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Abstract

The existence of waiting times, before boundary motion sets in, for a diffusion-diffusion reaction equation with a discontinuous switch mechanism is demonstrated. Limit cases of the waiting times are discussed in mathematical rigor. Further, analytic solutions for planar and circular wounds are derived. The waiting times as predicted using these analytic solutions are perfectly between the derived bounds. Furthermore, it is demonstrated by both physical reasoning and mathematical rigor that the movement of the boundary can be delayed once it starts moving. The proof of this assertion resides on continuity and monotonicity arguments. The theory sustains the construction of analytic solutions. The model is applied to simulation of biological processes with a threshold behavior, such as wound healing or tumor growth.

1 INTRODUCTION

In the present paper, we consider a discontinuous switch mechanism both for a (production) reaction term for a reaction-diffusion equation and for the movement of an interface. Models with a discontinuous switch are not uncommon in chemical and biological models. An example from chemistry was studied in, among others [Vermolen et al. 2001], where precipitation of a chemical takes place once the solute concentration exceeds a threshold value. The precipitation, reaction and adorption kinetics were modeled macroscopically with a set of hyperbolic transport equations with a discontinuous switch mechanism to take the precipitation phenomenon into account. An other example is provided by the model due to [Adam 1999, Vermolen et al 2006] and [Adam 1987, Shymko and Glass 1976, Britton and Chaplain 1993, Gao and Bu 2003] for (intra-osseous) wound healing and tumor growth respectively. These models all contain discontinuous switch mechanisms in which a production term is discontinuous and / or an interface starts moving once a generic chemical reaches a threshold or no longer exceeds this threshold. The mathematical analysis of these models is still of interest, since these models yield very quick qualitative insight into the results of mathematical models with soft tissues. Of course, we are aware of the existing models with a higher sophistication. The presentation of the results in this present paper is mainly focused on a simplified model for wound healing. Though, the conclusions can be extrapolated to more generic models with discontinuous switch mechanisms. For the sake of completeness, we give an introduction into mathematical models in biology.

Bone regeneration and wound healing are very complicated processes from a biological point of view. The first process involves cell migration and a chain of differentiations of several cell-types triggered by bone fracture. Under certain conditions, cartilage formation, mineralization, formation of fibrous tissue take part in the callus in which the bone heals. Some complicated mathematical models for bone regeneration have been reported in the literature, [Huiskes et al. 1997, Ament and Hofer 2000, Andreykiv 2006, Bailon-Plaza and van der Meulen 2001], to mention just a few. Application to bone ingrowth into implants are described by [Andreykiv 2006], [Huiskes et al. 1997] and [Vermolen et al. 2008] among many others. The second process, wound healing

or soft tissue regeneration, involves cell migration, production and decay of growth factors and (re-)establishment of the vascular network surrounding the area with an increased mitotic activity. Experimental validation of the models of both complicated biological processes is indispensable. The present paper focuses on the closing of epidermic or intra-osseous wounds.

When a wound occurs, blood vessels are cut and blood enters the wound. Due to coagulation of blood inside the wound, the wound is temporarily closed and as a result the blood vessels adjacent to the wound are also closed. In due course contaminants will be removed from the wounded area and the blood vessel network will be restored, but initially due to insufficient blood supply, there will be a low concentration of nutrients which are necessary for cell division and wound healing. Wound healing, if it occurs, proceeds by a combination of several processes: chemotaxis (movement of cells induced by a concentration gradient), wound contraction caused by ingress of fibroblasts that start pulling, neo-vascularization, synthesis of extracellular matrix proteins, and scar modeling. Previous models incorporate cell mitosis, cell proliferation, cell death, capillary formation, oxygen supply and growth factor generation, including studies by [Sherratt and Murray 1991], [Filion and Popel 2004], [Maggelakis 2003], [Gaffney et al. 2002], [Olsen et al. 1995], [Vermolen and Adam 2007] and [Vermolen 2008], to mention just a few. A recent work devoted to mathematical biology has been written by [Murray 2004], in which the issue of wound healing is also treated. The wound healing process can roughly be divided into the following partially overlapping consecutive stages:

1. Formation of a blood clot on the wound to prevent undesired chemicals from entering the tissue of the organism (blood clothing/inflammatory phase);

2. Formation of a network of tiny arteries (capillaries) for blood flow to supply the necessary nutrients for wound healing;

3. Division and growth of epidermal cells (mitosis), taking place during the actual healing of the wound (proliferative phase).

A good supply of oxygen, nutrients and constituents is necessary for the process of cell division and cellular growth. For this purpose tiny capillaries are formed during the process of angiogenesis. Some models for capillary network formation have been proposed by [Gaffney et al. 2002] and [Maggelakis 2004].

Epidermal wound closure is modeled by [Sherratt and Murray 1991], among others, who consider cell division and growth factor generation simultaneously for healing of epidermal wounds. Their model consists of a system of reaction-diffusion equations. We also refer to [Vermolen et al. 2007] for a description of several models for wound healing and several aspects of wound healing, such as wound closure and angiogenesis. Until now, the conditions for wound healing were only analyzed for geometries where only one spatial co-ordinate could be used. As far as we know, in all the mathematical studies mentioned before, either neo-vascularization or wound closure is modeled. Hence, these processes are considered to be sequential. However, according to the medical literature [Stadelman et al. 1997], these sequential processes partially overlap. A first attempt to combine the effects of angiogenesis and wound closure is made by [Vermolen and Adam 2007] and [Vermolen 2008]. In the aforementioned papers, the influence of angiogenesis on wound closure is dealt with. The influence of wound closure on angiogenesis was not taken into account.

Some models for wound healing and tumor growth rely on following a level of a solution to a system of partial differential equations, such as the studies due to [Sherratt and Murray 1991] and [Gaffney et al. 2002], to mention a few of them. Some other models are based on a discontinuous switch mechanism in which wound healing or tumor growth takes place if and only if the concentration of a growth factor or nutrient or oxygen exceeds a threshold value. The model that is analyzed in this paper is also based on a discontinuous switch mechanism. For some other studies on the models with a discontinuous switch mechanism, we refer to the work of [Shymko and Glass 1976], [Britton and Chaplain 1993], [Adam 1987], [Adam 1999], [Gao and Bu 2003] and [Hogea et al. 2006].

We are aware of the literature existing of studies that couple wound closure or neo-vascularization with mechanical strains and stresses, for instance [Murray 2003, Murray 2004] and [Olsen et al. 1995]. These mechanical influences are important for the modeling of deeper wounds and it will be a topic for future study. In these models a convection term for the cell density appears due to the rate of displacement. Further, the diffusion coefficients will depend on local strain and become directionally dependent. An other example of the significance of the mechanical loading on wound healing is the experimentally sustained observation that wounds aligned with the lines of skin tension tend to heal with better results. The present model is a simplification of reality, since, in reality a large number of growth factors should be taken into account and the picture is even more complicated than that. In [Wearing and Sherratt 2000], the signaling of keratinocyte growth factors, originating from mesenchymal cells, acting on epithelial cells is considered. This is crucially important for the building blocks of the micro-vascular network and skin consisting of layers of cells (epithelium). They develop a mathematical model for which traveling wave solutions are constructed as well as one-dimensional finite difference solutions. An interesting review on the modeling of angiogenesis in the context of tumor growth was written by [Alarcon et al. 2006]. In their paper, it is claimed that the modeling of the coupling between angiogenesis and tumor growth is crucially important. Furthermore, the assumption that the local concentration of oxygen is proportional to the density of the endothelial cells is debated by them. An other issue concerns the heterogeneities of the vascular system, resulting into a heterogeneous blood flow. The issues dealt with in the present paper, only involve chemistry and mechanical issues are presently ignored. In the future, mechanical effects will be covered. Some papers that treat angiogenesis in relation with tumor growth are due to [Balding and McElwain 1985], [Mantzaris et al. 2004] and [Alarcon et al. 2006].

Since wounds possibly occur after a traumatic event or surgery, a good and efficient healing is crucial. Several treatments are known to enhance wound healing. In order to design alternative and hopefully more efficient treatments, a thorough knowledge of the process is indispensable. Furthermore, a good mathematical model for wound healing could be useful for surgeons to determine how a post-operative wound heals. From a mathematical point of view, the setting up of such a model in terms of a nonlinear set of partial differential equations and boundary conditions is a challenge. An other challenge is a parameter sensitivity analysis, which reveals the most significant parameters of the model with respect to the model results. The mathematical models can be used to examine the effects of wound geometry on the healing time, or on the local injection of certain hormones, *i.e.* certain growth factors, to enhance wound healing. For these purposes, a calibrated mathematical model can provide quicker insights than animal experiments. An other issue concerns wound therapies related to strain lines or addition of drugs. The models can be helpful to investigate the impact of certain treatments on wound healing.

The present paper is mainly mathematical and it is organized as follows. First, the model, based on the ideas of Adam, is introduced. Subsequently, analytic solutions are given and a waiting time, before healing sets in, is analyzed. Wound healing, being modeled as a moving boundary problem, is analyzed in terms of a possible retardation. Finally, some conclusions are drawn.

We would like to emphasize that the present study is an attempt to get a qualitative mathematical model for tissue regeneration. A quantitative model taking into account the numerous growth factors and elastic strains is beyond the scope of this paper. In a future study, the models will be enriched with the mechanical issues, such as strain dependent diffusion coefficients. The phenomenon of tissue healing itself is still being investigated. A rather complete state-of-the-art picture from the medical literature can be found in the thesis due to [Lamme 1999].

2 THE MATHEMATICAL MODEL

In this section the model based on the ideas of [Adam 1999] is presented. Firstly, the model for the regeneration, decay and transport of the growth factor is given, and subsequently the healing process as a result of the presence of the growth factor is described (see [Vermolen et al 2006]). Finally, a description of the coupling of the two models is presented.

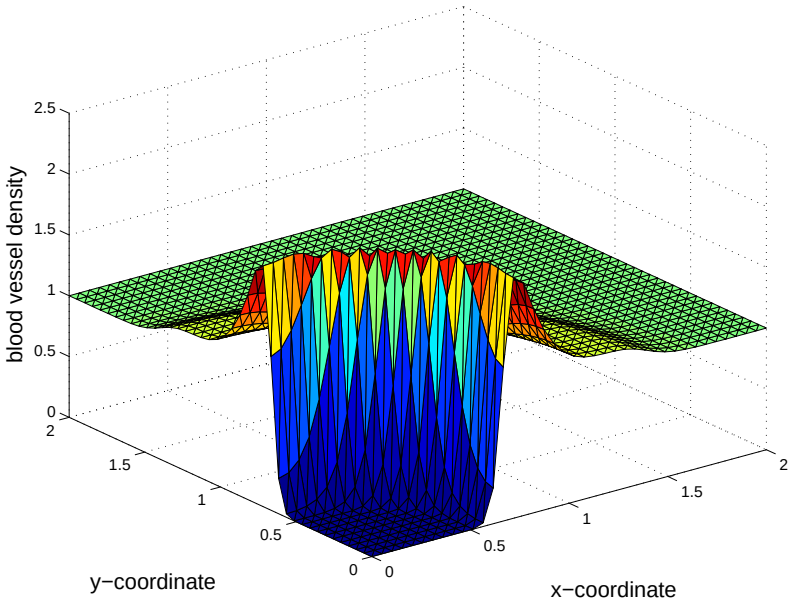

Figure 1: The increased blood vessel density at the wound edge, computed from the model due to [Gaffney et al. 2002].

2.1 The growth factor distribution

Wound healing is caused by, among others, mitotic generation and cell migration. If healing occurs, then, it is enhanced by the presence of a growth factor that stimulates cellular growth and cell-division. We will analyze a necessary condition for wound healing and analyze the subsequent step of healing. Wound healing is a complicated biological process and therefore some simplifications are needed for a feasible mathematical model within the scope of this paper. An interesting model on the healing of cutaneous wounds is presented by [Gaffney et al. 2002]. As their paper involves the solution of a set of partial differential equations, our study attempts to arrive at a relatively simple model for wound or bone healing.

Due to the angiogenetic response, there is an increased number of capillaries (tiny arteries) near the edge of the wound. An example is presented in Figure 1, where the model due to [Gaffney et al. 2002] has been used to obtain the result. The wound edge is located at positions where the blood vessel density drops dramatically as one progresses towards the wound center in $(0, 0)$.

This gives an increased activity of cellular growth, cell-division and production of the growth factor that enhances wound healing. This motivates that the production of the epidermic growth factor is neglected outside a ring around the wound. Hence, we assume that (significant) production of epidermic growth factor only takes place in the vicinity of the wound. Further, the thickness of this layer, d, is taken constant. The situation is as sketched in Figure 2.

Further, we assume that healing takes place if and only if the concentration of the growth factor at the wound edge, see Figure 2, exceeds a threshold value $\hat{c}$.

