Published in final edited form as:

Int J Numer Method Biomed Eng. 2014 June ; 30(6): 616–633. doi:10.1002/cnm.2621.

Non-linear finite element simulations of injuries with free boundaries: application to surgical wounds

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SUMMARY

Wound healing is a process driven by biochemical and mechanical variables in which new tissue is synthesised to recover original tissue functionality. Wound morphology plays a crucial role in this process, as the skin behaviour is not uniform along different directions. In this work we simulate the contraction of surgical wounds, which can be characterised as elongated and deep wounds. Due to the regularity of this morphology, we approximate the evolution of the wound through its cross-section, adopting a plane strain hypothesis. This simplification reduces the complexity of the computational problem while maintaining allows for a thorough analysis of the role of wound depth in the healing process, an aspect of medical and computational relevance that has not yet been addressed. To reproduce wound contraction we consider the role of fibroblasts, myofibroblasts, collagen and a generic growth factor. The contraction phenomenon is driven by cell-generated forces. We postulate that these forces are adjusted to the mechanical environment of the tissue where cells are embedded through a mechanosensing and mechanotransduction mechanism. To solve the non-linear problem we use the Finite Element Method and an updated Lagrangian approach to represent the change in the geometry. To elucidate the role of wound depth and width on the contraction pattern and evolution of the involved species, we analyse different wound geometries with the same wound area. We find that deeper wounds contract less and reach a maximum contraction rate earlier than superficial wounds.

Keywords

Finite Elements; free boundary problem; wound healing; non-linear convection-diffusion-reaction; mechanosensing and mechanotransduction

1. INTRODUCTION

Skin is the protective barrier between internal organs and external aggressions.

Occasionally, this barrier is damaged and a number of complicated processes are needed to recover the initial functionality of the skin. Different injuries such as burns, cuts, ulcers and

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surgery scars cause a reduction in skin quality making the wound healing process to recover the appropriate properties crucial [1].

Wound healing is mainly driven by different cellular species (fibroblasts, myofibroblasts, epithelial cells and macrophages) and growth factors (MDGF, TGF- α , TGF- β , PDGF and VEGF). These species undergo several processes (proliferation, differentiation, migration and apoptosis) that modify their concentration regulating the evolution of the wound.

Wound healing is usually divided into three stages: inflammation, tissue formation and scar remodeling [2]. During the inflammation stage, a fibrin clot is formed at the wound site and a number of growth factors are released. During the second stage, different cellular species are attracted to the clot by the growth factors released during inflammation. Epidermal cells proliferate into the wound area, granulation tissue appears and new blood vessels begin to grow to supply oxygen and nutrients to the new tissue [1]. Fibroblasts secrete collagen to create a new extracellular matrix (ECM) that will replace the temporary fibrin clot. In this stage, the wound reduces its size and acquires a tensional state that will slowly relax. Finally, in the remodelling stage, previously synthesised collagen fibres align with tension lines in such a way that the damaged tissue gradually recovers most of its initial functionality. In the last stage, previously initiated processes end, and cells that are no longer needed die and are removed.

Wound contraction is one of the most important processes during wound healing. This process is strongly influenced by not only cellular and chemical species, but also mechanics. Cells feel the mechanical changes on the substrate in which they are embedded and regulate the forces they exert corresponding to this mechanical environment [3, 4, 5]. Therefore, most wound healing studies include both biological and mechanical factors in their models [6, 7, 8, 9, 10]. In addition, wound geometry is one of the most important characteristics in determining the evolution of the healing process. Wounds in the skin can be classified according to their dimensions. Wounds with a large superficial area and a shallow depth should be treated differently than deep wounds with a relevant depth.

For a number of years, mathematical models have been developed to study different biological and physiological processes [11]. Prior wound healing works have focused on tracking the wound superficial area over time, neglecting any influence of wound depth on the contraction kinetics [12, 6, 9]. Previous works on wound healing [13, 14, 15, 8] and wound contraction [12, 16, 9], have mostly studied wounds from a one-dimensional (1-D) perspective or under the assumption of plane stress. These models consider simple axisymmetric geometries and allow the spatial problem to be reduced to a one-dimensional model. Recent works have considered more realistic wound geometries [6, 10], solving the two-dimensional (2-D) spatial problem but neglecting the wound depth. Two-dimensional models allow the study of complex wounds with more realistic geometries. From a numerical perspective planar wounds are easier to model as the boundary conditions are the same for the whole boundary and the natural boundary conditions do not need to be taken into account. Therefore, in this work we focus on the numerical solution of the governing system without boundary simplification to obtain a model applicable to both wound types. Hence, we present a mathematical model that can reproduce the evolution of both (superficial and deep) wounds. We focus on the simulation of deep and elongated wounds to

consider the different behaviours of wounds along different directions. The healing of deep and elongated wounds varies from that of planar wounds because all involved phenomena mainly occur, along the wound depth. From a mechanical perspective the hypotheses of plane strain and a free boundary on the top surface of the wound are adopted. Note, moreover, that this approach to wound healing is the closest approximation to a three-dimensional spatial model of wound healing. Three-dimensional models are desirable to capture more realistic and complex wound morphologies. However, they are much more complex to develop and more expensive computationally. There are still many hypotheses on cell and tissue behaviour that need to be properly addressed using the predictive power of three-dimensional wound healing models. Therefore, from a modeling and simulation point of view, two-dimensional models present the most affordable option with less simplification of hypotheses than one-dimensional models. To the best of our knowledge a model with these characteristics has not been developed previously.

A Finite Element Method (FEM) is used to conveniently manage the complex wound geometries and free boundary. A non-linear finite element is implemented to solve the mechanical equilibrium of the tissue and evolution of the chemical and cellular species simultaneously. The finite element approximation of the highly non-linear and coupled convection-diffusion-reaction governing equations allows us to propose a strict linearisation of the governing equations which yields a linear system of equations that are easy to solve on each time increment.

2. MATHEMATICAL MODEL

The aim of this work is to address the difference between planar and long deep wounds, specifically the effects of wound morphology and mechanical behaviour. Superficial wounds are studied assuming a plane stress approach because their depths are much smaller than their other dimensions. In contrast, long deep wounds are studied under a plane strain approach because the wound behaviour is assumed to be the same along their lengths, and thus, only the transversal section should be studied. Furthermore, in long deep wounds, the upper part of the wound edge is in contact with the external environment with no constraints on its movement, which allows a different contraction pattern.

In this work we present the formulation and numerical solution of a model that reproduces the contraction of elongated and deep wounds. The model formulation used here, based on the mechano-chemical coupling of different cellular species, growth factors and the ECM, is similar to those in earlier works [12, 6, 9], but fewer simplifications are assumed in its implementation than in previous models.

Thus, to reproduce the wound status over time, we take into account biological and mechanical factors that affect both the cellular kinetics and ECM mechanical evolution. This mechano-chemical coupling is supported by experimental results proving that cells not only respond to biochemical stimulus but also modify their behaviour depending on the mechanical evolution of the skin [3, 4]. Moreover, the mechanical contribution of the skin determines the way the wound contracts, a crucial element of the healing process.

