A Cut-Cell Finite-Element Method for a Discontinuous Switch Model for Wound Closure

S.V. Zemskov, F.J. Vermolen, E. Javierre, and C. Vuik

Abstract A mathematical model for epidermal wound healing is considered. The model is based on a moving boundary problem for the wound edge in which the edge moves if a generic epidermal growth factor exceeds a given threshold value. We use a Galerkin finite-element method to solve the equations for the growth factor concentration. The moving boundary (wound edge) is tracked using a level-set method with a local adaptive mesh refinement in the interface region. To deal with the reaction-diffusion equation for the growth factor, a cut-cell method has been implemented. This cut-cell method warrants the integration over a continuous reaction term elementwisely. The results improved with respect to the results that were obtained without the use of the cut-cell method.

1 Introduction

Wound healing or soft tissue regeneration, involves cell migration, the production and decay of growth factors and a (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 a very simplified model for wound closure. This model can be used for intra-osseous and epidermal wound healing. Since the thickness of the epidermis is in the order of 1 mm, it suffices to consider a two-dimensional approach

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for epidermal closure (re-epithelialization). Hence, we consider a two-dimensional model in the present paper.

When a wound occurs, blood vessels are cut and blood enters the wound. Due to blood coagulation, 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: wound contraction (due to pulling forces caused by fibroblasts entering the wound area underneath the epidermal cells), chemotaxis (movement of cells induced by a concentration gradient), neo-vascularization (formation of network of capillaries), synthesis of extracellular matrix proteins, and scar remodeling. Previous models incorporate cell mitosis, cell proliferation, cell death, capillary formation, oxygen supply and growth factor generation. These models contain visco-elasticity problems coupled with reaction-transport equations. We refer to [6] for an overview.

There is a lot of mathematical models in literature for wound healing and wound closure. In this paper, we do not intend to discuss the variety of models, but we aim at a description of the numerical solution method for one class of models: the models with a discontinuous switch mechanism. This model was initially proposed by [1] and enriched with a moving boundary formulation in [8]. A numerical procedure based on the finite-element method with a level set method is used to track the moving wound edge, is presented in [2]. Existence, uniqueness and mathematical properties of solutions of this problem were demonstrated in [7].

The start of the present paper is the introduction of the discontinuous switch model for re-epithelialization. Subsequently, the cut-cell method for an accurate determination of the solution in the vicinity of the interface is presented. Then, the cut-cell method is numerically compared with the classical finite-element method and finally some conclusions are drawn.

2 The Model

In this section the model based on the ideas of [1] is presented. Firstly, the model for the regeneration, decay and transport of a generic growth factor is given, and subsequently the healing process as a result of the presence of the growth factor is described (see [8]). Finally, a description of the coupling of the two models is presented.

We use Ω_1, Ω_2 and Ω_3 to denote the wound itself, the active layer and the outer tissue respectively. The active layer Ω_2 is a ring surrounding the wound region Ω_1. Since the wound is healing, the areas Ω_1, Ω_2 and Ω_3 are functions of time and to be determined as a part of the solution. Far away from the wound, that is at the boundary of the domain of computation, $\partial\Omega$, 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 $W(t)$ (i.e., $W = \overline{\Omega}_1 \cap \overline{\Omega}_2$).

Let the total domain of interest be given by $\overline{\Omega} = \cup_{i=1}^{3} \overline{\Omega}_i$, which is Lipschitz, then, following [1], we state the fundamental equation for the transport, production and decay of the growth factor concentration, c, which reads as:

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

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

$$\text{where } \mathbf{1}_{\Omega_2(t)}(\mathbf{x}) = \begin{cases} 1, \text{ for } \mathbf{x} \in \Omega_2(t) \\ 0, \text{ for } \mathbf{x} \in \Omega \setminus \Omega_2(t) \end{cases}, \tag{3}$$

As the initial condition, we have

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

In the equations, the constants 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 (1) respectively account for growth factor transport and growth factor loss. The right-hand side of (1) accounts for the production of the growth factor. Equation (2) represents the boundary condition and the indicator function $\mathbf{1}_{\Omega_2(t)}(\mathbf{x})$ accounts for the growth factor production taking place in the active layer only.

Healing at a certain location of the interface implies that the inward normal component of the velocity pointing into the wound, v_n, of the interface W is positive. In the present paper we use the assumption from [1] that the interface moves if and only if the growth factor concentration exceeds a threshold concentration $\hat{c}$. 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.

As it has been motivated in [8], we assume that the healing rate is proportional to the local curvature of the wound. Hence, in agreement with (5), the velocity component in the outward (from Ω_1, that is the wound) normal direction is given by

$$v_n = -(\alpha + \beta\kappa) w(c(t, \mathbf{x}) - \hat{c}), \text{ for } (t, \mathbf{x}) \in (0, T] \times W(t), \tag{5}$$

where κ is the local curvature and $\alpha, \beta \geq 0$ 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

$$H : s \to \begin{cases} 0, & \text{if } s < 0, \\ \in [0, 1], & \text{if } s = 0, \\ 1, & \text{if } s > 0. \end{cases} \tag{6}$$

Some models with the same principles as the active layer and / or the discontinuous switch condition can be found in other works, see references in [7]. Further, the existence and uniqueness of solutions in $C^1((0,T);H^1(\Omega)) \cap C^0([0,T);H^1(\Omega))$ was demonstrated and analytic solutions in this function space were constructed in that paper as well.