In Figure 2 we use Ω_1, Ω_2 and Ω_3 to denote the wound itself, the active layer and the outer tissue respectively. Far away from the wound, that is at the boundary of the domain of computation, Γ as in Figure 2, we assume that there is no transport of growth factor. The wound edge, the interface between the wound (Ω_1) and the active layer (Ω_2), is indicated by W (*i.e.* $W = \overline{\Omega}_1 \cap \overline{\Omega}_2$).

Let the total domain of computation be given by Ω, which is Lipschitz, then, following [Adam

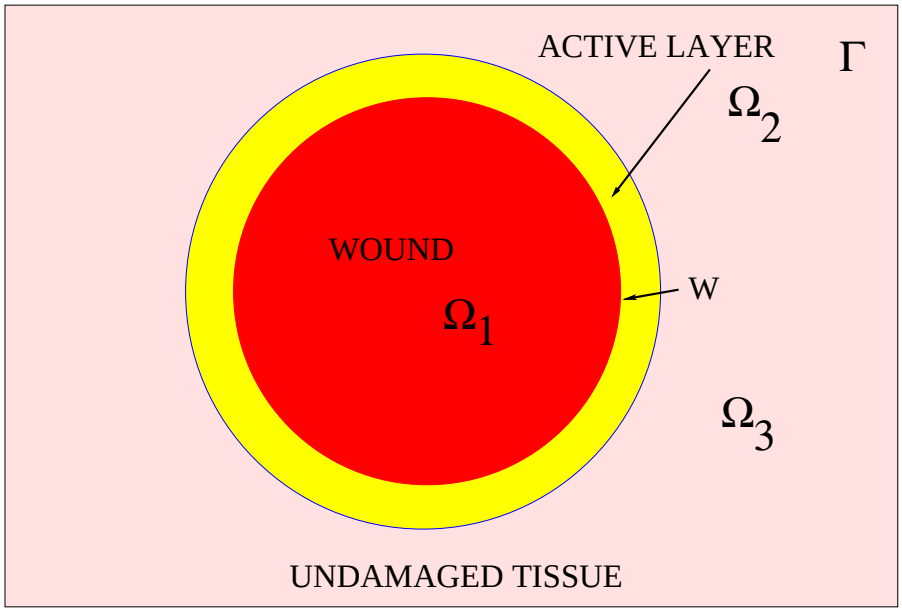

Figure 2: The geometry of a circular wound.

1999], we state the fundamental equation for the transport, production and decay of the growth factor concentration, c, which reads as:

$$\frac{\partial c}{\partial t} - D \text{ div grad } c + \lambda c = P\mathbf{1}_{\Omega_2}(\mathbf{x}), \text{ for } (t,\mathbf{x}) \in (0,T] \times \Omega, \tag{1}$$

$$\frac{\partial c}{\partial n} = 0, \text{ for } (t,\mathbf{x}) \in (0,T] \times \partial\Omega, \tag{2}$$

$$\text{where } \mathbf{1}_{\Omega_2}(\mathbf{x}) = \begin{cases} 1, & \text{for } \mathbf{x} \in \Omega_2 \\ 0, & \text{for } \mathbf{x} \in \Omega_1 \cup \Omega_3 \end{cases}, \tag{3}$$

As the initial condition, we have

$$c(0,\mathbf{x}) = 0, \text{ for } \mathbf{x} \in \Omega. \tag{4}$$

In the equations D, P and λ denote the constant diffusion coefficient, production rate constant and the decay coefficient of the growth factor. These constants are non-negative in our parabolic PDE. The growth factor concentration, c, is to be determined. Further, the second and third term in equation (1) respectively account for growth factor transport and growth factor loss. The right-hand side of equation (1) accounts for the production of the growth factor. Equation (2) represents the boundary condition and the step-function f accounts for the growth factor production taking place in the active layer only. We will see that if Ω_2 is closed there is an inconsistency as $D \to 0$. [Adam 1999] points out that for the derivation of a *critical size defect*, which is the smallest wound that does not heal, the time derivative in the diffusion reaction equation does not have to be taken into account.

Healing at a certain location of the wound edge implies that the inward normal component of the velocity, v_n, of the 'interface' W is positive. In the present paper we use the assumption from [Adam 1999] that the wound heals if and only if the growth factor concentration exceeds a threshold concentration $\hat{c}$, hence

$$\begin{aligned} &v_n > 0 \text{ if and only if } c(t,\mathbf{x}) \geq \hat{c} \text{ for } \mathbf{x} \in W, \\ &\text{else } v_n = 0. \end{aligned} \tag{5}$$

This implies that in order to determine whether the wound heals at a certain location on W at a certain time t, one needs to know the growth factor concentration there.

Adam considers analytic expressions for the time independent case for several geometries: planar (linear) geometry [Adam 1999], a circular wound on a spherical surface [Adam 2002], a circular wound on a planar surface [Adam 2004]. A wound in spherical symmetry is considered in terms of analytic expressions by Arnold [Arnold 2001].

As it has been motivated in [Vermolen et al 2006], we assume that the healing rate is proportional to the local curvature of the wound. Hence, in agreement with equation (5), the velocity component in the outward (from Ω_1, that is the wound) normal direction is given by

$$v_n = -(\alpha + \beta\kappa)w(c(t, \mathbf{x}) - \hat{c}), \text{ for } \mathbf{x} \in W, \tag{6}$$

where κ is the local curvature and $\alpha, \beta > 0$ are considered as non-negative constants, prohibiting growth of the wound if $\kappa \geq 0$. Further, the function $w(s)$ falls within the class of heaviside functions, that is $w(s) \in H(s)$, where $H(.)$ represents the family of heaviside functions, for which we have

$$H : s \rightarrow \begin{cases} 0, & \text{if } s < 0, \\ [0, 1], & \text{if } s = 0, \\ 1, & \text{if } s > 0. \end{cases} \tag{7}$$

Some models with the same principles as the active layer and / or the discontinuous switch condition can be found in [Hogea et al. 2006], [Adam 1987], [Adam 1999], [Gao and Bu 2003], [Shymko and Glass 1976], [Britton and Chaplain 1993].

3 ANALYSIS OF THE STATE PRIOR TO INTERFACE MOTION

In this section, we assume that $D,\ \lambda,\ P > 0$. First, we consider the integral of the growth factor concentration, which is the 'total mass' of the growth factor, defined by $m(t) := \int_\Omega c\, d\Omega$. Due to the initial condition for the concentration, the total mass is zero initially, that is $\int_\Omega c(x, y, 0)\, d\Omega = 0$. Integration of the PDE (1) over Ω, gives with the use of the boundary condition

$$\frac{dm}{dt} = -\lambda m + P \int_{\Omega_2} d\Omega.$$

We define $A_\delta := \int_{\Omega_2} d\Omega$, which is constant in time since the wound does not move yet, then the only solution of this ordinary differential equation is given by

$$m(t) = \frac{PA_\delta}{\lambda}(1 - e^{-\lambda t}) > 0 \text{ for } t > 0. \tag{8}$$

This implies that $c > 0$ for $t > 0$ in (part of) Ω at least. In this section, we will see further that healing sets in after some time that is needed for the concentration at the wound edge to reach the threshold value. The time at which healing sets in, is referred as the *waiting time*. In this section, a bound for the waiting time is given. In order to analyze the waiting time, the PDE for the epidermic growth factor has to be solved. The solution can be obtained using discretization techniques, such as the Finite Element Method. In this section, analytic expressions as fundamental solutions for the growth factor concentration are also derived for planar and circular wounds. These expressions are contractive semigroups and demonstrate the existence of a solution for elementary geometries. For generic wound geometries, it is no longer possible to give analytic expressions, and for this purpose a bound for the waiting time is derived. We would like to address the existence of solutions for more generic geometries in a later study.

3.1 Existence, uniqueness and convergence to steady-state

By the use of fundamental solutions, see for instance [Friedman 1964], [Pao 1992], [Ito 1992], applied to the parabolic differential equation, existence of solutions can be demonstrated. An important matter is that the analysis in the aforementioned works is carried out under certain smoothness requirements: f is assumed to be Hölder continuous in space and time. In our application, f does not satisfy this requirement, hence classical smooth solutions do not exist. Therefore, for the analysis, we will limit our attention to a weak form of the partial differential equation:

Definition 3.1.1 *The weak form of equations (1–4) is given by:*

$$\begin{cases} \text{Find } c \in V, \text{ subject to } c(0,\mathbf{x}) = 0 \text{ in } \overline{\Omega}, \text{ such that} \\ \left(\dfrac{\partial c}{\partial t}, \phi\right) + a(c,\phi) = (Pf(\mathbf{x}), \phi), \qquad \forall \phi \in H^1(\Omega), \end{cases} \tag{9}$$

with

$$(u,v) := \int_\Omega uv \; d\Omega, \tag{10}$$

as the inner product of the functions u and v over Ω, and the bilinear form $a(u,v)$ defined by

$$a(u,v) := \int_\Omega \{D\nabla u \cdot \nabla v + \lambda uv\} \; d\Omega. \tag{11}$$

The function space V in which we look for the solution is defined by

$$V := C^1[(0,T]; H^1(\Omega)] \cap C^0[[0,T]; H^1(\Omega)].$$

The existence and uniqueness of a steady-state solution in $H^1(\Omega)$ can be demonstrated in a straightforward way. Formally, we have

Theorem 3.1.1 *Let $\frac{\partial c_E}{\partial t} = 0$ in Ω be the steady-state solution of equation (9), if $D, \lambda > 0$, then c_E uniquely exists in $H^1(\Omega)$.*

A similar theorem was demonstrated by [Britton and Chaplain 1993] for a slightly different problem with a classical solution with respect to smoothness.

Proof of Theorem 3.1.1

The steady-state version of equation (9) is given by

$$a(c_E, \phi) = (P\mathbf{1}_{\Omega_2}, \phi) \qquad \forall \phi \in H^1(\Omega), \tag{12}$$

with inner product and bilinear form defined in (10) and (11), respectively. It is straightforward to demonstrate that the bilinear form is symmetric (and hence continuous due to Schwarz inequality). Further, we get

$$a(u,u) = \int_\Omega \left\{D||\nabla u||^2 + \lambda u^2\right\} d\Omega \geq \lambda \int_\Omega u^2 d\Omega =: \lambda ||u||_0^2,$$

and hence the bilinear form is coercive. Subsequently, we show that $(P\mathbf{1}_{\Omega_2}, \phi)$ is bounded:

$$|(P\mathbf{1}_{\Omega_2}, \phi)| \leq ||P \cdot \mathbf{1}_{\Omega_2}||_0 \cdot ||\phi||_0 = P \cdot (\text{meas.}\Omega_2) \cdot ||\phi||_0 \leq$$

$$P \cdot (\text{meas.}\Omega_2) \cdot \{||\phi||_0 + ||\nabla\phi||_0\} =: P \cdot (\text{meas.}\Omega_2) \cdot ||\phi||_1.$$

The first step follows from the application of Cauchy-Schwarz's inequality. In the above inequality, we define meas.$\Omega := \int_\Omega d\Omega$, which gives an area if $\Omega \subset \mathbb{R}^2$ and the norm $||\phi||_1 := ||\phi||_0 + ||\nabla\phi||_0$.

The right hand side is bounded since P and meas.Ω_2 are bounded and $\phi \in H^1(\Omega)$. Hence all the requirements of Lax-Milgram's Theorem, see for instance [Kreyszig 1989], are satisfied. Herewith, application of the Lax-Milgram Theorem, gives that the solution exists in $H^1(\Omega)$ uniquely. □

Besides to the existence and uniqueness of a steady-state solution, one can prove that there is at most one solution in the sense of Definition 3.1.1 and that this solution converges to the steady-state solution c_E. This is formalized in:

Theorem 3.1.2 *For $D, \lambda > 0$, there exists at most one solution in the sense of Definition 3.1.1 and this solution converges to the steady-state solution c_E as $t \to \infty$, that is $\lim_{t\to\infty} c(t, \mathbf{x}) = c_E(\mathbf{x})$.*

Proof of Theorem 3.1.2

First we deal with uniqueness. Suppose there are two solutions c_1 and c_2 in the sense of Definition 3.1.1. Then, $v := c_2 - c_1$ satisfies

$$v \in V \text{ such that } \int_\Omega \frac{\partial v}{\partial t}\phi d\Omega = -\int_\Omega \{D\nabla v \cdot \nabla\phi + \lambda v\phi\}\, d\Omega, \text{ for all } \phi \in H^1(\Omega). \tag{13}$$

Take $\phi = v$, and use $v(0, \mathbf{x}) = 0$ in Ω, then

$$\frac{1}{2}\int_\Omega v^2 d\Omega = -\int_0^t \left\{ \int_\Omega \left(D||\nabla v||^2 + \lambda v^2 \right) d\Omega \right\} ds \le -\lambda \int_0^t \left\{ \int_\Omega v^2 d\Omega \right\} ds.$$

Suppose that $v(\hat{t}, \hat{\mathbf{x}}) \neq 0$ for a $(\hat{t}, \hat{\mathbf{x}}) \in (0, T) \times \Omega$, then by continuity in space and time, there is a ball $B_\varepsilon = \left\{ (t, \mathbf{x}) \in (0, T) \times \Omega : |t - \hat{t}| < \varepsilon,\ ||\mathbf{x} - \hat{\mathbf{x}}|| < \varepsilon \right\}$ such that $v(t, \mathbf{x}) \neq 0$ for $(t, \mathbf{x}) \in B_\varepsilon$. Hence the integrand is strictly positive and implies that $\int_\Omega v^2 d\Omega < 0$, by which we arrive at a contradiction. Hence, $v = 0$ on Ω for $t > 0$ and this implies that there is at most one solution.