2.1. Governing equations

The model reproduces the temporal and spatial evolution of four different species within the wound space and surrounding tissue. Following previous works [12, 6, 9] we considered two different cellular species: fibroblasts and myofibroblasts. Fibroblasts (n) are motile cells inside the skin that secrete extra-cellular matrix (ECM) and exert traction forces on the tissue in which they are embedded. Myofibroblasts (m) are non-motile cells that appear in the skin due to the combined action of inflammatory growth factors and mechanical stimulus, and amplify the forces exerted by fibroblasts [17, 18]. The secreted ECM is mainly composed of collagen (ρ), which gives structural support to the skin and determines its mechanical properties. Collagen forms fibres that are synthesised and degraded by fibroblasts and myofibroblasts [19]. Thus, we assume that collagen is the main component in the skin that causes the stiffening effect of the newly synthesised ECM. The elastic modulus (E) is therefore dependent on the collagen density through the equation $E = E_0\rho/\rho_0$, where E_0 and ρ_0 are the elastic modulus and collagen density of the undamaged skin, respectively, considering that the skin becomes stiffer as the collagen density increases [20, 21]. Finally, we consider a generic growth factor (c) accumulated at the wound site during the inflammatory phase that regulates cell migration and cell function during the contraction process.

Each of the above-mentioned cellular and chemical species follows a conservation law that incorporates the biological cues previously described. In general terms this conservation law can be expressed as

$$\frac{\partial Q}{\partial t} + \nabla \cdot \mathbf{J}_Q = f_Q, \quad (1)$$

where $\mathbf{J}_Q$ denotes the net flux of the species Q and its net production, f_Q .

If we single out this equation for each of the four species, we find that the corresponding laws can be written for fibroblasts (Eq (2)), myofibroblasts (Eq (3)), collagen (Eq (4)) and growth factor (Eq (5)) as follows,

$$\begin{aligned} \frac{\partial n}{\partial t} + \nabla \cdot \left(\underbrace{-D_n \nabla n}_{\text{random migration}} + \underbrace{\frac{a_n}{(b_n + c)^2} n \nabla c}_{\text{chemotaxis}} + \underbrace{n \frac{\partial \mathbf{u}}{\partial t}}_{\text{passive convection}} \right) &= \underbrace{\left(r_n + \frac{r_{n, \max} c}{C_{1/2} + c} \right) n \left(1 - \frac{n}{K} \right)}_{\text{proliferation}} \\ &- \underbrace{\frac{k_{1, \max} c}{C_k + c} \frac{p_{\text{cell}}(\theta)}{\tau_d + p_{\text{cell}}(\theta)} n}_{\text{differentiation}} + \underbrace{k_2 m}_{\text{dedifferentiation}} - \underbrace{d_n n}_{\text{death}} \end{aligned} \quad (2)$$

$$\frac{\partial m}{\partial t} + \nabla \cdot \left(\underbrace{m \frac{\partial \mathbf{u}}{\partial t}}_{\text{passive convection}} \right) = \underbrace{\epsilon_r \left(r_n + \frac{r_{n,max} c}{C_{1/2} + c} \right) m \left(1 - \frac{m}{K} \right)}_{\text{proliferation}} + \underbrace{\frac{k_{1,max} c}{C_k + c} \frac{p_{cell}(\theta)}{\tau_d + p_{cell}(\theta)} n}_{\text{differentiation}} - \underbrace{k_2 m}_{\text{dedifferentiation}} - \underbrace{d_m m}_{\text{death}} \quad (3)$$

$$\frac{\partial \rho}{\partial t} + \nabla \cdot \left(\underbrace{\rho \frac{\partial \mathbf{u}}{\partial t}}_{\text{passive convection}} \right) = \underbrace{\left(r_\rho + \frac{r_{\rho,max} c}{C_\rho + c} \right) \frac{n + \eta_b m}{R_\rho^2 + \rho^2}}_{\text{production}} - \underbrace{d_\rho (n + \eta_d m) \rho}_{\text{degradation}} \quad (4)$$

$$\frac{\partial c}{\partial t} + \nabla \cdot \left(\underbrace{-D_c \nabla c}_{\text{diffusion}} + \underbrace{c \frac{\partial \mathbf{u}}{\partial t}}_{\text{passive convection}} \right) = \underbrace{\frac{k_c (n + \zeta m) c}{\Gamma + c}}_{\text{production}} - \underbrace{d_c c}_{\text{degradation}} \quad (5)$$

where $\mathbf{u}$ represents the tissue displacements. The parameter values and descriptions can be found in Tables I and II.

As the model reproduces wound contraction we consider that wound healing is driven by not only biochemical laws but also mechanical stimuli. Regarding the mechanical behaviour of the system, we express the balance between the internal stresses and the external forces as

$$\nabla \cdot (\boldsymbol{\sigma}_{ecm} + \boldsymbol{\sigma}_{cell}) = \mathbf{f}_{ext}, \quad (6)$$

where $\boldsymbol{\sigma}_{ecm}$ denotes the ECM stress contribution. Following most works in wound contraction [12, 6, 9], we assume that the skin behaves as a viscoelastic material. Therefore, $\boldsymbol{\sigma}_{ecm}$ can be written as

$$\boldsymbol{\sigma}_{ecm} = \mu_1 \frac{\partial \varepsilon}{\partial t} + \mu_2 \frac{\partial \theta}{\partial t} \mathbf{I} + \frac{E}{1 + \nu} \left(\varepsilon + \frac{\nu}{1 - 2\nu} \theta \mathbf{I} \right), \quad (7)$$

where the elastic modulus of the ECM varies with the collagen density, θ denotes the volumetric strain of the ECM, ε denotes the ECM deformation and $\mathbf{I}$ refers to the second order identity tensor. In contrast, $\boldsymbol{\sigma}_{cell}$ represents the stress exerted by the cells in the ECM

$$\boldsymbol{\sigma}_{cell} = p_{cell}(\theta) (1 + \xi m) \frac{n \rho}{R_\tau^2 + \rho^2} \mathbf{I}. \quad (8)$$

Cell densities play a crucial role in determining the contractile stress [18, 19], which is limited by the collagen density and modulated by a mechanical stimulus, p_{cell} . This stimulus represents the net stress of one cell per unit of ECM [22] and is a function of the matrix volumetric strain (θ),

$$p_{cell}(\theta) = \frac{K_{act}p_{max}}{K_{act}\theta_1 - p_{max}} (\theta_1 - \theta) \chi_{[\theta_1, \theta^*]}(\theta) + \frac{K_{act}p_{max}}{K_{act}\theta_2 - p_{max}} (\theta_2 - \theta) \chi_{(\theta^*, \theta_2]}(\theta) + K_{pas}\theta. \quad (9)$$

In this expression, the contributions of two different components of the cell to the generation of stresses are considered following the assumptions proposed by Moreo et al. (2008) [22]. The active contribution is a linear stiffness-dependent actuator that corresponds to the contractile mechanism, simulating the force provided by the actin and myosin cross-bridges at the sarcomere level during shortening. In fact, p_{max} , is the maximum force provided by the acto-myosin system. Following this approach, the series element K_{act} corresponds to the stiffness of the actin components that are aligned with the acto-myosin motors. This model also considers a parallel component, K_{pas} , which corresponds to the stiffness of different mechanical components of cells, such as, the membrane, microtubules and cytoplasm.

Finally, $\mathbf{f}_{ext}$ denotes the tethering forces created by the attachments to the underlying tissue, which are proportional to the collagen density and the tissue displacements,

$$\mathbf{f}_{ext} = s\rho\mathbf{u}. \quad (10)$$

The parameter values and descriptions of the mechanical equilibrium equations can be found in Table III.