3 The Method

The mathematical model described falls within the class of moving boundary problems. The position of interface, $W(t)$, has to be determined at each time step t what leads to re-identifying the parts of the computation domain ($\Omega_1(t)$, $\Omega_2(t)$ and Ω_3(t)).

As in [2], the Level Set method [3] is used to follow the evolution of the interface W during the simulation. The interface is identified as the zero level set of a continuous function ϕ which is defined at the initial time $t = 0$ by the following way:

$$\phi(0,\mathbf{x}) = \begin{cases} +\text{dist}(\mathbf{x}, W(0)), & \mathbf{x} \in \Omega_1(0), \\ 0, & \mathbf{x} \in W(0), \\ -\text{dist}(\mathbf{x}, W(0)), & \mathbf{x} \in \overline{\Omega}_2(0) \cap \overline{\Omega}_3(0). \end{cases}$$

Thus, ϕ is defined to be positive inside the wound and negative outside.

Subsequently, a convection equation is solved for the level-set function ϕ in which the velocity at the interface is determined from the local curvature of ϕ at the interface. The velocity is extended onto the entire domain of computation by advection in the appropriate upwind direction. For the following numerical reasons, it is attractive that ϕ is a signed distance function: 1. a reliable inverse interpolation to get the wound edge position, and 2. the straightforward computation of the local curvature. In order to enjoy this property, a reinitialization step is carried out so that $|\nabla\phi| = 1$ in Ω. In this work, a fast-marching method has been selected [4]. More details can be found in [2].

3.1 The Cut-Cell Approach

Since the interface moves only if locally the threshold $\hat{c}$ has been exceeded, an accurate approximation of the concentration at the interface is indispensible. The mathematical model and Level Set method described in the previous sections were implemented by Javierre et al. [2] using a finite-element method with piecewise linear basis functions. A structured triangulation with linear elements is used as a fixed basis mesh. The elements close to the active layer are refined according to certain criteria at each time step.

In the standard finite-element method, the interface concentration is determined by interpolation of the growth factor concentration at the wound edge. The right-hand side of (1) is discontinuous what leads to numerical wiggles at the edges of the active layer. A regularized version χ_ε of the characteristic function χ is used in [2] in order to diminish possible oscillations at the interface. A good approximation of the concentration is crucial for the determination whether or not the interface will move locally.

To eliminate this defect, we propose the use of a cut-cell approach which allows to adapt the existing triangulation to the edges of the active layer at each time step. In application to the model considered, the cut-cell method consists of an additional refinement of FE mesh on the elements intersected by either the interface W or the outer boundary of the active layer $\overline{\Omega}_2 \cap \overline{\Omega}_3$. Such an approach allows to apply the developed technique of numerical integration over new elements where the integrand remains continuous.

The level set function ϕ representing the distance to the interface is defined in each node of the FE mesh (positive for nodes inside the wounded region and negative outside). We have created a module to find elements intersected by a defined level line of ϕ and to perform the subdivision of each element found into triangular sub-elements.

To avoid the appearance in the new refinement of ill-shaped triangles which might be too small with respect to already existing elements, we assume that the distance d between an intersection point and the nearest node fulfils the following condition

$$d < \frac{\min(\Delta_x, \Delta_y)}{10},$$

where Δ_x and Δ_y are horizontal and vertical steps of initial Cartesian mesh respectively. Under such a condition, there are three possible cases for dividing an intersected element (Fig. 1).

Hence, if the intersection point is too close to one of the existing nodes, such an intersection is not registered and we do not add any new point to the set of nodes. In case of subdividing an element into three sub-elements (i.e., by two registered intersection points), one new triangular element is formed immediately by cutting

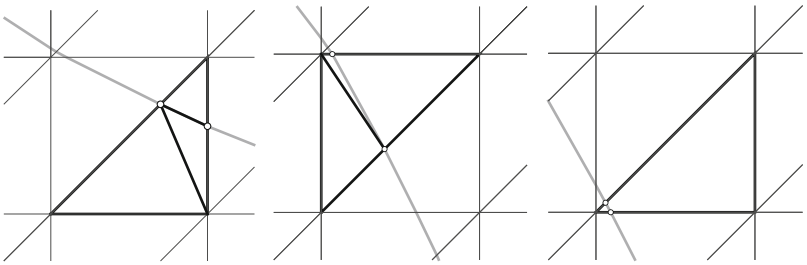

Fig. 1 Intersected element is divided by three sub-elements (*left*), two sub-elements (*center*) or is not divided (*right*)

off from the initial element. From two possible of element divisions, we exclude the variant with the most obtuse angle. During calculations each new point is tested whether it belongs to the element inside the active layer or not and receives the corresponding value.