Let us note that, after use of coercivity, one could alternatively have applied Grönwall's Lemma to

$$\frac{1}{2}\frac{d}{dt}||v||_0^2 + \lambda||v||_0^2 \le 0 = \frac{1}{2}\frac{d}{dt}||v||_0^2 + a(v, v),$$

with $||v(0, \mathbf{x})||_0^2 = 0$, which implies $||v||_0^2 = 0$ for $t > 0$, and hence $v(t, \mathbf{x}) = 0$ a.e. in Ω. Since we limit our solutions in the class V, $v = 0$ in Ω for $t > 0$ by necessity.

Next, we deal with the convergence to the steady-state solution. Subtraction of (12) from (9) and defining $v := c - c_E$ in Ω, gives

$$\int_\Omega \frac{\partial v}{\partial t}\phi d\Omega = -D\int_\Omega \nabla v \cdot \nabla\phi d\Omega - \lambda \int_\Omega v\phi d\Omega, \text{ for all } \phi \in H^1(\Omega).$$

After choosing $\phi = v$, and applying Friedrich's inequality, we get

$$\frac{d}{dt}\int_\Omega v^2 d\Omega = -D\int_\Omega ||\nabla v||^2 d\Omega - \lambda \int_\Omega v^2 d\Omega \le -\lambda \int_\Omega v^2 d\Omega.$$

Grönwall's Lemma gives

$$\int_\Omega v^2 d\Omega \le e^{-\lambda t}\int_\Omega v^2(0, \mathbf{x}) d\Omega,$$

where $v(0, \mathbf{x}) = -c_E(\mathbf{x})$, and hence $\lim_{t\to\infty} v(t, \mathbf{x}) = 0$ a.e. in Ω. Since $v \in H^1(\Omega)$, it follows that $\lim_{t\to\infty} c(t, \mathbf{x}) = c_E(\mathbf{x})$ in Ω. □

Theorem 3.1.3 *There exists an interval $t \in (0, T)$, with $T > 0$, in which equations (1–4) have a solution in V (in the sense of Definition 3.1.1).*

Proof of Theorem 3.1.3

We already demonstrated that if a solution to equations (1–4) exists, then it converges to the steady-state solution $c_E(\mathbf{x}) \in H^1(\Omega)$. Furthermore, the solution is continuous in t, and since $c = 0$ at $t = 0$, then for any $\hat{c}$ there exists a minimal T during which $c < \hat{c}$ on W. Next, we subtract the steady-state equation (12) from equation (9) and define $u(t, \mathbf{x}) := c(t, \mathbf{x}) - c_E(\mathbf{x})$, to obtain

$$\text{Find } u \in V \text{ such that } (u_t, \phi) + a(u, \phi) = 0, \text{ subject to } u(0, \mathbf{x}) = -c_E(\mathbf{x}).$$

This problem has a classical solution. Since $c = u + c_E$ in which $c_E \in H^1(\Omega)$, this implies that c is not classical, but only exists in V. □

Of course Theorems 3.1.3 and 3.1.2 are related.

3.2 Fundamental solutions

In this section, we show a procedure to construct analytic solutions. These analytic solutions are also useful for a validation of finite element solutions. Since the solutions, we are interested in, are continuous in t, there is an interval $(0, T)$ in which $c < \hat{c}$. The solutions that we construct are valid within this time interval. The first type of solution lies in V, and its construction is inspired by the proof of the existence theorem (Theorem 3.1.3). The second type is constructed using classical solutions from a decomposition of the discontinuous source term. Since the solution in V is classical almost everywhere in Ω (except on $\delta\Omega_2$), the solutions are the same almost everywhere in the limit ($k \to \infty$). The second solution, not being in V, but in convergence is reached. In the analytic solution of this section, we consider the case in which the wound edge concentration is below the threshold concentration $\hat{c}$. The time, at which the wound edge concentration equals $\hat{c}$, is referred to as the *waiting time*, we denote this time by τ.

3.2.1 Construction of solutions in V

We let the construction of solutions in V be inspired by the proof of the existence Theorem 3.1.3. In this section, we will sketch the general idea, and apply this to a planar case.

Suppose, that for any geometry we found a steady-state solution $c_E \in H^1(\Omega)$, then setting $u(t, \mathbf{x}) := c(t, \mathbf{x}) - c_E(\mathbf{x})$, we have the following problem, which has a classical solution

$$\frac{\partial u}{\partial t} = D\Delta u - \lambda u, \text{ in } (0, t) \times \Omega.$$

Subject to $u(0, \mathbf{x}) = -c_E(\mathbf{x})$ and homogeneous Neumann boundary conditions. Let $\phi_k(\mathbf{x})$ be the orthonormal eigenfunctions of the differential operator $-\Delta + \lambda I(.)$, then the solution of the above equation is represented as

$$u(t, \mathbf{x}) = \sum_{k=0}^{\infty} u_k(t)\phi_k(\mathbf{x}).$$

Let $\mu_k^2 = \lambda + D\lambda_k^2$ be the eigenvalues of the operator $-\Delta + \lambda I$ (note that λ_k^2 represent the eigenvalues of $-\Delta$) corresponding to $\phi_k(\mathbf{x})$, then one obtains for $u_k(t)$

$$u_k(t) = u_k(0)e^{-\mu_k^2 t},$$

where $u_k(0)$ follows from the initial condition, which gives

$$u_k(0) = -\int_{\Omega} c_E(\overline{\mathbf{x}})\phi_k(\overline{\mathbf{x}})d\Omega.$$

The overbar on $\overline{\mathbf{x}}$ is used to indicate that this is the variable over which we integrate. Hence, we get for the analytic solution for u

$$u(t, \mathbf{x}) = -\int_{\Omega} G(t, 0, \mathbf{x}, \overline{\mathbf{x}})c_E(\overline{\mathbf{x}})d\Omega,$$

where $\overline{\mathbf{x}}$ is the spatial variable over which we integrate, and $G(t, s, \mathbf{x}, \overline{\mathbf{x}})$ is the Green's function defined by

$$G(t, s, \mathbf{x}, \overline{\mathbf{x}}) := \sum_{k=0}^{\infty} e^{\mu_k^2 (s-t)} \phi_k(\mathbf{x}) \phi_k(\overline{\mathbf{x}}).$$

Since $G(t, 0, \mathbf{x}, \overline{\mathbf{x}})$ is infinitely differentiable with uniformly bounded derivatives on $0, T) \times \Omega$, we have $u \in C^{\infty}((0, T) \times \Omega)$. From direct substitution, it is shown that u solves the homogeneous PDE and homogeneous boundary condition, since G does.

Next, we consider

$$\left|u(t, \mathbf{x}) + c_E(\mathbf{x}^0)\right| = \left|c_E(\mathbf{x}^0) - \int_{\Omega} c_E(\overline{\mathbf{x}}) G(t, 0, \mathbf{x}, \overline{\mathbf{x}}) d\Omega\right| =$$

$$\left|\int_{\Omega} (G(0, 0, \mathbf{x}^0, \overline{\mathbf{x}}) - G(t, 0, \mathbf{x}, \overline{\mathbf{x}})) c_E(\overline{\mathbf{x}}) d\Omega\right| \leq$$

$$\int_{\Omega} \left|G(0, 0, \mathbf{x}^0, \overline{\mathbf{x}}) - G(t, 0, \mathbf{x}, \overline{\mathbf{x}})\right| c_E(\overline{\mathbf{x}}) d\Omega \to 0 \text{ as } (t, \mathbf{x}) \to (0, \mathbf{x}^0).$$

The last step follows from G being (Lipschitz) continuous both in t and $\mathbf{x}$. Hence the initial condition is satisfied. We used similar principles as in [Evans 1998] to demonstrate that u solves the homogeneous PDE, boundary condition and initial condition.

Subsequently, the generalized solution $c(t, \mathbf{x}) \in V$ (since $c_E \in H^1(\Omega)$) is obtained by

$$\begin{aligned} c(t, \mathbf{x}) = c_E(\mathbf{x}) + u(t, \mathbf{x}) = c_E(\mathbf{x}) - \int_{\Omega} G(t, 0, \mathbf{x}, \overline{\mathbf{x}}) c_E(\overline{\mathbf{x}}) d\Omega = \\ \int_{\Omega} \left\{c_E(\overline{\mathbf{x}}) \left(\delta(\mathbf{x} - \overline{\mathbf{x}}) - G(t, 0, \mathbf{x}, \overline{\mathbf{x}})\right)\right\} d\Omega. \end{aligned} \tag{14}$$

The above solution is valid as long as $c < \hat{c}$ on W. Since the solution is continuous in t, there exists a $T > 0$ for which the above expression is valid. Formally, this is summarized in the following assertion:

Theorem 3.2.1 *Let $c(t, \mathbf{x})$ be given by equation (14), then $c \in V$, and*

$$\frac{\partial c}{\partial t} - D\Delta c + \lambda c = P\mathbf{1}_{\Omega_2}, \text{ for } t \in (0, t), \ \mathbf{x} \in \Omega,$$

and $\lim_{(t, \mathbf{x}) \to (0, \mathbf{x}^0)} c(t, \mathbf{x}) = 0$ for each point $\mathbf{x}^0 \in \Omega$.

Example 3.2.1 *For a planar wound, we have $\mu_k = k\pi/L$ and $\phi_k(x) = \sqrt{2/L}\cos(\mu_k x)$ for $k \in \mathbb{N} \setminus \{0\}$ and $\phi_0(x) = \sqrt{1/L}$. Further, following [Adam 1999] we have for $c_E(x)$:*

$$c_E(x) = \begin{cases} a_1 e^{\sqrt{\frac{\lambda}{D}} x} + a_2 e^{-\sqrt{\frac{\lambda}{D}} x}, & 0 < x < R, \\ a_3 e^{\sqrt{\frac{\lambda}{D}} x} + a_4 e^{-\sqrt{\frac{\lambda}{D}} x} + \frac{PD}{L}, & R < x < R + \delta, \\ a_5 e^{\sqrt{\frac{\lambda}{D}} x} + a_6 e^{-\sqrt{\frac{\lambda}{D}} x}, & R + \delta < x < L. \end{cases}$$

The boundary conditions and continuity of c_E and c'_E define the values for $a_1, \ldots, a_6$ uniquely.

$$a_1 = \frac{PD\left(e^{\sqrt{\frac{\lambda}{D}}(2L-R-\delta)} + e^{\sqrt{\frac{\lambda}{D}}R} - e^{\sqrt{\frac{\lambda}{D}}(R+\delta)} - e^{\sqrt{\frac{\lambda}{D}}(2L-R)}\right)}{2\lambda\left(e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)} - e^{\sqrt{\frac{\lambda}{D}}(2L-R-\delta)}\right)} e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)},$$

$$a_2 = a_1,$$

$$a_3 = \frac{PD\left(-e^{\sqrt{\frac{\lambda}{D}}(2L-R-\delta)} - e^{\sqrt{\frac{\lambda}{D}}R} + e^{\sqrt{\frac{\lambda}{D}}(R+\delta)} + e^{-\sqrt{\frac{\lambda}{D}}R}\right)}{2\lambda\left(-e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)} + e^{\sqrt{\frac{\lambda}{D}}(2L-R-\delta)}\right)} e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)},$$

$$a_4 = \frac{PD\left(-e^{\sqrt{\frac{\lambda}{D}}(2L-R-\delta)} + e^{\sqrt{\frac{\lambda}{D}}(2L-R)} + e^{\sqrt{\frac{\lambda}{D}}(R+\delta)} - e^{-\sqrt{\frac{\lambda}{D}}(2L+R)}\right)}{2\lambda\left(-e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)} + e^{\sqrt{\frac{\lambda}{D}}(2L-R-\delta)}\right)} e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)},$$

$$a_5 = \frac{PD\left(e^{\sqrt{\frac{\lambda}{D}}R} - e^{-\sqrt{\frac{\lambda}{D}}R} - e^{\sqrt{\frac{\lambda}{D}}(R+\delta)} + e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)}\right)}{2\lambda\left(e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)} - e^{\sqrt{\frac{\lambda}{D}}(2L-R-\delta)}\right)} e^{-\sqrt{\frac{\lambda}{D}}(R+\delta)},$$

$$a_6 = a_5 e^{2\sqrt{\frac{\lambda}{D}}L}.$$

Using these constants, one constructs the steady-state solution $c_E(x)$. Note that c_E is not classical. The solution for $u := c - c_E$ is reconstructed from

$$u(t,x) = \sum_{k=0}^{\infty} u_k(t)\phi_k(x), \text{ with } u(0,x) = -c_E(x) = \sum_{k=0}^{\infty} u_k(0)\phi_k(x).$$

The $u_k(0)$ and $u)_k$ follow from the orthonormality and substitution into the PDE

$$u_k(0) = -\int_0^L c_E(x)\phi_k(x)dx, \text{ and } u_k(t) = u_k(0)e^{-(\lambda + D\lambda_k^2)t}.$$

Herewith the solution $u(t,x)$ and $c(t,x)$ are reconstructed.