2.2. Boundary conditions

When modelling deep wounds, special attention should be paid to the evolution of species and mechanical tension along the wound depth. Thus, detailed descriptions of the boundary conditions for the different species are given in this section.

Given the fixed morphology of the wound (deep and elongated), we assume that the mechanical evolution of the wound follows the plane strain hypotheses, neglecting deformations along the longitudinal direction of the wound. Furthermore, we simulate only the cross-section of the wound. The wound is assumed to behave in the same way in all its cross-sections, except near the two ends, considering the wound length is much larger than its other two dimensions (Figure 1). Let us denote the computational domain as Ω (see Figure 1). The computational domain consists of two parts, the wound and the surrounding undamaged tissue. The undamaged tissue consists of two layers, the dermis and the underlying tissue. The boundary of the domain Ω consists of two distinct and non-intersecting parts: the free boundary (Γ_t), which is in contact with the environment and can move freely, and the fixed boundary (Γ_u) which is attached to the underlying tissue. Mathematically, it can be written as $\Omega = \Gamma_u \cup \Gamma_t$ with $\Gamma_u \cap \Gamma_t = \emptyset$.

The computational domain Ω is large enough so that boundary effects on the evolution of the species can be disregarded. Hence, on the outer boundary Γ_u diffusive fluxes and displacements are not allowed:

$$\nabla Q \cdot \mathbf{n}_\perp = 0 \quad \text{and} \quad \mathbf{u} = \mathbf{0} \quad \text{on} \quad \Gamma_u, \quad (11)$$

for all species Q that migrate or diffuse through the tissue (that is, fibroblasts n and the generic growth factor c). Here $\mathbf{n}_\perp$ denotes the normal vector pointing out from Ω . On the upper boundary Γ_t the situation is slightly different. The mass conservation of species Q implies, again, that there is no diffusive flux. However, there is no constrain on the displacement profile. Consequently, the stress vector $\mathbf{t} = \boldsymbol{\sigma} \mathbf{n}_\perp$ should be zero, which yields

$$\nabla Q \cdot \mathbf{n}_\perp = 0 \quad \text{and} \quad \mathbf{t} = \mathbf{0} \quad \text{on} \quad \Gamma_t. \quad (12)$$

Hence, Γ_t behaves as a free boundary. Note that models focusing on the evolution of the wound surface do not address this moving boundary, and, therefore the boundary conditions in those cases are given in Eq. (11) for the complete boundary.

2.3. Initial conditions

We initialise the analysis at the beginning of the proliferative stage, when cells have not yet begun to appear in the wound site. As initial conditions we fix the concentration of the species in the entire domain. The cellular species, fibroblasts and myofibroblasts, are not yet present in the wound. However, the undamaged tissue is full of fibroblasts; myofibroblasts are not present here because they only appear where damage has occurred. The new ECM has not begun to form in the wound site, and thus there is only a small concentration of collagen belonging to the temporary fibrin clot. The undamaged tissue has a normal collagen density. Finally, because during the previous stages, different growth factors were released into the wound site, we initiate our analysis with the wound site full of growth factors, but no growth factors present in the undamaged skin.

3. NUMERICAL METHOD

3.1. Weak formulation

Using Gauss' theorem, the integrals over the domain of computation of Eqs. (1) and (6) multiplied by sufficiently smooth weighting function v_Q and $\mathbf{v}$, respectively, result in

$$\int_{\Omega} \frac{\partial Q}{\partial t} v_Q d\Omega - \int_{\Omega} \mathbf{J}_Q \cdot \nabla v_Q d\Omega = \int_{\Omega} f_Q v_Q d\Omega - \int_{\partial\Omega} \mathbf{J}_Q \cdot \mathbf{n}_\perp v_Q d\Gamma, \quad (13)$$

$$\int_{\Omega} \boldsymbol{\sigma} : \frac{1}{2} (\nabla \mathbf{v} + \nabla \mathbf{v}^T) d\Omega = \int_{\Omega} \mathbf{f}_{ext} \cdot \mathbf{v} d\Omega + \int_{\partial\Omega} \mathbf{t} \cdot \mathbf{v} d\Gamma, \quad (14)$$

where $\mathbf{n}_\perp$ denotes the normal vector pointing out from Ω and $\boldsymbol{\sigma}$ comprises the ECM stress contribution and the stress exerted by the cells

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_{ecm} + \boldsymbol{\sigma}_{cell}. \quad (15)$$

For all considered species, the flux term $\mathbf{J}_Q$, consists of a passive convection term $Q \frac{\partial \mathbf{u}}{\partial t}$ and additional diffusive fluxes. Given there are no diffusive fluxes across the boundaries $\Gamma_{\mathbf{u}}$ and $\Gamma_{\mathbf{t}}$, and $\mathbf{u} = \mathbf{0}$ on $\Gamma_{\mathbf{u}}$, we can write the boundary integral in Eq. (13) as

$$\int_{\partial\Omega} \mathbf{J}_Q \cdot \mathbf{n}_{\perp} v_Q d\Gamma = \int_{\Gamma_{\mathbf{t}}} Q v_Q \frac{\partial \mathbf{u}}{\partial t} \cdot \mathbf{n}_{\perp} d\Gamma \quad (16)$$

without a loss of generality. Due to the boundary conditions, $\mathbf{v}$ satisfies $\mathbf{v} = \mathbf{0}$ on $\Gamma_{\mathbf{u}}$ and $\mathbf{t} = \mathbf{0}$ on $\Gamma_{\mathbf{t}}$. Hence, the boundary integral in Eq. (14) vanishes

$$\int_{\partial\Omega} \mathbf{t} \cdot \mathbf{v} d\Gamma = \int_{\Gamma_{\mathbf{v}}} \mathbf{t} \cdot \mathbf{v} d\Gamma + \int_{\Gamma_{\mathbf{t}}} \mathbf{t} \cdot \mathbf{v} d\Gamma = 0. \quad (17)$$

Therefore, the weak formulation of the problem results in

$$\begin{aligned} \int_{\Omega} \frac{\partial Q}{\partial t} v_Q d\Omega - \int_{\Omega} \mathbf{J}_Q \cdot \nabla v_Q d\Omega &= \int_{\Omega} f_Q v_Q d\Omega - \int_{\Gamma_{\mathbf{t}}} Q v_Q \frac{\partial \mathbf{u}}{\partial t} \cdot \mathbf{n}_{\perp} d\Gamma, \\ \int_{\Omega} \sigma : \frac{1}{2} (\nabla \mathbf{v} + \nabla \mathbf{v}^T) d\Omega &= \int_{\Omega} \mathbf{f}_{ext} \cdot \mathbf{v} d\Omega, \end{aligned} \quad (18)$$

for all weighting functions v_Q and $\mathbf{v}$ that are sufficiently differentiable and satisfy $\mathbf{v} = \mathbf{0}$ on $\Gamma_{\mathbf{u}}$. Note that due to the considered wound morphology, an integral over the free boundary of the domain arises. As the wound geometry dynamically changes, the position of $\Gamma_{\mathbf{t}}$ and the computation of the normal vector $\mathbf{n}_{\perp}$ need to be updated for each time increment. We nevertheless assume an small deformation approach during each time increment. The geometry was updated after each time increment using an updated Lagrangian approximation to take the change in the normal outward vector and the change in the wound geometry into account.

