time being, that after $\bar{t}$ we have in some interval two solutions for which the interface $r=\rho_N(t)$ is a material surface. Let us compare two such solutions. The basic formulas for σ are $(i=1,2)$

$$\sigma_i(r,t) - \sigma_i(\rho_{N_i}(t),t) = \int_r^{\rho_{N_i}(t)} r' \log\frac{r'}{r} f(\sigma_i)\nu_i\, dr'\,, \tag{3.76}$$

$$\sigma^\star - \sigma_i(\rho_{N_i}(t),t) = \int_{r_0}^{\rho_{N_i}(t)} r \log\frac{r}{r_0} f(\sigma_i)\nu_i\, dr\,, \tag{3.77}$$

implying

$$\sigma_i - \sigma^\star = \int_r^{\rho_{N_i}} r' \log\frac{r'}{r} f(\sigma_i)\nu_i\, dr' - \int_{r_0}^{\rho_{N_i}} r \log\frac{r}{r_0} f(\sigma_i)\nu_i\, dr\,. \tag{3.78}$$

We remark that in the present case, since $\rho_{N_1}(\bar{t}) = \rho_{N_2}(\bar{t})$, we have for $t > \bar{t}$

$$\delta\rho_N = \int_{\bar{t}}^t [u_1(\rho_{N_1}(\tau),\tau) - u_2(\rho_{N_2}(\tau),\tau)]\, d\tau\,, \tag{3.79}$$

thus

$$|\delta\rho_N(t)| \leq \int_{\bar{t}}^t \left(|\delta u|_{r=\rho_{min}(\tau)} + \left\|\frac{\partial u}{\partial r}\right\| |\delta\rho_N(\tau)|\right) d\tau\,. \tag{3.80}$$

In the following we will denote by M_i some a-priori computable constants. First we note that, for $r \leq \rho_{min}(t)$,

$$|\delta u| \leq M_1|\delta\sigma| + M_2|\delta\nu|\,, \tag{3.81}$$

so that (3.80) produces the Gronwall type inequality

$$|\delta\rho_N(t)| \le \int_{\bar t}^{t} \left(M_3|\delta\sigma|_{r=\rho_{min}(\tau)} + M_4|\delta\nu|_{r=\rho_{min}(\tau)}\right) d\tau + M_5 \int_{\bar t}^{t} |\delta\rho_N(\tau)|\, d\tau\,, \tag{3.82}$$

thus giving an estimate of $|\delta\rho_N(t)|$ in terms of $\int_{\bar t}^{t} |\delta\sigma|_{r=\rho_{min}(\tau)} d\tau$ and $\int_{\bar t}^{t} |\delta\nu|_{r=\rho_{min}(\tau)} d\tau$. Combining (3.78) and the latter result, by means of the same technique used in the previous case, we see that under condition (3.57) and for $t-\bar t$ sufficiently small, we arrive at the conclusion

$$\|\delta\sigma\|_{[\bar t,t]} \le M_6 \|\delta\nu\|_{[\bar t,t]}\,. \tag{3.83}$$

From this point on, the rest of the proof follows the pattern of the previous case. Starting from a time instant in the interval in which uniqueness is guaranteed, the previous argument can be repeated, yielding uniqueness until $r=\rho_N(t)$ is a material boundary. The procedures seen above can be applied after each switch to solutions having the interface ρ_N of the same type (both non-material or material).

We observe now that the evolutive problem in which the constraint (1.13) is not imposed, and ρ_N and σ are defined by (1.15), (1.17), (1.19)-(1.20), cannot have more than one solution (the comparison technique is the same as the one used above), and the same holds for the evolutive problem in which constraint (1.22) is not imposed, ρ_N is defined by (1.21), and σ by (1.15), (1.17) and (1.20). Therefore, we can exclude that after $\bar t$, or any other switching point, there can be a time interval in which our problem has a solution of one type and another solution of different type. This, in fact, would imply that different unconstrained solutions should exist in a time interval after $\bar t$, since it is the behaviour of such unconstrained solutions that governs the switch of ρ_N from one type to the other.

Hence, it only remains to examine the case in which we suppose to have two solutions having infinitely many switching points in any right neighbourhood of the time $\bar t$ (the reader can remark that the comparison between two solutions of different type after $\bar t$, which we avoided on the basis of the argument above, is *de facto* included in the analysis that follows). The argument proceeds in a very similar way. The main difference occurs in the comparisons of the quantities σ_1,σ_2 and ρ_{N_1},ρ_{N_2}. We consider an interval $(\bar t, \bar t+\varepsilon)$ and its partition in intervals in which the two solutions we are comparing are both of the same type and in intervals in which they are of different type. We fix our attention on the second class of intervals. To be specific, let us assume that the ρ_N interface is non-material for the solution labeled by "1" and material for the solution labeled by "2". Subtracting (3.77) with $i=2$ from (3.61) with $i=1$, we get