3.2.2 Constructions of 'classical' solutions

The fundamental solutions shown in the present section are valid in Ω, except on $\delta\Omega_2$, on which the reaction term with the indicator function is discontinuous. This is a consequence of Fourier's Theorem which says that at a discontinuity of a piecewise continuous function, the series gives the average of the values obtained by passing the limit over space to the discontinuity from both sides. Therefore, the better alternative is to construct the solution in a way that is inspired by the proof of Theorem 3.1.3 as been presented in the previous section.

Hence, the source function $P\mathbf{1}_{\Omega_2(t)}$, which is piecewise continuous, can be written as a unique linear combination of the eigenfunctions, say

$$P\mathbf{1}_{\Omega_2} = \sum_{k=0}^{\infty} b_k\phi_k(\mathbf{x}), \qquad \text{a.e. in } \Omega,$$

where the functions $\phi_k(\mathbf{x})$ represent the eigenfunctions of the operator $-\Delta + \lambda I$. Due to completeness and linear independence of the eigenfunctions of the self-adjoint differential operator, the solution u can be written as an eigenfunction expansion

$$c(t,\mathbf{x}) = \sum_{k=0}^{\infty} c_k(t)\phi_k(\mathbf{x}).$$

Substitution into the weak differential form (see Definition 3.1.1), gives

$$c_k' + \mu_k^2 c_k = (P\mathbf{1}_{\Omega_2}, \phi_k),$$

where the eigenfunctions ϕ_k are orthonormal. This implies that the solution is given by

$$c_k = P \int_0^t (\mathbf{1}_{\Omega_2}, \phi_k) e^{\mu_k^2 (s-t)} ds.$$

Hence the solution is formally given by

$$c(t, \mathbf{x}) = P \sum_{k=0}^{\infty} \phi_k(\mathbf{x}) \int_0^t (\mathbf{1}_{\Omega_2}, \phi_k) e^{\mu_k^2 (s-t)} \, ds.$$

We define the Green's function by

$$G(t, s, \mathbf{x}, \overline{\mathbf{x}}) := \sum_{k=0}^{\infty} e^{\mu_k^2 (s-t)} \phi_k(\mathbf{x}) \phi_k(\overline{\mathbf{x}}),$$

to write the solution as

$$c(t, \mathbf{x}) = P \int_0^t \int_{\Omega} \mathbf{1}_{\Omega_2(\overline{\mathbf{x}})} G(t, s, \mathbf{x}, \overline{\mathbf{x}}) \, d\Omega \, ds.$$

where $\overline{\mathbf{x}}$ is the spatial variable over which one integrates. The above equation represents the general solution as long as $t \in (0, \tau)$. Using this solution, one can demonstrate by substitution into the PDE and realizing that the Green's functions G satisfy the PDE that

$$c_t - D\Delta c + \lambda c = P \int_{\Omega} \mathbf{1}_{\Omega_2}(\overline{\mathbf{x}}) G(t, t, \mathbf{x}, \overline{\mathbf{x}}) d\Omega =$$

$$P \sum_{k=0}^{\infty} \phi_k(\mathbf{x}) \int_{\Omega_2} \phi_k(\overline{\mathbf{x}}) d\Omega = \sum_{k=0}^{\infty} b_k \phi_k(\mathbf{x}).$$

Using Fourier's Theorem, we get

$$c_t - D\Delta c + \lambda c = \begin{cases} 0, & \mathbf{x} \in \Omega \setminus \overline{\Omega}_2, \\ P, & \mathbf{x} \in \Omega_2, \\ P/2, & \mathbf{x} \in \partial\Omega_2. \end{cases} \tag{15}$$

On $\partial\Omega_2$ the situation differs. To illustrate this solution, we consider a planar and a circular example.

Example 3.2.2 *It can be shown that fundamental solutions to the homogeneous partial differential equation can be written as* $exp(-(\lambda + \frac{k^2\pi^2}{L^2} D)t) \cos(\frac{k\pi x}{L})$, *where* $\mu_k = k\pi/L$. *The normalized eigenfunctions are given by*

$$\phi_k(x) = \sqrt{2/L} \cos(k\pi x/L), \text{ for } k \in \mathbb{N} \setminus \{0\}, \text{ and } \phi_0(x) = 1/\sqrt{L}. \tag{16}$$

The right-hand side is written as

$$f(x) = \sum_{k=0}^{\infty} \gamma_k \phi_k(x), \text{ a.e. in } \Omega, \tag{17}$$

where

$$\gamma_k = \int_0^L f(x)\phi_k(x)dx = P\int_R^{R+\delta} \phi_k(x)dx = \frac{2\sqrt{2L}P}{k\pi}\sin(\frac{k\pi\delta}{2L})\cos(\frac{k\pi(2R+\delta)}{2L}),\ \textit{for } k \in \mathbb{N}\setminus\{0\}.$$

$$\gamma_0 = \frac{P\delta}{\sqrt{L}}. \tag{18}$$

These expressions are substituted into the nonhomogeneous PDE, we realize that the eigenfunctions are an orthonormal set, then this yields

$$\begin{aligned} c_k' + (\mu_k^2 D + \lambda)c_k &= \gamma_k, \\ c_k(0) &= 0. \end{aligned} \tag{19}$$

Using $\mu_k = k\pi/L$, the solution of the above equation is given by

$$c_k(t) = \frac{\gamma_k}{\lambda + \frac{k^2\pi^2 D}{L^2}}\left(1 - \exp(-(\frac{k^2\pi^2 D}{L^2} + \lambda)t)\right), k \in \mathbb{N}. \tag{20}$$

This implies that the solution is given by

$$\begin{aligned} c(t,x) = &\frac{P\delta}{\lambda L}\left(1 - \exp(-\lambda t)\right) + \\ &\frac{4P}{\pi}\sum_{k=1}^{\infty}\frac{\sin(\frac{k\pi\delta}{2L})}{k}\frac{\cos(\frac{k\pi(2R+\delta)}{2L})}{\lambda + \frac{k^2\pi^2 D}{L^2}}\left(1 - \exp(-(\lambda + \frac{k^2\pi^2 D}{L^2})t)\right)\cos(\frac{k\pi x}{L}). \end{aligned} \tag{21}$$

The above equation shows that if the active layer thickness is small, the concentration depends linearly on the thickness.

Example 3.2.3 *Here we consider a circular case (axially symmetric) in which polar coordinates are used. First, we consider the homogeneous partial differential equation on which we apply separation of variables and consider solutions in the form of $c(t,r) = \rho(r)T(t)$, this implies, after some re-arrangement*

$$\frac{T'}{DT} + \lambda = \frac{1}{r\rho}\left[r\rho\right]' = -\mu_k^2. \tag{22}$$

The right-hand side constant must be nonnegative in order to have nontrivial solutions. From this, one gets the following ordinary equation for T

$$T' + (\lambda + \mu_k^2 D)T = 0, \tag{23}$$

and eigenvalue problem for $\rho(r)$, in which we determine μ_k such that

$$\left[r\rho'\right]' + \mu_k^2 r\rho = 0, \qquad \rho'(0) = \rho'(L) = 0, \tag{24}$$

for nonzero $\rho(r)$. The above differential equation admits solutions of the form

$$\rho(r) = c_1 J_0(\mu_k r) + c_2 Y_0(\mu_k r), \tag{25}$$

where J_0 and Y_0 are the Bessel- and Weber-Bessel functions of zeroth order respectively. Since $\lim_{r\to 0^+}\rho(r)$ must be finite, and since $\lim_{r\to 0^+} Y_0(\mu_k r)$ does not exist, we have $c_2 = 0$, hence the solutions are given by

$$\rho(r) = c_1 J_0(\mu_k r). \tag{26}$$

By some manipulations with the Bessel functions, we arrive at the following set of orthonormal eigenfunctions:

$$\phi_k(r) = \frac{\sqrt{2}}{L}\frac{J_0(\mu_k r)}{J_0(\mu_k L)},\ \textit{for } k \in \mathbb{N}. \tag{27}$$

Next, we deal with the non-homogeneous partial differential equation. For this reason, the right-hand side function $f(r)$ is expanded into a linear combination of the above orthonormal eigenfunctions:

$$f(r) = \sum_{k=0}^{\infty} \gamma_k \phi_k(r). \tag{28}$$

Using the orthonormality property, we get

$$\gamma_k = P\int_0^L \phi_k(r) r dr = P\int_R^{R+\delta} \phi_k(r) r dr. \tag{29}$$

Hence

$$\gamma_k = \frac{P\sqrt{2}}{\mu_k J_0(\mu_k L) L}\left[(R+\delta)J_1(\mu_k(R+\delta)) - RJ_1(\mu_k R)\right], \tag{30}$$

and $\gamma_0 = \frac{\sqrt{2}PR\delta}{L}(1+\frac{\delta}{2R})$. For the solution of the non-homogeneous partial differential equation, we substitute

$$c(t,r) = \sum_{k=0}^{\infty} c_k(t)\phi_k(r), \tag{31}$$

to obtain

$$\begin{aligned} &c_k' + (\mu_k^2 D + \lambda)c_k = \gamma_k,\ \textit{for } t > 0,\\ &c_k(0) = 0. \end{aligned} \tag{32}$$

The solution of the above differential equation is given by

$$c_k(t) = \frac{\gamma_k}{\mu_k^2 D + \lambda}\left(1 - \exp(-(\mu_k^2 D + \lambda)t)\right). \tag{33}$$

The expressions $c_k(t)\phi_k(r)$ give the fundamental solutions to the non-homogeneous partial differential equation. The general solution is the sum of them, that is

$$\begin{aligned} c(t,r) = &\frac{2PR\delta(1+\frac{\delta}{2R})}{\lambda L^2}(1-\exp(-\lambda t)) + \\ &\frac{2P}{L^2}\sum_{k=1}^{\infty}\frac{(R+\delta)J_1(\mu_k(R+\delta)) - RJ_1(\mu_k R)}{\mu_k J_0^2(\mu_k L)(\mu_k^2 D+\lambda)} J_0(\mu_k r)\left(1-\exp(-(\mu_k^2 D+\lambda)t)\right). \end{aligned} \tag{34}$$

Here the expressions for γ_k have been used. With the eigenvalue equation $J_1(\mu_k L) = 0$, the above equation gives the concentration of the growth factor. In Figure 3 we give several plots of the growth factor concentration profile at a certain time using various numbers of basis functions. It can be seen that convergence, especially near the Neumann boundaries, is slow and that the use of a large number of basis functions is necessary. Further, a comparison to a finite element solution is shown in Figure 4.

3.3 Generic analysis of the waiting time

Since for generic geometries, the waiting times are hard to determine, we derive a bound for the waiting time. Further, we consider the solution c in Ω for a time span $(0,T)$, where $T > 0$ is a finite time. We emphasize that the analysis in this section applies for the state prior to healing, that is $t < \tau$, hence the wound edge does not move yet. We will demonstrate the following theorems:

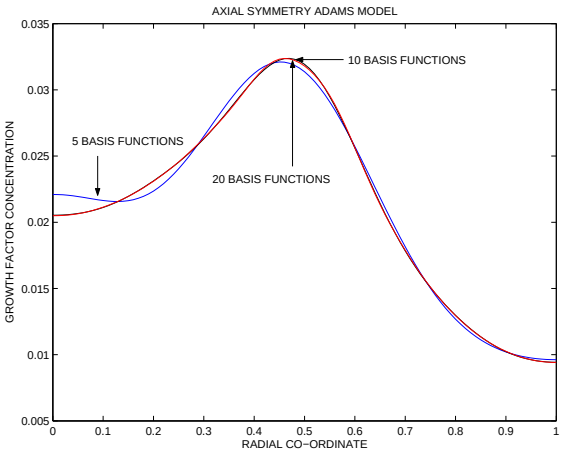

Figure 3: The analytic solution for circular wounds using various numbers of basis functions.