We implement and calculate all integrals that are not present in existing wound contraction works due to their plane stress assumptions. Nevertheless, it is necessary to calculate these terms only for those elements that belong to the free boundary in the plane strain or three-dimensional simulations. In this work, this effect can not be neglected as the boundary is moving and its contribution is significant.

3.2. Finite element approximation

To reach the Finite Element approximation it is necessary to express the primary unknowns in terms of their nodal values through their associated shape functions [27]:

$$Q^h(\mathbf{x}, t) = \mathbf{N}_Q(\mathbf{x}) \mathbf{Q}(t), \quad \mathbf{u}^h(\mathbf{x}, t) = \mathbf{N}_u(\mathbf{x}) \mathbf{U}(t), \quad (19)$$

where the finite element solution is denoted by the superscript h . The final discrete and nonlinear system of equations is reached by substituting these approximations into the weak formulation (Eq.(13) and Eq.(14)) and setting the weighting functions equal to the shape functions. The time-dependent nodal values of the primary unknowns are determined from the resulting system of equations, which can be expressed as a balance of internal and external forces matrices

$$\mathbb{F}(\mathbb{Z}_{n+1}) := \mathbb{F}^{int}(\mathbb{Z}_{n+1}) - \mathbb{F}^{ext}(\mathbb{Z}_{n+1}) = \mathbf{0}, \quad (20)$$

where $\mathbb{F}^{int}$ comprises the temporal derivative and flux terms and $\mathbb{F}^{ext}$ the reaction terms on the governing equations. The vector of unknowns, $\mathbb{Z}$, denotes the ordered primary variables nodal values

$$\mathbb{Z} = (\mathbf{n}^T \mathbf{m}^T \boldsymbol{\rho}^T \mathbf{c}^T \mathbf{U}^T)^T. \quad (21)$$

Hence, nodal submatrices for the fibroblasts are given by

$$\mathbf{F}_n^{int} = \int_{\Omega} \mathbf{N}_n^T \frac{\partial n}{\partial t} d\Omega + \int_{\Omega} \nabla \mathbf{N}_n^T \left[D_n \nabla n - \frac{a_n}{(b_n + c)^2} n \nabla c - n \frac{\partial \mathbf{u}}{\partial t} \right] d\Omega + \int_{\Gamma_t} \mathbf{N}_n^T n \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \quad (22)$$

$$\mathbf{F}_n^{ext} = \int_{\Omega} \mathbf{N}_n^T \left[\left(r_n + \frac{r_{n,max}c}{C_{1/2} + c} \right) n \left(1 - \frac{n}{K} \right) - \frac{k_{1,max}c}{C_k + c} \frac{p_{cell}(\theta)}{\tau_d + p_{cell}(\theta)} n + k_2 m \right] d\Omega - \int_{\Omega} \mathbf{N}_n^T d_n n d\Omega \quad (23)$$

The remainder matrices are included in Appendix A. To obtain the solution of the resulting nonlinear system of equations we use an explicit time integration method [28] and a

Newton-Raphson linearisation. The non-zero entries of the Jacobian matrices $\frac{\partial \mathbb{F}^{int}}{\partial \mathbb{Z}}$ and $\frac{\partial \mathbb{F}^{ext}}{\partial \mathbb{Z}}$ are presented in Appendix A.

To properly reproduce the natural boundary conditions on the free boundary, it is necessary to compute the corresponding boundary integrals. As our model is two-dimensional the element integrals are surface integrals, and the boundary integrals are line integrals. To determine the boundary conditions, we need to calculate the boundary integrals only for those elements that belong to the free boundary and only in those element faces that belong to the boundary, as they are zero in the rest of the domain.

The Finite Element formulation is implemented using an updated Lagrangian approach. Hence, the reference configuration is updated after each time increment, even though a small strain assumption is considered. This update is needed to accurately compute the boundary conditions effect on the process, which depends strongly on the surface of the wound, as the natural boundary conditions contribution changes along the outwards normal direction. To perform the calculation process, we initially have the wound geometry, the species densities along the entire wound and the boundary conditions. We simulate the wound evolution over 30 days, in shorter steps of 0.1 days, to obtain an accurate model of the evolution of the geometry. After the first analysis (corresponding to one step of 0.1 days), we update the wound geometry and perform a new analysis. This process can be repeated as many times as needed to complete the total time studied.

4. EXAMPLE OF APPLICATION

Two different wound geometries are studied in this work: two long wounds with a semicircular or semielliptical transverse section. These wounds are characterised by having a large length and a non-depreciable depth. Therefore, the wounds can be studied through their transverse sections using the plane strain approach (Figure 2). The semicircular wound has a diameter (d) of 0.5 cm, whereas the semielliptical wound has an aspect ratio of two, that is, its depth (b) is twice its width (a). The dimensions of the semielliptical wound are such that it has the same cross-sectional area as the semicircular wound. Both wounds are surrounded by healthy skin, with the domain being sufficiently large to neglect the boundary effects. The undamaged tissue consists of two different layers, the dermis and the underlying tissue. Human dermis varies in depth depending on its anatomical location; it can have a thickness between 1 and 4 mm [29]. Here, we assume that the dermis has a depth of 1.5 mm and that the simulated wounds are deep enough to penetrate the dermis. Considering the symmetry of the wound and the surrounding skin, we simulate half of the entire geometry.

5. RESULTS

First, we study the spatial contraction and temporal evolution of the wound. In Figure 3, we present the normalised contraction curve for the two studied geometries. In this curve we represent the area of the simulated domain (half of the wound) during the simulated time (30 days) with respect to its initial area. We observe that, for both wounds, the main part of the contraction occurs during the first few days, after which the wound contracts more slowly. The highest contraction percentage occurs around day 10 in the semielliptical wound and around day 12 in the semicircular wound. From this point to the end of the 30 days, the wounds expand slowly. If we compare the contraction of both wounds, we see that the semicircular wound contracts more than the semielliptical one, reducing its size to 84.2% of its initial area, whereas the semielliptical wound contracts to 86.5% of its initial size. In the early stages of wound contraction (5 days), the semicircular wound contracts faster than the semielliptical wound. After this transitory phase, both wounds seem to reach a stationary state at the same time. We observe that the wound centre (see Figure 2) is the point where the downward boundary displacement is the highest, approximately 0.66 mm in the semicircular wound and 0.82 mm in the semielliptical one. We also observe that, the further we move from this point, the smaller the downward displacement of the free surface is.

Regarding the final geometry of the wound, Figure 4 shows the evolution of the wound geometry at different times and how the free boundary of the wound moves down due to the myofibroblasts contraction forces. Observing the evolution of different species in the wound (Figure 4) we see fibroblasts invade the wound site as the wound heals. The fibroblasts movement in the semielliptical wound is faster than in the semicircular wound; the semielliptical wound site is almost saturated with fibroblasts by day 3 whereas the semicircular one never reaches this level within the simulated period. The fibroblasts concentration far from the wound site remains invariable during the entire process. Similarly, we observe the evolution of myofibroblasts in both wounds (Figure 5). Myofibroblasts quickly appear in the wound and in the closest healthy skin when there is

damage and disappear after contraction. We observe that the higher contractions occur while myofibroblasts are in the tissue and the wound stabilises when they disappear.