4 Comparison Between Cut-Cell and Classical Finite-Element Method

To compare the cut-cell method with the classical Galerkin finite-element method, we plot the wound edge concentration profile of an elliptical wound in Fig. 2 for

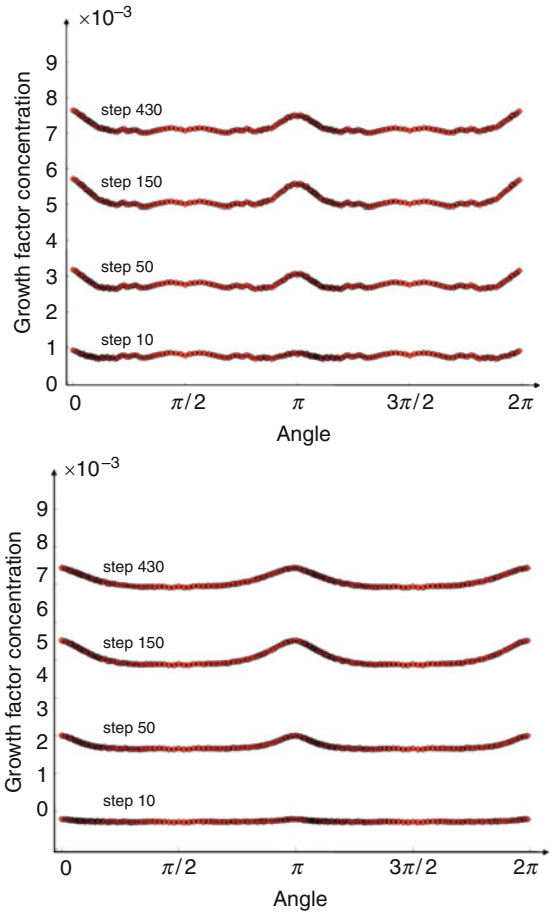

Fig. 2 The epidermal growth factor concentration on the interface after 10, 50, 150 and 430 time steps. At the *top* and *bottom*, the classical FEM and cut-cell method has been used respectively

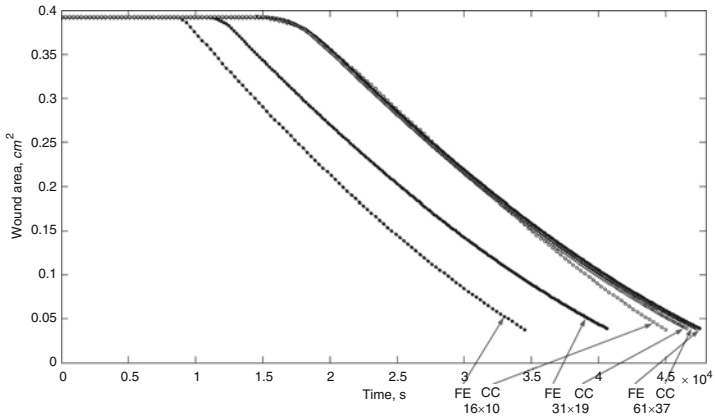

Fig. 3 Change of the wound area during the simulation for 16×10, 31×19 and 61×37 gridnodes for the cut-cell (CC) and standard finite-element method (FE)

the two methods. It can be seen that the peripheral concentration profile in the classical method exhibits an oscillatory behavior due to the interpolation step and due to the integration of a discontinuous reaction term over an element intersected by the wound edge. This will lead to a worse prediction of the wound edge velocity since the concentration on $W(t)$ will oscillate around the threshold concentration $\hat{c}$. The profile from the cut-cell method looks much smoother due to the appropriate integration of the continuous function over the newly formed elements along the interface.

From the more reliable approximations of the interface concentrations, the threshold condition for interface motion can be examined in a more accurate way. Therefore, this results into a more reliable prediction of the interface motion and wound healing kinetics. An example of the evolution of the wound area as a function of time for an elliptic wound is shown in Fig. 3. At the earliest stages, the concentration at the wound edge $W(t)$ has to increase from zero up to the threshold concentration $\hat{c}$. During this stage, the wound edge does not move yet, *that is* $W(t) = W(0)$. As soon as the interface concentration reaches $\hat{c}$, the wound starts to shrink. Further, it can be seen that the standard FEM exhibits a slower convergence behavior than the cut-cell method if the global grid is refined. We note that an adaptive mesh with refinement in the area near the edge was used in all the simulations. From these results, it can be concluded that the cut-cell method gives a significant improvement with respect to the standard finite-element method.

5 Conclusions

The model of epidermal wound healing is improved by using the cut-cell method. The interface points obtained with the cut-cell are used to adapt the triangulation to the wound edge position at each time step. The advantage of such an approach

is that the new subdivision is built without destroying the original FE mesh and altering the level set function.

The results obtained using cut-cell method are significantly better than previous ones. It can be seen clearly that the cut-cell method decreases the oscillatory behavior of the solution.

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