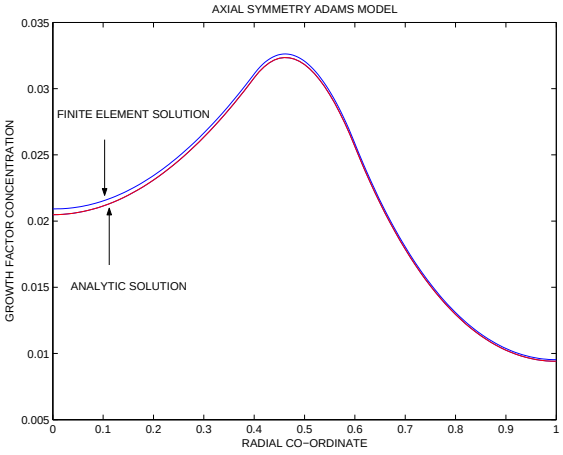

Figure 4: A comparison between the analytic solution and the numerical solution.

Theorem 3.3.1 *Let equations (1–4) be satisfied, with $D, \lambda > 0$, and A_δ and A_Ω be the non-zero area of the active layer and domain of computation respectively, then,*

1. *For the wound edge concentration, $c(t)$, we have*

$$\begin{aligned} c(t) &= \frac{PA_\delta}{\lambda A_\Omega}(1 - exp(-\lambda t)), && \text{as } D \to \infty \\ c(t) &= \frac{P}{\lambda}(1 - exp(-\lambda t)), && \text{if } D = 0 \text{ and } \Omega_2 \text{ is closed,} \\ c(t) &= 0, && \text{if } D = 0 \text{ and } \Omega_2 \text{ is open.} \end{aligned} \tag{35}$$

2. *Furthermore, there exists a waiting time, τ, before healing sets in, and this waiting time has the following limits*

$$\begin{aligned} &\lim_{D\to 0} \tau = \frac{1}{\lambda} ln\left(\frac{1}{1 - \frac{\hat{c}\lambda}{P}}\right), \text{ if } \Omega_2 \text{ is closed;} \\ &\lim_{D\to \infty} \tau = \frac{1}{\lambda} ln\left(\frac{1}{1 - \frac{\hat{c}\lambda A_\delta}{PA_\Omega}}\right), \text{ if } \quad \frac{\hat{c}\lambda A_\delta}{PA_\Omega} < 1. \end{aligned} \tag{36}$$

Theorem 3.3.2 *Let equations (1–4) be satisfied, and $\Omega_2 \subset \Omega$, with meas.$\Omega_2 \neq 0$, then $c(t, \mathbf{x}) > 0$ for $(t, \mathbf{x}) \in \overline{\Omega} \times (0, T)$.*

Theorem 3.3.3 *Let c_1 and c_2 satisfy equations (1–4) for the same wound edge position and outer bound position (*i.e. *for the same wound) with active layers respectively given by Ω_2^1 and Ω_2^2 and let the respective waiting times be given by τ_1 and τ_2, then*

$$\Omega_2^1 \subset \Omega_2^2 \Rightarrow c_1 < c_2 \text{ in } \Omega \text{ and } \tau_2 < \tau_1.$$

[Britton and Chaplain 1993] proved two theorems similar to Theorems 3.3.2 and 3.3.3 for a slightly different problem with a classical smooth solution for one spatial coordinate and under the conditions of the parabolic comparison Theorem.

Theorem 3.3.4 *Let equations (1–4) be satisfied. Then the growth factor concentration $c(x, y, t)$, and waiting time, τ, change continuously with the extension of active layer.*

Theorem 3.3.5 *Let equations (1–4) be satisfied, and $\Omega_2 \subset \Omega$, where meas.$\Omega_2 \neq 0$, then we have*

$$0 < c(t, \mathbf{x}) < \frac{P}{\lambda}(1 - exp(-\lambda t)), \text{ for } (t, \mathbf{x}) \in (0, T) \times \Omega, \tag{37}$$

and herewith

$$0 < c(t) < \frac{P}{\lambda}(1 - exp(-\lambda t)), \tag{38}$$

at the wound edge W. Hence the waiting time is bounded from below by

$$\tau > \frac{1}{\lambda} ln\left(\frac{1}{1 - \frac{\hat{c}\lambda}{P}}\right). \tag{39}$$

Note that the above theorem implies the existence of a non-zero waiting time before healing takes place. In the next section, these assertions will be proved.

3.3.1 Proofs of theorems

Before we prove the theorems of the previous subsections, we establish the following lemma:

Lemma 3.3.1 *Let equations (1–4) be satisfied, then for weak solutions $c \in V$ there exists a function $\overline{c}(t)$, for which*

$$\lim_{D\to\infty} c(t,\mathbf{x}) = \overline{c}(t). \tag{40}$$

Proof of Lemma 3.3.1

Since $f \notin C^0(\Omega)$, we consider solutions in the sense of Definition 3.1.1. After redefining

$$\overline{T} = \frac{Dt}{L^2}, \qquad \mathbf{x} = \frac{\mathbf{x}}{L},$$

then we obtain a scaled version of the solutions in the sense of Definition 3.1.1:

$$\begin{cases} \text{Find } c \in V, \text{ subject to } c(0,\overline{\mathbf{x}}) = 0, \text{ such that} \\ \\ \displaystyle\int_\Omega \frac{\partial c}{\partial \overline{T}}\phi d\Omega = -\int_\Omega \nabla c\cdot\nabla\phi d\Omega + \frac{PL^2}{D}\int_{\Omega_2}\phi d\Omega - \frac{\lambda L^2}{D}\int_\Omega c\phi d\Omega, \\ \\ \forall\phi \in H^1(\Omega). \end{cases} \tag{41}$$

Note that the Jacobian for the spatial co-ordinate transformation is constant and the same in all the integrals in the above expression. Furthermore, Ω formally transforms in the new co-ordinates. Since this is not relevant for the proof of Lemma 3.3.1, and to avoid confusion with the notation of the closure of Ω, we keep on using Ω as the domain. Theorems 3.1.1 and 3.1.2 imply that the steady-state solution is uniquely defined and that the only solution converges to this steady-state in Ω. Note that as $D \to \infty$, we have $\overline{T} \to \infty$, and hence equation (41) changes into

$$c \in H^1(\Omega), \text{ such that } \quad 0 = -\int_\Omega \nabla c\cdot\nabla\phi d\Omega, \quad \forall\phi \in H^1(\Omega). \tag{42}$$

The solution of the above equation does not depend on space or on $\overline{T}$. Therefore, it may only depend on t, that is $c(\overline{T},\mathbf{x}) = \overline{c}(t)$. Hence, we demonstrated that there exists a $\overline{c}(t)$ such that

$$\lim_{D\to\infty} c(t,\mathbf{x}) = \overline{c}(t), \text{ for } \mathbf{x} \in \Omega,$$

which proves Lemma 3.3.1. □

Proof of Theorem 3.3.1:

The function $\overline{c}(t)$ from Lemma 3.3.1 is substituted into (9) to get

$$\overline{c}'(t)\int_\Omega \phi d\Omega = P\int_{\Omega_2}\phi d\Omega - \lambda\overline{c}(t)\int_\Omega \phi d\Omega, \qquad \forall\phi \in H^1(\Omega). \tag{43}$$

Take $\phi = 1$ on Ω, to get

$$\overline{c}'(t)A_\Omega = PA_\delta - \lambda\overline{c}(t)A_\Omega, \quad \overline{c}(0) = 0. \tag{44}$$

Hence, we solve

$$\begin{cases} \overline{c}'(t) + \lambda\overline{c}(t) = P\dfrac{A_\delta}{A_\Omega}, \\ \\ \overline{c}(0) = 0. \end{cases} \tag{45}$$

The exact solution of the above problem is given by

$$\overline{c}(t) = \frac{P}{\lambda}\cdot\frac{A_\delta}{A_\Omega}\cdot(1-\exp(-\lambda t)). \tag{46}$$

Herewith, part 1 of Theorem 3.3.1 has been proved for the limit case $D \to \infty$.

Note that

$$\lim_{t\to\infty} \overline{c}(t) = \frac{PA_\delta}{\lambda A_\Omega},$$

and hence for a wound to start healing at all, we require that

$$\frac{PA_\delta}{\lambda A_\Omega} \geq \hat{c}. \tag{47}$$

We will demonstrate that this is a sufficient condition for healing to start. From equation (46), it is straightforward to derive that the waiting time is given by

$$\lim_{D\to\infty} \tau = -\frac{1}{\lambda} ln\left(1 - \frac{\lambda A_\delta \hat{c}}{PA_\Omega}\right). \tag{48}$$

This proves part 2 of Theorem 3.3.1 for the limit case $D \to \infty$. Next, we consider the case $D \to 0$, where Ω_2 is closed. For $D = 0$, we have from equations (1-4)

$$c = c(t, \mathbf{x}) = \begin{cases} \frac{P}{\lambda}(1 - \exp(-\lambda t)), & \text{for } \mathbf{x} \in \Omega_2, \\ 0, & \text{for } \mathbf{x} \in \Omega \setminus \Omega_2. \end{cases} \tag{49}$$

This result can be used easily to verify that

$$\lim_{D\to 0} \tau = -\frac{1}{\lambda} ln\left(1 - \frac{\lambda \hat{c}}{P}\right). \tag{50}$$

The case that Ω_2 is open is trivial, since it implies $c(t, \mathbf{x}) = 0$ for $D = 0$ on W. Hence $c(t) = 0$ for $t > 0$. Herewith Theorem 3.3.1 has been proved. □

Proof of Theorem 3.3.2:

Rewriting equation (1) gives $D\Delta c - \lambda c - c_t = -Pf(\mathbf{x}) \leq 0$ in $(0, T) \times \Omega$. The theorem is direct consequence of combination of the maximum principle as is stated in Theorems 2.7–2.9 in [Sperb 1981], which gives:

Let u be a nonconstant solution of $Lu - u_t \geq 0$ in $(0, T) \times \Omega$, where L is uniformly elliptic, then u can attain its maximum only for $t = 0$ or on the boundary Γ (where $\frac{\partial c}{\partial n} > 0$ with n the unit normal vector out of Ω).

A proof of this assertion can be found in [Protter and Weinberger 1967]. Since, in our case the inequality is opposite and strict on a nonzero measure, there can only be a minimum at $t = 0$ or on $\partial\Omega$. At $t = 0$, we have $c = 0$ in Ω and realizing that we have homogeneous Neumann conditions, implies that $c > 0$ in $\overline{\Omega} \times (0, T)$. □

Proof of Theorem 3.3.3:

Let $v := c_2 - c_1$, then first we will demonstrate that $v > 0$. Note that meas.Ω_2^2 > meas.Ω_2^1. This gives

$$\frac{\partial v}{\partial t} = D\Delta v - \lambda v + P(\mathbf{1}_{\Omega_2^2} - \mathbf{1}_{\Omega_2^1}) = D\Delta v - \lambda v + P\mathbf{1}_{\Omega_2^2 \setminus \Omega_2^1}, \text{ in } \Omega.$$

Then, as a consequence of Theorem 3.3.2, it follows that $v > 0$ in Ω and hence $c_2 > c_1$ in Ω, hence also on W. Since τ is determined by

$$\max_{(x,y)\in W} c(\tau, \mathbf{x}) = \hat{c},$$

we have

$$\max_{\mathbf{x}\in W} c_1(\tau, \mathbf{x}_2) < \max_{\mathbf{x}\in W} c_2(\tau, \mathbf{x}_2) = \hat{c},$$

hence at the time that healing sets in on the domain with Ω_2^2 as the active layer, healing did not yet start in the domain with Ω_2^1 as the active layer. Hence $\tau_1 > \tau_2$. □

Proof of Theorem 3.3.4:

Consider the two solutions c_1 and c_2 with respective active layers Ω_2^1 and Ω_2^2, such that $\Omega_2^1 \subset \Omega_2^2$. Then, the difference $v := c_2 - c_1$ satisfies

$$\frac{\partial v}{\partial t} = D\Delta v - \lambda v + P\mathbf{1}_{\Omega_2^2 \setminus \Omega_2^1}, \text{ in } \Omega, \tag{51}$$

with a homogeneous Neumann boundary condition at $\partial\Omega$ and $v(0, \mathbf{x}) = 0$ in $\overline{\Omega}$ as initial condition. Integration over Ω gives

$$\frac{d}{dt}\int_\Omega v d\Omega = -\lambda \int_\Omega v d\Omega + P\nu,$$

where $\nu := \text{meas.}(\Omega_2^2 \setminus \Omega_2^1)$. Let $\overline{v} := (\text{meas.}\Omega)^{-1} \int_\Omega v d\Omega$, where $\text{meas.}\Omega = A_\Omega$ in $\mathbb{R}^2$, then dividing by meas.Ω gives

$$\frac{d\overline{v}}{dt} + \lambda\overline{v} = P\overline{\nu},$$

where $\overline{\nu} := (\text{meas.}\Omega)^{-1}\nu$. Herewith, we get

$$\overline{v}(t) = \frac{P}{\lambda}\overline{\nu}\left(1 - e^{-\lambda t}\right). \tag{52}$$