Finally, we observe how the volumetric strain of the wound and the surrounding tissue evolves (Figure 6) over time. The volumetric strain (θ) denotes how much the tissue has deformed (contracted or expanded) from its initial state. During the entire process the tissue that is far from the wound does not experience any contraction. Inside the wound site, we observe that contraction begins at the boundary between the wound and healthy skin. Furthermore, as the cell concentration increases and cells invade the wound centre, the wound contracts. We observe that the final contraction is highest in the wound centre. The distributions remain without changes from the moment that the contraction becomes stabilised in the contraction curve (Figure 3).

6. DISCUSSION

Computational models have become more important during recent years [11, 30]. These models can reproduce the evolution of wounds, which has not been deeply studied experimentally. There are few computational studies on human wounds and those in the literature have mostly study planar wounds. Long, deep wounds are more difficult to study computationally than planar wounds. Because long deep wounds are more complex; a deeper knowledge of the different phenomena that occur during wound healing is essential to establishing a successful healing model. In this work, we present a model that predicts how deep elongated wounds contract depending on how different species that are present in the skin evolve and behave. Our work follows the work of Javierre et al. [6], which was based on a previous biochemical wound contraction model developed [12]. Javierre et al. [6] studied the behaviour of two-dimensional planar wounds with different sizes and geometries. There are a number of models [12, 9, 15], that also studied planar wounds but took a one-dimensional perspective with simpler and more restrictive models. Although those models properly reproduce the healing process, they are only useful for a small number of wound geometries (straight and circular); they are not applicable to real complex wounds.

All the previous 1D and 2D models, only reproduced the behavior of planar wounds. These wounds are superficial and their area determines the healing process of the wound.

There are few animal models for the study of wound contraction [31, 32]. Most of them study superficial wounds, not examining the processes that occur along the transversal section of the wound. The present model elucidates the role of wound depth on contraction kinetics; hence, one of the most relevant outcomes of this work is the direct relationship among wound morphology, wound contraction and scar formation. As wound contraction represents an intermediate step between healing and scar formation, the results here obtained could predict the final scar aspect from wound geometry. Wound contraction will determine the posterior size and shape of the scar. In fact, we expect that deeper wounds will lead into more pronounced scars, because the downward tissue displacement is higher in deeper wounds. Thus, scars from deeper wounds are expected to be more perceptible. This model is a step forward to analyse suture patterns in a three dimensional model. This relationship

could be used to identify a suture pattern that minimises the contraction of the wound and consequently results in a smaller scar [33]. This prediction would be of special interest in plastic surgery, where the size and visibility of scars is one of the most important factors.

More serious wounds, such as ulcers and surgery scars are not comparable with planar wounds. In these wounds, the transversal behaviour (along its depth) is more relevant than the superficial behaviour. Most of the change in the geometry is due to the movement of the free boundary, which is in contact with the environment and can move without any impediment. These wounds have more importance as they more closely resemble real clinical wounds, which are often difficult to heal and usually require help to heal properly. Previous models cannot reproduce these wounds as they do not mimic the real behaviour of the species in the free boundary. A first attempt to study deep wounds was made in [7]. However, this work focused on the coupling of wound closure, angiogenesis and contraction.

In this work, we present a model to simulate deep wounds and reproduce the behaviour along their depths. Although these wounds are more similar to real wounds, their behaviour is also much more difficult to reproduce. Mathematically, the difficulty of these wounds is translated into a higher number of terms in the weak formulation. As the effect of the free boundary is not negligible, it is necessary to solve both the element and the boundary integrals that define the problem. In planar wounds, the boundary integrals vanish during the formulation. To the best of our knowledge, long deep wounds have not been previously studied and these equations have not been solved without neglecting the natural boundary conditions term and updating the geometry using an updated Lagrangian approach. Wounds with different areas and same depth were also analysed (not included in the paper). Results for those geometries shown a similar evolution of the wound area (normalised with respect to the initial wound size). From this observation we can conclude that wound depth has a larger influence on the contraction kinetics than wound width. Deeper wounds, with less area in contact with the surrounding environment with respect to its depth, contract less than wider wounds, similar to semicircular wounds. Although there are no other studies on the wound contraction process in deep wounds our results qualitatively agree with experimental works [34, 35] and computational [12, 13] results for the contraction curves of planar wounds. The major difference in these curves is that the contraction is faster in deep wounds.

To perform this analysis, several simplifications were needed. First, the model considers a small strain approach and uses an updated Lagrangian approach; we update the reference configuration every time increment. The deformations in the tissue are small enough to satisfy the small strain hypothesis (lower than 0.6% at all time increments).

The contraction process is also known to be appreciably influenced by the relative position of the wound with the skin tension lines. Wounds parallel to tension lines heal better, creating smaller scars, whereas wounds perpendicular to tension lines generate larger scars [36]. Another limitation of the model is that we neglect the effect of the collagen fibres orientation in the tissue, which would modify the effect of the stress exerted by cells. Including the effect of these fibres would provide the model with more realistic anisotropic

behaviour. In the simulated contraction stage, the wound fibres are randomly dispersed in the matrix; its reorganisation takes several months [14]. The effect of the collagen fibres would be more important during the remodelling phase.

Wound healing in the skin is one of today's major medical challenges. Although surgery techniques have improved and surgeons can now perform a number of different surgeries, the most severe difficulties, caused by scarring, usually occur after surgery. Moreover, ulcers and cuts are difficult wounds to control. Thus, mathematical models that reproduce the healing process can help us understand the healing mechanism and learn how to improve it.

ACKNOWLEDGEMENTS

This research was supported by the Spanish Ministry of Economy and Competitiveness (Grant DPI2012-32880 and BES2010-037281). Financial support of the European Research Council (ERC) through project ERC-2012-StG 306751 is gratefully acknowledged.

A. MATRICES OF THE INTERNAL AND EXTERNAL FORCES

The matrices of the internal and external forces appearing in Eq.(20) can be written

$$\mathbf{F}_n^{int} = \int_{\Omega} \mathbf{N}_n^T \frac{\partial n}{\partial t} d\Omega + \int_{\Omega} \nabla \mathbf{N}_n^T \left(D_n \nabla n - \frac{a_n}{(b_n+c)^2} n \nabla c - n \frac{\partial \mathbf{u}}{\partial t} \right) d\Omega + \int_{\Gamma_t} \mathbf{N}_n^T n \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \quad (24)$$

$$\mathbf{F}_m^{int} = \int_{\Omega} \mathbf{N}_m^T \frac{\partial m}{\partial t} d\Omega - \int_{\Omega} \nabla \mathbf{N}_m^T m \frac{\partial \mathbf{u}}{\partial t} d\Omega + \int_{\Gamma_t} \mathbf{N}_m^T m \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \quad (25)$$

$$\mathbf{F}_{\rho}^{int} = \int_{\Omega} \mathbf{N}_{\rho}^T \frac{\partial \rho}{\partial t} d\Omega - \int_{\Omega} \nabla \mathbf{N}_{\rho}^T \rho \frac{\partial \mathbf{u}}{\partial t} d\Omega + \int_{\Gamma_t} \mathbf{N}_{\rho}^T \rho \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \quad (26)$$

$$\mathbf{F}_c^{int} = \int_{\Omega} \mathbf{N}_c^T \frac{\partial c}{\partial t} d\Omega + \int_{\Omega} \nabla \mathbf{N}_c^T \left(D_c \nabla c - c \frac{\partial \mathbf{u}}{\partial t} \right) d\Omega + \int_{\Gamma_t} \mathbf{N}_c^T c \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \quad (27)$$