$$\sigma_2(\rho_{N_2}(t),t)-\sigma_N = \int_{r_0}^{\rho_{min}} r\log\frac{r}{r_0}[f(\sigma_1)\nu_1 - f(\sigma_2)\nu_2]\,dr + (-1)^{j+1}\int_{\rho_{min}}^{\rho_{max}} r\log\frac{r}{r_0} f(\sigma_j)\nu_j\,dr \tag{3.84}$$

which replaces (3.62). Thus we may derive an inequality similar to (3.65):

$$|\delta\rho_N| \le K_1 \int_{r_0}^{\rho_{min}} r\left(\|f\|\,|\delta\nu| + \|f'\|\,|\delta\sigma|\right)\log\frac{r}{r_0}\,dr + K_1|\sigma_2(\rho_{N_2}(t),t)-\sigma_N|\,. \tag{3.85}$$

Now we can write

$$|\sigma_2(\rho_{N_2},t) - \sigma_N| \le |\delta\sigma(\rho_{N_2},t)| + \sigma_1(\rho_{N_2},t) - \sigma_N\,, \tag{3.86}$$

if, *e.g.*, $\rho_{N_1} > \rho_{N_2}$. Moreover,

$$\sigma_1(\rho_{N_2},t) - \sigma_N = \left|\frac{\partial\sigma_1}{\partial r}(\bar r,t)\right| |\delta\rho_N|\,, \tag{3.87}$$

with $\bar{r}$ between ρ_{N_2} and ρ_{N_1}. Since $\partial\sigma_1/\partial r$ vanishes for $r=\rho_{N_1}$, we can also say that

$$\left|\frac{\partial\sigma_1}{\partial r}(\bar{r},t)\right| \leq \left\|\frac{\partial^2\sigma_1}{\partial r^2}\right\| |\delta\rho_N| \,.$$

If instead $\rho_{N_1} < \rho_{N_2}$, we have similar inequalities in which the indices are interchanged. Thus from (3.86) we deduce

$$|\sigma_2(\rho_{N_2},t) - \sigma_N| \leq |\delta\sigma(\rho_{N_2},t)| + C|\delta\rho_N|^2 \,, \tag{3.88}$$

with $C>0$ known a priori. On the other hand, we may take ε so small that in $(\bar{t},\bar{t}+\varepsilon)$ we have $K_1 C|\delta\rho_N| < 1/2$, thanks to the fact that for both solutions we know an upper bound for $|\dot{\rho}_{N_i}|$. Thus, we may rewrite (3.85) in the form

$$|\delta\rho_N| \leq 2K_1 \int_{r_0}^{\rho_{min}} r\big(\|f\|\,|\delta\nu| + \|f'\|\,|\delta\sigma|\big) \log\frac{r}{r_0}\,dr + 2K_1|\delta\sigma(\rho_{N_2}(t),t)| \,. \tag{3.89}$$

We must now replace (3.63) by

$$\delta\sigma + \sigma_2(\rho_{N_2},t) - \sigma_N = (-1)^{j+1}\int_{\rho_{min}}^{\rho_{max}} r'\log\frac{r'}{r} f(\sigma_j)\nu_j\,dr'$$
$$+ \int_r^{\rho_{min}} r'\log\frac{r'}{r}[f(\sigma_1)\nu_1 - f(\sigma_2)\nu_2]\,dr' \,. \tag{3.90}$$

Combining (3.90) and (3.84) we obtain precisely the same inequality (3.66), eventually implying (3.68) with the norm referring to the appropriate time interval.

For the first class of intervals, *i.e.*, the intervals in which the two solutions are both of the same type, the estimates for $|\delta\sigma|$ and $|\delta\rho_N|$ are the same we have already used, except for a small change concerning the comparison of solutions which have both a material ρ_N interface. Indeed, in (3.79) the term $\delta\rho_N(\hat{t})$ (where $\hat{t}$ now denotes the initial time of the interval we are considering) must be added on the r.h.s. Such a term is inherited from the previous interval in which the solutions are of different type and therefore it is expressed in the way we have just seen, that is by means of (3.89). This same term must be added on the r.h.s. of (3.82), and recalling (3.68) we end up once more with (3.83). Therefore, we can conclude that also in this case the solution is unique. ∎

4. Concluding comments

As a final comment, we stress that some of the simplifying assumptions made in the development of the present model could be relaxed with some further refinements. For simplicity, we have taken here $\sigma^\star$ constant, but the whole theory can be extended to the case of $\sigma^\star$ variable with the time, assuming $\sigma^\star(t)$ in a space of functions with Hölder continuous derivative, provided it remains strictly above σ_P. We could also consider a flux condition instead of (1.17). Similarly, condition (1.28) has no crucial role in the treatment and could be substituted by a flux condition. Finally, a dependence of cell proliferation on treatment could be taken into account by representing the proliferation rate as a function $\chi(\sigma,c,t)$. The numerical solution of the evolutive problem under various therapeutic treatment modalities will be presented in a forthcoming paper. Preliminary results show that the switching from a non-material ρ_N interface to a material interface, and viceversa, is indeed a common feature of the solution.

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