This implies with $v(t, \mathbf{x}) > 0$ from the strict inequality on a nonzero measure and as a consequence of Theorem 3.3.2 that $0 < \overline{v} < \frac{P}{\lambda}\overline{\nu}$. Hence $\lim\limits_{\overline{\nu}\to 0} \overline{v} = 0$, and hence by necessity $\lim\limits_{\overline{\nu}\to 0} v(t, \mathbf{x}) = 0$ a.e. in Ω. Since $v \in V$ is continuous, we get $v(t, \mathbf{x}) \to 0$ as $\Omega_2^2 \to \Omega_2^1$ from above. Hence $\lim\limits_{\nu\to 0} |c_2(t, \mathbf{x}) - c_1(t, \mathbf{x})| = 0$ in Ω for $t > 0$, herewith $c(t, \mathbf{x})$ depends on ν continuously, and hence on the extension of Ω_2 continuously. Since c is continuous in t, the waiting time depends on ν continuously. □

Proof of Theorem 3.3.5:

We use a comparison argument to establish our statement. The PDE in equation (1) is estimated with the following upper bound

$$\frac{\partial c}{\partial t} = D\Delta c + Pf(\mathbf{x}) - \lambda c \le D\Delta c + P - \lambda c, \qquad \text{for } \mathbf{x} \in \Omega. \tag{53}$$

We will show that the solution, c_1, of

$$\frac{\partial c_1}{\partial t} = D\Delta c_1 + Pf(\mathbf{x}) - \lambda c_1, \qquad \text{for } \mathbf{x} \in \Omega, \tag{54}$$

is bounded from above by the solution, c_2, of

$$\frac{\partial c_2}{\partial t} = D\Delta c_2 + P - \lambda c_2, \qquad \text{for } \mathbf{x} \in \Omega. \tag{55}$$

By direct substitution, it is verified that the only solution of the above equation (55) is given by $c_2(t, \mathbf{x}) = \frac{P}{\lambda}(1 - \exp(-\lambda t))$. Further, equation (55) models the case that $\Omega_2 = \Omega$. Since Theorems 3.3.3 and 3.3.4 imply that c increases continuously and strictly monotonically with the extension of Ω_2, and since Ω is the maximum extension of Ω_2, the solution c_1 is strictly bounded from above by c_2. In other words, we have $c_1 < c_2 = \frac{P}{\lambda}(1 - \exp(-\lambda t))$ in $(0, T) \times \Omega$. Since $c_1 \in H^1(\Omega) \subset C(\Omega)$, we have that $c_1(t, \mathbf{x}) \le \max\limits_{\Omega} c_1(t, \mathbf{x}) < c_2(t)$, continuity of c_2 and continuity with the dependence of the extension of Ω_2 imply that the waiting time is bounded from below by $\tau > -\frac{1}{\lambda}\ln\left(1 - \frac{\hat{c}\lambda}{P}\right)$, which corresponds to the waiting time for c_2. □

4 THE MOVING BOUNDARY PROBLEM

A high value of the threshold condition will give a long waiting time before the actual healing sets in. An other interesting issue concerns the situation once healing sets in. There are two competing processes: 1. the movement of the wound edge; 2. the diffusional transport of the growth factor. If the movement of the wound edge is faster than the transport of the diffusing growth factor, then we will see that the movement of the wound edge is delayed since the growth factor concentration at the wound edge does not exceed the threshold concentration any longer. On the other hand, if diffusion is sufficiently fast then wound healing proceeds, provided that $\frac{\hat{c}\lambda A_\Omega}{PA_\delta} < 1$. In the following subsections, we will address this issue in more detail for planar wounds. First, we will give a physical argument.

We observe in our numerical solutions that once healing starts, for some cases the healing curve exhibits a stair-case behavior. As the time-step tends to zero, the size of the steps converges to zero. Hence the limit of a zero time step gives a continuous curve. To examine this curious behavior, we first use a physical argument:

The displacement of a point on the wound edge is given by $v_n h$ during a time step with size h. Further, from the wound edge, the diffusional penetration depth is given by $\sqrt{\pi D h}$ within a period of h. In order to have a wound edge concentration of at least the threshold concentration, we need a sufficient penetration depth relative to the wound edge displacement. Hence, we need

$$v_n h < \sqrt{\pi D h}. \tag{56}$$

Taking the square of the above equation and dividing by $v_n \neq 0$, gives

$$h < \frac{\pi D}{v_n^2}. \tag{57}$$

From the above equation, it is clear that if $D > 0$, then one can always choose a time step h such that the above condition holds. Hence the staircase behavior disappears in the limit for $h \to 0$. This explains why the curve is continuous once healing sets in. Healing proceeds until the wound edge concentration drops below the threshold concentration. This depends on the evolution of the area of the active layer.

In spite of the continuity of the healing curve, the healing speed is reduced if the rate parameters α and β are too high in relation to the diffusive transport rate. We will analyze this phenomenon for planar wounds in the subsequent subsections. Before we do so, we will present a condition for continuation of wound healing for a limit case under a change of the area of the active layer.

4.1 Continuation of healing

In this section, we consider the solution after the waiting time has elapsed, that is, we analyze the solution for $t > \tau$. First we demonstrate that for a given healing velocity profile over the wound edge, the solution is uniquely defined. A defined velicity pattern at $W(t)$ and $t > \tau$, will determine a movement of the subdomain $\Omega_2(t)$, subject to the initial condition at $t = \tau$, where the solution follows from the state prior to τ. We formulat this in the following assertion:

Theorem 4.1.1 *Let equations (1–4) and (7) be satisfied with a defined moving interface for $t > \tau$, then there exists at most one solution in V.*

Proof of Theorem 4.1.1:

Suppose that two solutions exist, $c_1,\ c_2 \in V$. Both solutions satisfy the initial condition at $t = \tau$, that is $c_1(\tau, \mathbf{x}) = c_2(\tau, \mathbf{x}) = c(\tau, \mathbf{x})$. The difference between these two solutions, $v := c_2 - c_1$ satisfies

$$\frac{1}{2}\frac{d}{dt}||v||_0^2 + a(v, v) = 0, \text{ for } t > \tau, \text{ with } v(\tau, \mathbf{x}) = 0, \text{ in } \Omega,$$

in the sense of Definition 3.1.1. From the definition of the bilinear form $a(u,v)$, we have

$$\frac{1}{2}\frac{d}{dt}||v||_0^2 + \lambda||v||_0^2 \leq 0, \text{ for } t > \tau, \text{ with } v(\tau, \mathbf{x}) = 0, \text{ in } \Omega.$$

Then, similarly to the proof of Theorem 3.1.2, it follows that $v = 0$ in Ω for $t > \tau$, and hence there is at most one solution in V. □

From Theorem 3.3.3 we learn that the waiting time increases and that the wound edge concentration decreases with a decreasing area of the active layer. Further, since if the area of the active layer is zero (there is no active layer), the wound edge concentration remains zero and the waiting time gets unbounded. This suggests that wound healing may cease if the area of the active layer becomes too small. This is formulated in the following theorem:

Theorem 4.1.2 *Let equations (1–4) and (7) be satisfied with a moving interface for $t > \tau$, and let A_δ and A_Ω be the area of the active layer and domain of computation, then, for the limit $D \to \infty$:*

1. *Healing continues iff*
$$\hat{c}\left(1 - e^{\lambda(\tau - t)}\right) \leq \frac{P}{A_\Omega}\int_\tau^t A_\delta(s)e^{\lambda(s-t)}ds; \tag{58}$$

2. *If $A_\delta = A_\delta(0)$, then, healing will always proceed iff $\dfrac{\hat{c}\lambda A_\delta}{PA_\Omega} < 1$.*

Proof of Theorem 4.1.2:

In general the area of Ω_2 changes during the course of healing. This is caused by the contraction of the wound and the resulting decrease of the wound perimeter or by the change of the thickness of Ω_2, depending on the wound geometry or contraction rate equation used in the model. Consider the limit case of $D \to \infty$, then, Theorem 3.3.1 says that equation (45) holds true. For the case that A_δ depends on time, we obtain from using an integrating factor to solve (45) for $t > \tau$

$$\exp(\lambda t)\overline{c}(t) - \exp(\lambda\tau)\hat{c} = \frac{P}{A_\Omega}\int_\tau^t A_\delta(s)\exp(\lambda s)ds. \tag{59}$$

This gives

$$\overline{c}(t) = \exp(\lambda(\tau - t))\hat{c} + \frac{P}{A_\Omega}\exp(-\lambda t)\int_\tau^t A_\delta(s)\exp(\lambda s)ds \geq \hat{c}, \tag{60}$$

as a condition to start healing in a finite time. This implies

$$\hat{c}(1 - \exp(\lambda(\tau - t))) \leq \frac{P}{A_\Omega}\exp(-\lambda t)\int_\tau^t A_\delta(s)\exp(\lambda s)ds, \tag{61}$$

and the first part of Theorem 4.1.2 has been established.

Next, we set A_δ constant, say $A_\delta = A_\delta$, then the right hand side of the above inequality changes into

$$\frac{P}{A_\Omega}\exp(-\lambda t)\int_\tau^t A_\delta(s)\exp(\lambda s)ds = \frac{PA_\delta}{A_\Omega\lambda}\exp(-\lambda t)(\exp(\lambda t) - \exp(\lambda\tau)). \tag{62}$$

From this equation, one obtains

$$\frac{P}{A_\Omega}\exp(-\lambda t)\int_\tau^t A_\delta(s)\exp(\lambda s)ds = \frac{PA_\delta}{A_\Omega\lambda}(1 - \exp(\lambda(\tau - t))). \tag{63}$$

Combining this with inequality (61), yields

$$\hat{c}(1 - \exp(\lambda(\tau - t))) \leq \frac{PA_\delta}{A_\Omega\lambda}(1 - \exp(\lambda(\tau - t))). \tag{64}$$

Since, $t > \tau$, we have $0 < \exp(\lambda(\tau - t)) < 1$, and hence, the above condition for healing to proceed is satisfied if and only if

$$\frac{\hat{c}\lambda A_\Omega}{PA_\delta} < 1, \tag{65}$$

which is consistent with Theorem 3.3.1 to start healing. □

4.2 Construction of a planar moving solution

In this subsection, we consider the movement of the interface, which may be retardated for some cases. The intuitive argument at the beginning of this section revealed that the interface position is a continuous function of time. We will limit the discussion to planar wounds only. Hence, the curvature is zero, and therefore we are faced with the following problem:

$$\begin{aligned}
&\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \lambda c + P\mathbf{1}_{(R,R+\delta)}, \quad \text{in } (0,L),\\
&\frac{\partial c}{\partial x}(t,0) = \frac{\partial c}{\partial x}(t,L) = 0,\\
&c(0,x) = 0, \qquad\qquad\qquad\qquad \text{in } (0,L),\\
&\frac{dR}{dt} = -\alpha w(c(R(t),t) - \hat{c}),
\end{aligned} \tag{66}$$

where $R(t)$ denotes the position of the planar interface and note that $\alpha > 0$. Now we consider the solution to the above problem in the case that the interface moves. Hence, the solution for $t > \tau$ is of interest. We will show that a solution with a moving interface can be constructed, where the interface speed is constant. If v denotes the velocity of the interface, where $v \in [0, \alpha]$, then $R(t) = R_0 - \int_\tau^t v(s)ds$ for $t \geq \tau$. The eigenfunctions of the homogeneous problem are the same as before for the planar wound at $t < \tau$. However, the Fourier series for the production term changes due to the time-dependence, that is

$$P\mathbf{1}_{(R(t),R(t)+\delta)} = \sum_{k=0}^{\infty} \gamma_k(t)\phi_k(x),$$

where $\gamma_k(t)$ is the same as before for the planar case, but now one has to bear in mind that R varies with time. These expressions are substituted into the nonhomogeneous PDE, and we realize that the eigenfunctions are an orthonormal set, then this yields

$$\begin{aligned}
&c_k' + (\mu_k^2 D + \lambda)c_k = \gamma_k(t), \text{ for } t > \tau,\\
&c_k(\tau) \text{ follows the non-moving boundary solution.}
\end{aligned} \tag{67}$$

Using an integrating factor gives

$$c_k(t) = c_k(\tau)e^{(\mu_k^2 D+\lambda)(\tau - t)} + e^{-(\mu_k^2 D+\lambda)t}\int_\tau^t \gamma_k(s)e^{(\mu_k^2 D+\lambda)s}ds.$$

The formal solution to the initial boundary problem is given by

$$\begin{aligned}
c(t,x) = \sum_{k=0}^{\infty} c_k(t)\phi_k(x) = \sum_{k=0}^{\infty} c_k(\tau)e^{(\mu_k^2 D+\lambda)(\tau-t)}\phi_k(x) +\\
P\sum_{k=0}^{\infty}\phi_k(x)\int_\tau^t \left\{ e^{(\mu_k^2 D+\lambda)(s-t)}\int_{R(s)}^{R(s)+\delta}\phi_k(y)dy \right\} ds.
\end{aligned} \tag{68}$$

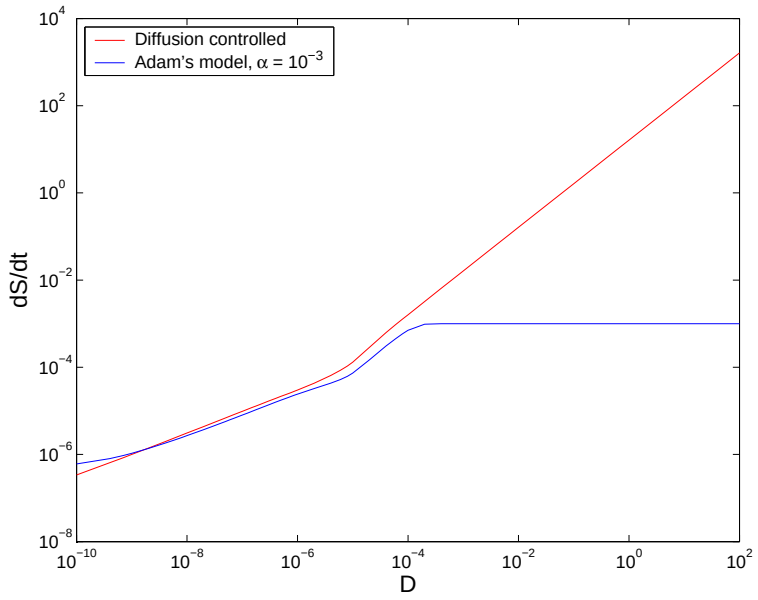

Figure 5: The interface speed as a function of the diffusivity. The blue curve corresponds to a numerical solution of Adam's model. The red curve gives the interfacial velocity for which the interface concentration is equal to the threshold concentration $\hat{c}$.