$$\mathbf{F}_u^{int} = \int_{\Omega} \mathbf{B}_u^T \left[\mathbf{D}_{elas} \frac{\rho}{\rho_0} \mathbf{B}_u \mathbf{U} + \mathbf{D}_{visco} \mathbf{B}_u \dot{\mathbf{U}} + p_{cell}(\theta) (1 + \xi m) \frac{n\rho}{R_z^2 + \rho^2} \mathbf{I} \right] d\Omega \quad (28)$$

and

$$\mathbf{F}_n^{ext} = \int_{\Omega} \mathbf{N}_n^T \left[\left(r_n + \frac{r_{n,max}c}{C_{1/2}+c} \right) n \left(1 - \frac{n}{K} \right) - \frac{k_{1,max}c}{C_k+c} \frac{p_{cell}(\theta)}{\tau_d + p_{cell}(\theta)} n + k_2 m \right] d\Omega - \int_{\Omega} \mathbf{N}_n^T d_n n d\Omega \quad (29)$$

$$\begin{aligned} \mathbf{F}_m^{ext} = & \int_{\Omega} \mathbf{N}_m^T \epsilon_r \left(r_n + \frac{r_{n,max}c}{C_{1/2}+c} \right) m \left(1 - \frac{m}{K} \right) d\Omega + \int_{\Omega} \mathbf{N}_m^T \frac{k_{1,max}c}{C_k+c} \frac{p_{cell}(\theta)}{\tau_d+p_{cell}(\theta)} n d\Omega \\ & - \int_{\Omega} \mathbf{N}_m^T (k_2 m + d_m m) d\Omega \end{aligned} \quad (30)$$

$$\mathbf{F}_{\rho}^{ext} = \int_{\Omega} \mathbf{N}_{\rho}^T \left[\left(r_{\rho} + \frac{r_{\rho,max}c}{C_{\rho}+c} \right) \frac{n+\eta_b m}{R_{\rho}^2+\rho^2} - d_{\rho} (n+\eta_d m) \rho \right] d\Omega \quad (31)$$

$$\mathbf{F}_c^{ext} = \int_{\Omega} \mathbf{N}_c^T \left(\frac{k_c (n+\zeta m) c}{\Gamma+c} - d_c c \right) d\Omega \quad (32)$$

$$\mathbf{F}_u^{ext} = - \int_{\Omega} \mathbf{N}_u^T s \rho u d\Omega \quad (33)$$

where all the terms containing $\mathbf{n}_{\perp}$ refer to the boundary and are the terms that allow us to reproduce the boundary behavior. To obtain the solution of the resulting system of equations we use an explicit integration method taking the non-zero entries of the Jacobian matrices

$$\frac{\partial \mathbb{F}^{int}}{\partial \mathbb{Z}} \text{ and } \frac{\partial \mathbb{F}^{ext}}{\partial \mathbb{Z}}.$$

$$\begin{aligned} \frac{\partial \mathbf{F}_n^{int}}{\partial \mathbf{n}} = & \frac{1}{\Delta t} \int_{\Omega} \mathbf{N}_n^T \mathbf{N}_n d\Omega + \int_{\Omega} \nabla \mathbf{N}_n^T D_n \nabla \mathbf{N}_n d\Omega - \int_{\Omega} \nabla \mathbf{N}_n^T \left[\frac{a_n}{(b_n+c)^2} \nabla c + \frac{\partial \mathbf{u}}{\partial t} \right] \mathbf{N}_n d\Omega \\ & + \int_{\Gamma_t} \mathbf{N}_n^T \mathbf{N}_n \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \end{aligned} \quad (34)$$

$$\begin{aligned} \frac{\partial \mathbf{F}_n^{int}}{\partial \mathbf{c}} = & - \int_{\Omega} \nabla \mathbf{N}_n^T \frac{a_n}{(b_n+c)^2} n \nabla \mathbf{N}_c d\Omega + \int_{\Omega} \nabla \mathbf{N}_n^T \frac{2a_n}{(b_n+c)^3} n \nabla c \mathbf{N}_c d\Omega \\ \frac{\partial \mathbf{F}_n^{int}}{\partial \mathbf{U}} = & - \frac{1}{\Delta t} \int_{\Omega} \nabla \mathbf{N}_n^T n \mathbf{N}_u d\Omega + \frac{1}{\Delta t} \int_{\Gamma_t} \mathbf{N}_n^T n \mathbf{N}_u \mathbf{n}_{\perp} d\Gamma \end{aligned} \quad (35)$$

$$\frac{\partial \mathbf{F}_m^{int}}{\partial \mathbf{m}} = \frac{1}{\Delta t} \int_{\Omega} \mathbf{N}_m^T \mathbf{N}_m d\Omega - \int_{\Omega} \nabla \mathbf{N}_m^T \frac{\partial \mathbf{u}}{\partial t} \mathbf{N}_m d\Omega + \int_{\Gamma_t} \mathbf{N}_m^T \mathbf{N}_m \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \quad (36)$$

$$\frac{\partial \mathbf{F}_m^{int}}{\partial \mathbf{U}} = - \frac{1}{\Delta t} \int_{\Omega} \nabla \mathbf{N}_m^T m \mathbf{N}_u d\Omega + \frac{1}{\Delta t} \int_{\Gamma_t} \mathbf{N}_m^T m \mathbf{N}_u \mathbf{n}_{\perp} d\Gamma \quad (37)$$

$$\frac{\partial \mathbf{F}_{\rho}^{int}}{\partial \rho} = \frac{1}{\Delta t} \int_{\Omega} \mathbf{N}_{\rho}^T \mathbf{N}_{\rho} d\Omega - \int_{\Omega} \nabla \mathbf{N}_{\rho}^T \frac{\partial \mathbf{u}}{\partial t} \mathbf{N}_{\rho} d\Omega + \int_{\Gamma_t} \mathbf{N}_{\rho}^T \mathbf{N}_{\rho} \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_{\perp} d\Gamma \quad (38)$$

$$\begin{aligned}\frac{\partial \mathbf{F}_\rho^{int}}{\partial \mathbf{U}} &= \frac{-1}{\Delta t} \int_\Omega \nabla \mathbf{N}_\rho^T \rho \mathbf{N}_\mathbf{u} d\Omega + \frac{1}{\Delta t} \int_{\Gamma_t} \mathbf{N}_\rho^T \rho \mathbf{N}_\mathbf{u} \mathbf{n}_\perp d\Gamma \\ \frac{\partial \mathbf{F}_c^{int}}{\partial \mathbf{c}} &= \frac{1}{\Delta t} \int_\Omega \mathbf{N}_c^T \mathbf{N}_c d\Omega + \int_\Omega \nabla \mathbf{N}_c^T D_c \nabla \mathbf{N}_c - \int_\Omega \nabla \mathbf{N}_c^T \left(\frac{\partial \mathbf{u}}{\partial t} \mathbf{N}_c d\Omega + \int_{\Gamma_t} \mathbf{N}_c^T \mathbf{N}_c \frac{\partial \mathbf{u}}{\partial t} \mathbf{n}_\perp d\Gamma \right) \quad (39)\end{aligned}$$

$$\frac{\partial \mathbf{F}_c^{int}}{\partial \mathbf{U}} = \frac{-1}{\Delta t} \int_\Omega \nabla \mathbf{N}_c^T c \mathbf{N}_\mathbf{u} d\Omega + \frac{1}{\Delta t} \int_{\Gamma_t} \mathbf{N}_c^T c \mathbf{N}_\mathbf{u} \mathbf{n}_\perp d\Gamma \quad (40)$$

$$\frac{\partial \mathbf{F}_\mathbf{u}^{int}}{\partial \mathbf{n}} = \int_\Omega \mathbf{B}_\mathbf{u}^T p_{cell}(\theta) (1 + \xi m) \frac{\rho}{R_\tau^2 + \rho^2} \mathbf{I} \mathbf{N}_n d\Omega \quad (41)$$

$$\frac{\partial \mathbf{F}_\mathbf{u}^{int}}{\partial \mathbf{m}} = \int_\Omega \mathbf{B}_\mathbf{u}^T p_{cell}(\theta) \frac{\xi n \rho}{R_\tau^2 + \rho^2} \mathbf{I} \mathbf{N}_m d\Omega \quad (42)$$

$$\frac{\partial \mathbf{F}_\mathbf{u}^{int}}{\partial \rho} = \int_\Omega \mathbf{B}_\mathbf{u}^T \left[\mathbf{D}_{elas} \frac{1}{\rho_0} \mathbf{B}_\mathbf{u} \mathbf{U} + p_{cell}(\theta) (1 + \xi m) \frac{n}{(R_\tau^2 + \rho^2)^2} (R_\tau^2 - \rho^2) \mathbf{I} \right] \mathbf{N}_\rho d\Omega \quad (43)$$

$$\begin{aligned}\frac{\partial \mathbf{F}_\mathbf{u}^{int}}{\partial \mathbf{U}} &= \frac{1}{\Delta t} \int_\Omega \mathbf{B}_\mathbf{u}^T \mathbf{D}_{visco} \mathbf{B}_\mathbf{u} d\Omega + \int_\Omega \mathbf{B}_\mathbf{u}^T \mathbf{D}_{elas} \frac{\rho}{\rho_0} \mathbf{B}_\mathbf{u} d\Omega \\ &+ \int_\Omega \mathbf{B}_\mathbf{u}^T K_{cell}(\theta) (1 + \xi m) \frac{n \rho}{R_\tau^2 + \rho^2} \mathbf{I} \tilde{\nabla} \mathbf{N}_\mathbf{u} d\Omega \quad (44)\end{aligned}$$

$$\begin{aligned}\frac{\partial \mathbf{F}_n^{ext}}{\partial \mathbf{n}} &= \int_\Omega \mathbf{N}_n^T \left(r_n + \frac{r_{n,max} c}{C_{1/2} + c} \right) \left(1 - \frac{2n}{K} \right) \mathbf{N}_n d\Omega \\ &- \int_\Omega \mathbf{N}_n^T \left(\frac{k_{1,max} c}{C_k + c} \frac{p_{cell}(\theta)}{\tau_d + p_{cell}(\theta)} + d_n \right) \mathbf{N}_n d\Omega \quad (45)\end{aligned}$$

$$\frac{\partial \mathbf{F}_n^{ext}}{\partial \mathbf{m}} = \int_\Omega \mathbf{N}_n^T k_2 \mathbf{N}_m d\Omega \quad (46)$$

$$\begin{aligned}\frac{\partial \mathbf{F}_c^{ext}}{\partial \mathbf{c}} &= \int_\Omega \mathbf{N}_n^T \left[\frac{r_{n,max} C_{1/2}}{(C_{1/2} + c)^2} n \left(1 - \frac{n}{K} \right) \right. \\ &\quad \left. - \frac{k_{1,max} C_k}{(C_k + c)^2} \frac{p_{cell}(\theta)}{\tau_d + p_{cell}(\theta)} n \right] \mathbf{N}_c d\Omega \quad (47)\end{aligned}$$

$$\frac{\partial \mathbf{F}_n^{ext}}{\partial \mathbf{U}} = - \int_\Omega \mathbf{N}_n^T \frac{k_{1,max} c}{C_k + c} \frac{\tau_d K_{cell}(\theta)}{(\tau_d + p_{cell}(\theta))^2} n \tilde{\nabla} \mathbf{N}_\mathbf{u} d\Omega \quad (48)$$

$$\frac{\partial \mathbf{F}_m^{ext}}{\partial \mathbf{n}} = \int_{\Omega} \mathbf{N}_m^T \frac{k_{1,max} c}{C_k + c} \frac{p_{cell}(\theta)}{\tau_d + p_{cell}(\theta)} \mathbf{N}_n d\Omega \quad (49)$$

$$\frac{\partial \mathbf{F}_m^{ext}}{\partial \mathbf{m}} = \int_{\Omega} \mathbf{N}_m^T \left[\epsilon_r \left(r_n + \frac{r_{n,max} c}{C_{1/2} + c} \right) \left(1 - \frac{2m}{K} \right) - k_2 - d_m \right] \mathbf{N}_m d\Omega \quad (50)$$

$$\begin{aligned} \frac{\partial \mathbf{F}_c^{ext}}{\partial \mathbf{c}} = & \int_{\Omega} \mathbf{N}_m^T \left[\epsilon_r \frac{r_{n,max} C_{1/2}}{(C_{1/2} + c)^2} m \left(1 - \frac{m}{K} \right) \right. \\ & \left. + \frac{k_{1,max} C_k}{(C_k + c)^2} \frac{p_{cell}(\theta)}{\tau_d + p_{cell}(\theta)} n \right] \mathbf{N}_c d\Omega \end{aligned} \quad (51)$$

$$\frac{\partial \mathbf{F}_m^{ext}}{\partial \mathbf{U}} = \int_{\Omega} \mathbf{N}_m^T \frac{k_{1,max} c}{C_k + c} \frac{\tau_d K_{cell}(\theta)}{(\tau_d + p_{cell}(\theta))^2} n \tilde{\nabla} \mathbf{N}_u d\Omega \quad (52)$$

$$\begin{aligned} \frac{\partial \mathbf{F}_\rho^{ext}}{\partial \mathbf{n}} = & \int_{\Omega} \mathbf{N}_\rho^T \left(r_\rho + \frac{r_{\rho,max} c}{C_\rho + c} \right) \frac{1}{R_\rho^2 + \rho^2} \mathbf{N}_n d\Omega \\ & - \int_{\Omega} \mathbf{N}_\rho^T d_\rho \rho \mathbf{N}_n d\Omega \end{aligned} \quad (53)$$

$$\begin{aligned} \frac{\partial \mathbf{F}_\rho^{ext}}{\partial \mathbf{m}} = & \int_{\Omega} \mathbf{N}_\rho^T \left(r_\rho + \frac{r_{\rho,max} c}{C_\rho + c} \right) \frac{\eta_b}{R_\rho^2 + \rho^2} \mathbf{N}_m d\Omega \\ & - \int_{\Omega} \mathbf{N}_\rho^T d_\rho \eta_d \rho \mathbf{N}_m d\Omega \end{aligned} \quad (54)$$

$$\frac{\partial \mathbf{F}_\rho^{ext}}{\partial \rho} = - \int_{\Omega} \mathbf{N}_\rho^T \left(r_\rho + \frac{r_{\rho,max} c}{C_\rho + c} \right) \frac{n + \eta_b m}{(R_\rho^2 + \rho^2)^2} 2\rho \mathbf{N}_\rho d\Omega \quad (55)$$