The first term originates from the solution at $t = \tau$, and the second term takes into account the movement of the production term for the growth factor. Combined with $\phi_k(x) = \sqrt{2/L}\cos(k\pi x/L)$ and $\phi_0 = 1/\sqrt{L}$, gives the formal solution. By these algebraic operations and since the integrals exist (have a finite value), the existence of a moving boundary solution for a planar wound for $t > \tau$, can be demonstrated with a given interfacial movement, in terms of a contractive semi-group. Theorem 4.1.1 infers that this is the only solution. As an illustration of this solution, we plot the interface rate v that corresponds to $c(R(t), t) = \hat{c}$ as a function of the diffusion coefficient in Figure 5. Note that in order to obtain this picture, the integrals have been evaluated, which is a straightforward, but tedious job. From this picture, it is suggested that for a given α there is a D^* for which $v = \alpha$ and $v < \alpha$ if $D < D^*$. The latter situation is where retardation of the interface speed comes in. If $D > D^*$ then $v = \alpha$. For a given value of α, the magnitude of the interface speed is bounded from above by α. Furthermore, we show some results with the same parameters but then with a Finite Difference method, see Figure 5. It can be seen that the solutions agree rather well, except for very small and very large values of the diffusion coefficient. We note that for $D > D^*$ the interface speed equals α by necessity, since $c(R(t), t) > \hat{c}$. Hence, for this case the interface speed stays constant at all times $t > \tau$ during the healing process. In the remaining text of this subsection, we will give some results from a qualitative analysis concerning several basic properties such as monotonicity, delay, uniqueness and existence of a solution.

Integration of the bottom equation in (66) over $(t, t + h)$ and taking the absolute value gives

$$|R(t + h) - R(t)| = \alpha \int_t^{t+h} w(s, c(R(s)) - \hat{c})ds \leq \alpha h. \tag{69}$$

Taking the limit $h \to 0$ implies that $R(t)$ is continuous. This could also be seen from the bottom equation of (66). Retardation of the solution is allowed since

$$R(t + h) - R(t) = -\alpha \int_t^{t+h} w(c(s, R(s)) - \hat{c})ds \geq -\alpha h, \tag{70}$$

where $w \in [0, 1]$ if $c(s, R(s)) = \hat{c}$. It can also be seen that $R(t + h) - R(t) \leq 0$. Hence, from this argument it can concluded that $R(t)$ is monotonic. So, the interface does not move in an

oscillatory manner. We note that if $c(t, R(t)) > \hat{c}$, then $w = 1$ and hence $R'(t) = -\alpha$, for which there is no retardation. Since $c(t, R(t)) = \hat{c}$ implies $w \in [0, 1]$, retardation possibly occurs.

As a degenerate case, we consider the situation in which $D = 0$. If $\Omega_2 = (R, R + \delta)$, that is Ω_2 is open, then

$$\begin{cases} \dfrac{\partial c}{\partial t} = P - \lambda c, & \mathbf{x} \in \Omega_2, \text{ open domain} \\ \dfrac{\partial c}{\partial t} = -\lambda c, & \mathbf{x} \in \Omega \setminus \Omega_2, \\ \text{with } c(0, \mathbf{x}) = 0, & \mathbf{x} \in \Omega. \end{cases} \tag{71}$$

Therewith $c(t, R(t)) = 0$ for $t > 0$, hence $c(t, R(t)) < \hat{c}$, and thus $R(t) = R_0$. The interface does not move in this case. Suppose, however, that one takes Ω_2 to be closed at R, that is $\Omega_2 = [R, R + \delta]$ for instance, then if $\frac{\hat{c}\lambda}{P} < 1$, there is a time $t = \overline{t}$ at which $c(\overline{t}, R(\overline{t})) = \hat{c}$. Suppose that the interface motion is zero, then for all $t > \overline{t}$ as a result of monotonicity (see [Pao 1992], Sections 5.2 and 5.3), we have $c(R(t), t) > \hat{c}$. This implies that $w = 1$ and hence the interface has to move. Here, we arrive at a contradiction. This implies that we should investigate whether solutions with interface movement exist for a closed active layer. For this purpose, we consider

$$R(t + h) - R(t) = -\alpha \int_t^{t+h} w(c(R(s), s) - \hat{c}) ds,$$

in which we assume that $c(s, R(s)) = \hat{c}$. If the interface moves, then $R(t + h) < R(t)$, then, since the diffusion coefficient is zero, $c(t + \varepsilon, R(t + \varepsilon)) = 0 < \hat{c}$ for an arbitrarily small $0 < \varepsilon \leq h < \tau$, where t is the waiting time. Hence, the interface cannot move. This implies that there is no solution if the active layer Ω_2 is closed and $D = 0$. From the arguments in this subsection, we demonstrated the following theorem:

Theorem 4.2.1 *Given the planar wound healing problem in* (66)*, then*

1. *The interface position is continuous and monotonic;*
2. *If $D = 0$ and Ω_2 is open, then $R(t) = R_0$ is the only solution (that is the interface does not move);*
3. *If $D = 0$ and Ω_2 is closed (at $R(t)$), then there is no solution for $t > \tau$, where τ represents the waiting time.*

Theorem 4.2.1 implies that the interface does not move if $D = 0$. Hence, retardation is real feature of the current model. Suppose that $D \to \infty$ and that $\frac{\hat{c}\lambda L}{P\delta} < 1$, then the interface will move if $t \geq \tau$. Further, if the active layer thickness remains equal to δ at all time, then the interface concentration stays above $\hat{c}$, that is $c(t, R(t)) > \hat{c}$ for all $t > \tau$, as a result of Theorem 3.3.1. This implies that the interface speed is given by $-\alpha$ and that

$$R(t) = R_0 - \alpha(t - \tau), \text{ for } \tau < t < \theta,$$

where $\theta = \tau + R_0/\alpha$ denotes the time at which the wound heals entirely. The wound heals at a constant pace. Due to a continuous dependence of the solution on the diffusion coefficient D, there exists a D^* for each α, P, and λ, such that

$$R'(t) = -\alpha, \text{ for } D > D^*, \text{ and}$$

$$-\alpha \leq R'(t) \leq 0, \text{ for } D \leq D^*, \text{ at which retardation takes place.}$$

We consider the case that the interface movement is delayed. Then, the solution can be constructed by the use of a retardation factor $\xi \geq 1$, such that

$$R'(t) = -\frac{\alpha}{\xi} > -\alpha \text{ for } c(t, R(t)) = \hat{c}.$$

Solutions with a larger magnitude of the interface speed such that $R'(t) < -\frac{\alpha}{\xi}$ imply that $c(t, R(t)) < \hat{c}$ which halts the interface until the concentration exceeds $\hat{c}$, because of

$$R(\tau + h) - R(\tau) = -\alpha \int_{\tau}^{\tau+h} w(c(t, R(t)) - \hat{c}) dt = 0,$$

due to $w = 0$ for $(\tau, \tau + h)$ for h arbitrarily small. This gives a contradiction. Hence, solutions for which $R'(t) < -\frac{\alpha}{\xi}$ do not exist. Next, we consider the case that the magnitude of the interface speed is smaller and hence satisfies $R'(t) > -\frac{\alpha}{\xi}$. For this case, we will get $c(t, R(t)) > \hat{c}$, but this implies $R'(t) = -\alpha < -\frac{\alpha}{\xi}$. This immediately gives a contradiction.

Next, we consider continuity of the solution with respect to the interface speed. Let $0 < \varepsilon < \delta$, then we consider the difference in solutions of

$$\begin{aligned} \frac{\partial c_1}{\partial t} &= D\frac{\partial^2 c_1}{\partial x^2} - \lambda c_1 + P\mathbf{1}_{R(t),R(t)+\delta}, \\ \frac{\partial c_2}{\partial t} &= D\frac{\partial^2 c_2}{\partial x^2} - \lambda c_2 + P\mathbf{1}_{R(t)+\varepsilon,R(t)+\varepsilon+\delta}. \end{aligned} \tag{72}$$

The above equations are subject to the same initial condition for $t = \tau$ and the same homogeneous Neumann boundary condition. The difference between the solutions of the above equations satisfies

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - \lambda u + \begin{cases} P, & x \in (R, R + \delta), \\ 0, & x \in [0, R) \cup (R + \varepsilon, R + \delta) \cup (R + \delta + \varepsilon, L], \\ -P, & x \in (R + \delta, R + \delta + \varepsilon). \end{cases} \tag{73}$$

Since $u(0, x) = 0$, we consider $u_E(x)$ where $\lim_{t\to\infty} u(t, x) = u_E(x)$, hence

$$-D\frac{\partial^2 u_E}{\partial x^2} + \lambda u_E = \begin{cases} P, & x \in (R, R + \delta), \\ 0, & x \in [0, R) \cup (R + \varepsilon, R + \delta) \cup (R + \delta + \varepsilon, L], \\ -P, & x \in (R + \delta, R + \delta + \varepsilon). \end{cases} \tag{74}$$

Using an analytic solution for u_E, constructed by a superposition of two particular solutions (one from the '+P-interval' and one from the '-P-interval'), we observe that

$$\lim_{\varepsilon\to 0} u_E(x) = 0 \Longrightarrow \lim_{\varepsilon\to 0} u(t, x) = 0.$$

Further, note that for $\varepsilon = 0$, we have $u_E(x) = 0$ and $u(t, x) = 0$. This implies that $c(t, x)$ is continuous with respect to the interface velocity, also at $\varepsilon = 0$. If $R'(\tau) = 0$, then due to monotonicity $\frac{d}{dt}c(\tau, R(\tau)) = \frac{d}{dt}c(\tau, R_0) > 0$. For a 'quickly' moving interface (such that $R(t) = 0$ for $t > \tau$), continuity of $c(t, 0)$ with respect to t and $c(\tau, 0) < \hat{c}$, imply $c(t, R(t)) < \hat{c}$ for t sufficiently short after τ. This implies that there is a $R'(\tau)$ such that $\frac{d}{dt}c(\tau, R(\tau)) = 0$. If $|R'(\tau)| < \alpha$, then retardation results, whereas if $|R'(\tau)| > \alpha$, then $\frac{d}{dt}c(\tau, R(\tau)) > 0$ for $t = \tau$ with $|R'(\tau)| = \alpha$.

Herewith, we demonstrated

Theorem 4.2.2 *Given the planar wound healing problem as defined by equations* (66)*, then*

1. *There exists a $D^* > 0$ for which wound healing is retardated if $D < D^*$;*
2. *For each $D < D^*$, $\lambda \geq 0$, $P > 0$, $\delta > 0$, $\hat{c} > 0$, there exists one and only one $\xi > 1$ such that $R'(t) = -\frac{\alpha}{\xi}$ for $t > \tau$;*
3. *The concentration, and hence also the interface concentration, is continuous with the interface speed.*

The retardated solution for a planar wound is constructed by imposing $c(t, R(t)) = \hat{c}$ for $t \geq \tau$, that is

$$\frac{dc(t, R(t))}{dt} = 0. \tag{75}$$

Application of the total derivative with respect to time, gives

$$\frac{\partial c(t, R(t))}{\partial t} + R'(t)\frac{\partial c(t, R(t))}{\partial x} = 0, \text{ for } t \geq \tau. \tag{76}$$

Hence, we have

$$\frac{\partial c(t, R(t))}{\partial t} = \frac{\alpha}{\xi}\frac{\partial c(t, R(t))}{\partial x}, \text{ for } t \geq \tau. \tag{77}$$

The parameter is determined from the above equation and the analytic solution for the planar case. Of course, the analytic solution that has been presented in this paper is adjusted where the production term changes in time due to the displacement of the boundary. For a circular case, the retardation may depend on the current wound radius. This is a topic for further research. Finally, we summarize the construction of analytic solutions for a planar wound.

1. For $t < \tau$, the concentration is determined by equation (21);
2. For $t \geq \tau$, the speed of the wound edge is constant and given by

$$\frac{dR}{dt} = -\frac{\alpha}{\xi}, \text{ where } \xi = \max\left\{1, \frac{\alpha\frac{\partial c(t,R(t))}{\partial x}}{\frac{\partial c(t,R(t))}{\partial t}}\right\}.$$

4.3 Illustrations of delayed healing

To illustrate the theoretical remarks presented in this section, the healing of a planar wound is simulated using the analytic solution extended with the moving boundary. The results are shown in Figure 6. For the case of a small diffusion coefficient, the waiting time is relatively small, so that healing starts rather soon. However, since there is a competition between diffusion and interfacial motion, the healing process is retardated. In this case, we clearly have that $D < D^*$. For the case of a fast diffusivity, we see that the waiting time is large. Physically, this can be attributed to the fact that the produced growth factor is smeared out over the entire domain of computation. See the limit case in Theorem 3.3.1. However, in this case, we clearly have that $D > D^*$ which gives no retardation of the interface motion. As an illustration of this, we plot (translated) curve in the case of no waiting time ($\hat{c} = 0$) next to the curve with the larger diffusion coefficient. It can be seen that these two curves are parallel indeed. For the two situations, the waiting time and healing rate differ, however, the healing times are the same.

As a further and more interesting application, we consider the influence of the diffusion coefficient on the waiting time and healing time, see Figure 7. It can be seen that the incubation times converge to the appropriate limits of Theorem 3.3.1 and 3.3.2 as $D \to \infty$ and $D \to 0$. It can be seen that there is region in the co-domain for the healing times, in which two diffusivities can be found for each healing time. From this behavior, we distinguish between two biological regimes: the diffusion controled regime for small dif fusion coefficients and the closure controled regime, when the diffusion coefficient is rather large. The two regimes might not give significant different healing times, however, the healing process is totally different. In Figure 8, we show the retardation factor as a function of the diffusion coefficient. It can be seen that the retardation factor increases (which implies that the interface motion is delayed) as the diffusion coefficient decreases. This is in line with the theory that has been developed in this study. Further, for diffusivities larger than D^* the retardation factor is one, which corresponds to healing without any delay.

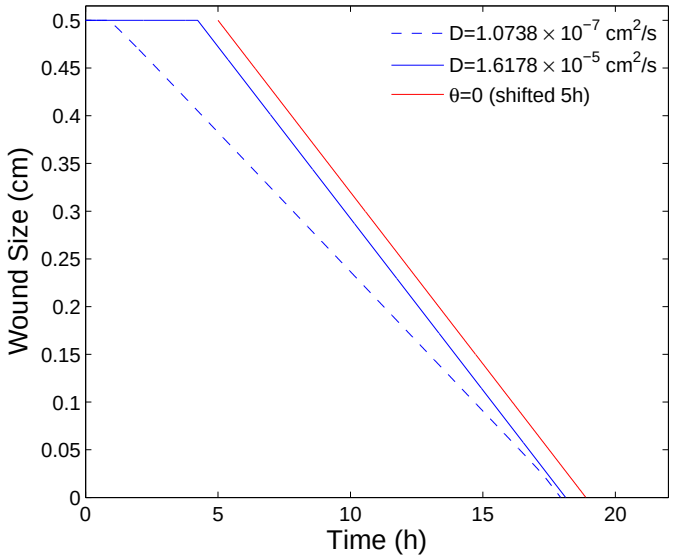

Figure 6: Wound healing behavior with a low and a high diffusivity. Calculated with the analytic series solution for a planar wound.

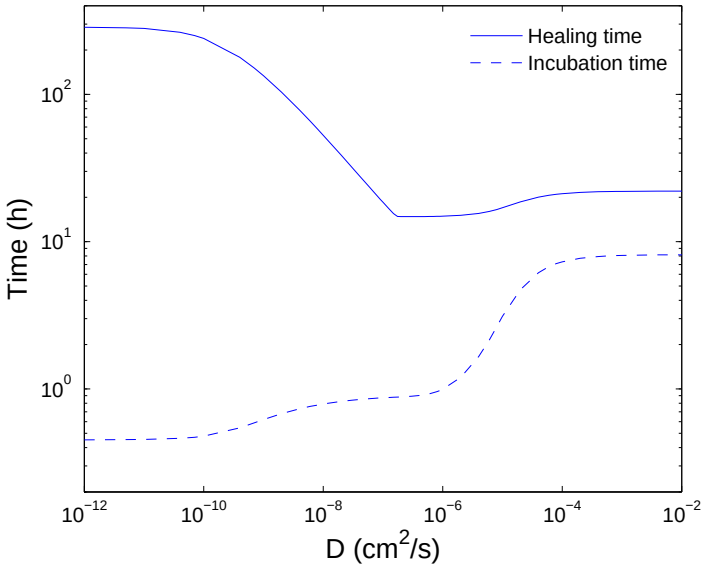

Figure 7: The healing time and waiting time as a function of the diffusivity.

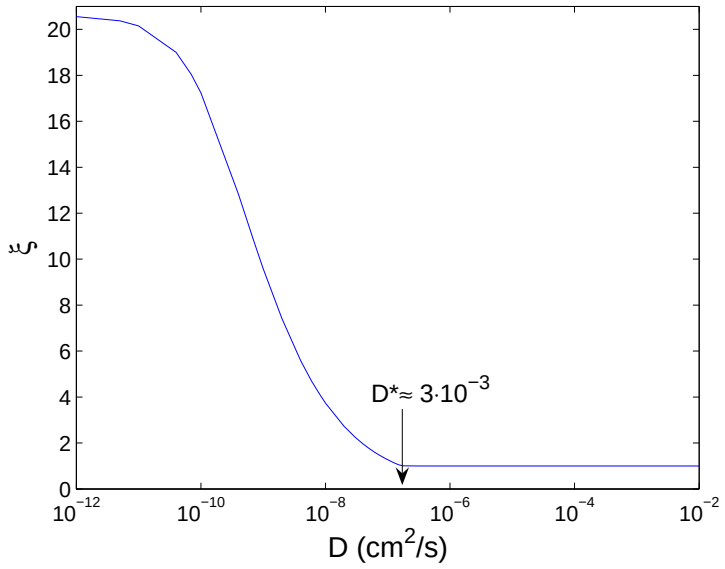

Figure 8: The retardation factor as a function of the diffusion coefficient. For diffusion coefficients that are lower than $D^* \approx 3 \cdot 10^{-3}$, the interface motion is delayed.

4.4 A note on the construction of the solution

The existence of a solution to the homogeneous problem, in which $P = 0$ is a standard result, see for instance [Friedman 1964] or [Pao 1992]. Since the differential operator $-\Delta + \lambda I$, with homogeneous Neumann conditions, is self-adjoint and positive definite for $\lambda > 0$, the infinite set of eigenvalues are real and bounded from below and its eigenfunctions are an orthogonal set. Hence, the source function $P\mathbf{1}_{\Omega_2(t)}$, which is piecewise continuous, can be written as a unique linear combination of the eigenfunctions, say

$$P\mathbf{1}_{\Omega_2(t)} = \sum_{k=0}^{\infty} b_k(t)\phi_k(\mathbf{x}), \qquad \text{a.e. in } \Omega,$$

where the functions $\phi_k(\mathbf{x})$ represent the eigenfunctions of the operator $-\Delta + \lambda I$. Due to completeness and linear independence of the eigenfunctions of the self-adjoint differential operator, the solution u can be written as an eigenfunction expansion

$$c(t, \mathbf{x}) = \sum_{k=0}^{\infty} c_k(t)\phi_k(\mathbf{x}).$$

Substitution into the weak differential form (see Definition 3.1.1), gives

$$c_k' + \mu_k^2 c_k = (P\mathbf{1}_{\Omega_2}, \phi_k),$$

where the eigenfunctions ϕ_k are orthonormal. This implies that the solution is given by

$$c_k = P \int_0^t (\mathbf{1}_{\Omega_2}, \phi_k) e^{\mu_k^2 (s-t)} ds.$$

Hence the solution is formally given by

$$c(t, \mathbf{x}) = P \sum_{k=0}^{\infty} \phi_k(\mathbf{x}) \int_0^t (\mathbf{1}_{\Omega_2}, \phi_k) e^{\mu_k^2 (s-t)} \, ds.$$

We define the Green's function by

$$G(t,s,\mathbf{x},\overline{\mathbf{x}}) := \sum_{k=0}^{\infty} e^{\mu_k^2(s-t)}\phi_k(\mathbf{x})\phi_k(\overline{\mathbf{x}}),$$

to write the solution as

$$c(t,\mathbf{x}) = P\int_0^t \int_\Omega \mathbf{1}_{\Omega_2(s,c(s,\mathbf{x}))} G(t,s,\mathbf{x},\overline{\mathbf{x}})\ d\Omega\ ds = P\int_0^t \int_{\Omega_2(s,c(s,\mathbf{x}))} G(t,s,\mathbf{x},\overline{\mathbf{x}})\ d\Omega\ ds.$$

where $\overline{\mathbf{x}}$ is the spatial variable over which one integrates. Further, one should realize that Ω_2 formally is a function of time and the solution. Note that $\Omega_2 = \Omega_2(0)$ for $t < \tau$ and that Ω_2 moves for $t > \tau$. The existence of the above integral (it exists since it contains an integration over the eigenfunctions and the integration with respect to time can be estimated using the eigenvalue zero), and a contraction argument (using the Banach contraction Theorem as in the spirit of the Picard fixed point method as in the Picard-Lindelöf Theorem) with respect to c, imply the existence of the solution. This is left for a future study.

In a generic setting, one can demonstrate by considering the integal $m(t) = \int_\Omega c d\Omega$ that

$$m(t) = P\int_0^t A_\delta(s)e^{\lambda(s-t)}ds, \tag{78}$$

whenever A_δ is not constant in time. This equation will be used for the energy integral. Choosing $\phi = c$ in Definition 3.1.1 gives

$$\frac{d}{dt}(c,c) = -2a(c,c) + 2(P\mathbf{1}_{\Omega_2}, c) \leq -2\lambda\ (c,c) + 2P(\mathbf{1}_{\Omega_2}, c), \tag{79}$$

where the last inequality follows from coercivity ($a(c,c) \geq \lambda(c,c)$) and from $\Omega_2 \subset \Omega$. Rearranging the above equation gives

$$\frac{d}{dt}(c,c) + 2\lambda(c,c) \leq 2P^2\int_0^t A_\delta(s)e^{\lambda(s-t)}ds. \tag{80}$$

Using an integrating factor and application of Grönwall's Lemma delivers

$$\begin{aligned}(c,c) &\leq 2P^2\int_0^t\int_0^\sigma A_\delta(s)e^{\lambda(s-\sigma)+2\lambda(t-\sigma)}dsd\sigma \leq \\ 2P^2A_\Omega\int_0^t\int_0^\sigma e^{\lambda(s-\sigma)+2\lambda(t-\sigma)}dsd\sigma &\leq \frac{2P^2}{\lambda}(t+\frac{1}{\lambda}).\end{aligned} \tag{81}$$

Hence for positive λ and finite time t, the solution is bounded in the L^2-norm over Ω. Note that the second inequality is equivalent with the upper solution with $\Omega_2 = \Omega$. This procedure was extended by [Gao and Bu 2003] to demonstrate existence of a solution with an active layer that has a continuous and piecewise linear behavior in the spatial coordinate. They did not include a moving interface.

5 CONCLUSIONS

In this study we demonstrated that the model due to Adam predicts the existence of a waiting time before healing sets in. We derived some necessary conditions. Furthermore, analytic solutions in terms of closed form expressions were derived for planar and circular wounds. These solutions can be used to obtain more accurate estimates of the waiting time. Further, these solutions are useful for a validation of the numerical solution.

Existence of a weak solution of the time-dependent problem has not been proved. The proof will contain adaptations in the existence proof with fundamental solutions for the case in which f is Hölder continuous. For a regularized version of f, say f_ε, existence of classical solutions follows from classical theorems. It would be desirable to demonstrate that as $\lim_{\varepsilon \to 0} f_\varepsilon(\mathbf{x})$ in Ω, that we have $\lim_{\varepsilon \to 0} c_\varepsilon = c$ in Ω and $t > 0$. This would make the proof on maximum principles more straightforward. These issues will be addressed in a future study.

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