$$\frac{\partial \mathbf{F}_\rho^{ext}}{\partial \mathbf{c}} = \int_{\Omega} \mathbf{N}_\rho^T \frac{r_{\rho,max} C_\rho}{(C_\rho + c)^2} \frac{n + \eta_b m}{R_\rho^2 + \rho^2} \mathbf{N}_c d\Omega \quad (56)$$

$$\frac{\partial \mathbf{F}_c^{ext}}{\partial \mathbf{n}} = \int_{\Omega} \mathbf{N}_c^T \frac{k_c}{\Gamma + c} c \mathbf{N}_n d\Omega \quad (57)$$

$$\frac{\partial \mathbf{F}_c^{ext}}{\partial \mathbf{m}} = \int_{\Omega} \mathbf{N}_c^T \frac{k_c \xi}{\Gamma + c} c \mathbf{N}_m d\Omega \quad (58)$$

$$\frac{\partial \mathbf{F}_c^{ext}}{\partial \mathbf{c}} = \int_{\Omega} \mathbf{N}_c^T \left(\frac{k_c (n + \zeta m) \Gamma}{(\Gamma + c)^2} - d_c \right) \mathbf{N}_c d\Omega \quad (59)$$

$$\frac{\partial \mathbf{F}_u^{ext}}{\partial \rho} = - \int_{\Omega} \mathbf{N}_u^T s \mathbf{u} \mathbf{N}_\rho d\Omega \quad (60)$$

$$\frac{\partial \mathbf{F}_u^{ext}}{\partial \mathbf{U}} = - \int_{\Omega} \mathbf{N}_u^T s \rho \mathbf{N}_u d\Omega \quad (61)$$

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Figure 1.
Boundary conditions.

Figure 2.
Scheme of the semicircular and the semielliptical wounds.

Figure 3.
Normalised contraction curve for the semicircular and the semielliptical wounds.

Figure 4. Fibroblast concentration in the semicircular (top) and semielliptical (bottom) wounds at different time points (from left to right, days 0, 3, 6, 15 and 30.)

Figure 5. Myofibroblast concentration in the semicircular (top) and semielliptical (bottom) wounds at different time points (from left to right, days 0, 3, 6, 15 and 30.)

Figure 6.

Total volumetric deformation in the semicircular (top) and semielliptical (bottom)wounds at different time points (from left to right, days 0, 3, 6, 15 and 30.)

Table I

List of model parameters related to fibroblasts and myofibroblasts kinetics.

Parameter	Description	Value	Observations
n_0	fibroblasts density in undamaged dermis	10^4 cells/cm ³	[12]
D_n	fibroblasts diffusion rate	$2 \cdot 10^{-2}$ cm ² /day	[23] [†]
a_n	together with b_n determines the maximal chemotaxis rate per unit of GF conc.	$4 \cdot 10^{-10}$ g/cm day	[6]
b_n	GF concentration that produces 25% of the maximal chemotactic response	$2 \cdot 10^{-9}$ g/cm ³	[6]
r_n	fibroblasts proliferation rate	0.832 day ⁻¹	[23]
$r_{n,max}$	maximal rate of GF induced fibroblasts proliferation	0.3 day ⁻¹	[6]
$C_{1/2}$	half-maximal GF enhancement of fibroblasts proliferation	10^{-8} g/cm ³	[12]
K	fibroblasts maximal capacity in dermis	10^7 cells/cm ³	[12]
$k_{1,max}$	maximal rate of fibroblasts differentiation	0.8 day ⁻¹	[6]
C_k	half-maximal GF enhancement of fibroblasts differentiation	10^{-8} g/cm ³	[6]
k_2	myofibroblasts dedifferentiation rate	0.693 day ⁻¹	[6]
d_n	fibroblasts death rate	0.831 day ⁻¹	$d_n = r_n \left(1 - \frac{n_0}{K}\right)^{\ddagger}$
e_r	proportionality factor	0.5	[12]
d_m	myofibroblasts death rate	$2.1 \cdot 10^{-2}$ day ⁻¹	[6]

[†] Adjusted to fit reported migration rate with a traveling wave model.[‡] Determined fibroblasts proliferation kinetics to remain in equilibrium away from the wound.

Table II

List of model parameters related to collagen and growth factor(GF) kinetics.

Parameter	Description	Value	Observations
ρ_0	collagen concentration in undamaged dermis	0.1 g/cm ³	[12]
ρ_{ini}	initial collagen concentration in the wound	10 ⁻³ g/cm ³	[12]
c_0	GF concentration in the wound	10 ⁻⁸ g/cm ³	[12]
r_ρ	collagen production rate	7.59·10 ⁻¹⁰ g ³ /cm ⁶ cell day	$r_\rho = d_\rho \rho_0 (R_\rho^2 + \rho_0^2)^{\frac{1}{2}}$
$r_{\rho max}$	maximal rate of GF induced collagen production	7.59·10 ⁻⁹ g ³ /cm ⁶ cell day	[12]
C_ρ	half-maximal GF enhancement of collagen synthesis	10 ⁻⁹ g/cm ³	[12]
η	proportionality factor	2	[12]
R_ρ	half-maximal collagen enhancement of ECM deposition	0.3 g/cm ³	[12]
d_ρ	collagen degradation rate per unit of cell density	7.59·10 ⁻⁸ cm ³ /cell day	[12]
D_c	GF diffusion rate	5·10 ⁻² cm ² /day	[12]
k_c	GF production rate per unit of cell density	7.5·10 ⁻⁶ cm ³ /cell day	[6] [§]
ζ	proportionality factor	1	[12]
Γ	half-maximal enhancement of net GF production	10 ⁻⁸ g/cm ³	[12]
d_c	GF decay rate	0.693 day ⁻¹	[6]

[‡]Determined collagen degradation kinetics to remain in equilibrium away from the wound.[§]Downestimated to prevent fibro-proliferative disorders [16] with the used GF decay rates.

Table III

List of model parameters related to the mechanical behavior of cells and ECM.

Parameter	Description	Value	Observations
p_{max}	maximal cellular active stress per unit of ECM	10^{-5} N g/cm ² cell	[6]
K_{pas}	volumetric stiffness moduli of the passive components of the cell	$2 \cdot 10^{-5}$ N g/cm ² cell	[22]
K_{act}	volumetric stiffness moduli of the actin filaments of the cell	10^{-4} N g/cm ² cell	[22]
θ_1	shortening strain of the contractile element	-0.6	[6]
θ_2	lengthening strain of the contractile element	0.5	[22]
τ_d	half-maximal mechanical enhancement of fibroblast differentiation	10^{-5} N g/cm ² cell	[6]
μ_1	undamaged skin shear viscosity	200 N day/cm ²	[6]
μ_2	undamaged skin bulk viscosity	200 N day/cm ²	[6]
E_d	dermis Young's modulus	33.4 N/cm ²	[24]
ν_d	dermis skin Poisson's ratio	0.3	[24]
E_{ut}	underlying tissue Young's modulus	0.82 N/cm ²	[25]
ν_{ut}	underlying tissue Poisson's ratio	0.459	[26]
ζ	myofibroblasts enhancement of traction per unit of fibroblasts density	10^{-3} cm ³ /g	[12]
R_t	traction inhibition collagen density	$5 \cdot 10^{-4}$ g/cm ³	[12]
s	dermis tethering factor	10^{-1} N/cm g	Estimated