Continuum-Scale Models for the Evolution of Hypertrophic Scars and Contractions After Burn Injuries

Fred Vermolen and Daniël Koppenol

Abstract We review several of our mathematical models that we constructed for the simulation of contractures and morpho-elastic scars that are typically associated with deep dermal (burn) injuries. The models are based on partial differential equations, which are solved by the use of finite-element methods. The models contain elements of non-isotropy, morpho-elasticity for the treatment of the mechanics of the skin. Furthermore, we take into account the balances of fibroblasts, myofibroblasts, collagen and a generic growth factor. Using the models, we are able to simulate permanent contractions using physically sound principles.

Introduction

Over the globe, about eleven million individuals are affected by burn injuries. In about six hundred thousand cases, the injury is so serious that the patient dies. After serious burns or incisions, hypertrophic scars may arise among patients, who need plastic surgery. Another side effect of burn injuries is the formation of contractures, which lead to permanent deformations and stresses in the skin of the patient. This causes a reduction of the mobility of the patient. This reduction is a consequence of the pulling forces that are exerted by the fibroblasts and myo-fibroblasts. These cells pull the surrounding tissue, by which the wound is contracted inwardly. This process is referred to as *contraction.* In the case that the deformations are small, the skin will recover mainly after the burn injury has healed. If, however, the deformations are large, which may happen in deep, serious burn injuries, the skin will no longer be able to recover. Then the patient suffers from a permanent deformation. If this deformation also deteriorates the mobility of the patient, then one speaks of a *contracture*.

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During the past decades, mathematical modeling has progressed considerably in simulating wound healing, organ development, wound contracture, healing of bones and in the initiation and spread of cancer. This kind of models is applied on several scales, which give models that are based on entirely different principles, between stochastic processes and fully deterministic processes in terms of partial differential equations. The models on the smallest scales treat cells as individual entities, or even treat one cell (or even just several parts of it) only. Other models are based on the migration and deformation of cells. One may think, for instance, of cancer cells which migrate through small apertures in extracellular material and through blood vessels in order to spread (metastasize) over the body of the patient. At a somewhat larger scale, one can consider cell colonies in which each individual cell has a predefined geometry, and where it is able to divide, die, migrate or to differentiate to another phenotype. Here, one may distinguish between models in which cells can take whatever spatial position in a given domain, and these models where can only be located on discrete lattice points (such as cellular automata models, in which cellular Potts models form an important subclass). We refer to Vermolen (2016) for a review of such models. If one wants to take each cell into account when simulating a biomechanical mechanism like the formation of contractures, then one needs a very powerful computational environment with a huge amount of memory. In general, this is hard to achieve, and therefore, continuum-based models, which are based on cell densities, are currently being developed.

In this manuscript, we will concentrate on several mathematical models that are based on continuum-scale formalisms, which are applied to hypertrophic scars and contractures in relation to burn injuries. The current manuscript is based on the modeling studies in Koppenol et al. (2016a, b), Koppenol and Vermolen (2017) and therewith it should be seen as an advertisement for reading the aforementioned papers.

Materials and Methods

In this manuscript, we only present a summary of our modeling efforts in the context of burn injuries, where we consider a sequence of results for hypertrophic scars and contractures. To put the modeling work into its context, we briefly describe the biological stages a skin goes through after damage that was inflicted. The healing process starts with haemostasis. This is a process that stops bleeding, in which small blood vessels are constricted, where platelets converge and in which extracellular material is deposited. The platelets are responsible for the secretion of chemokines, which influence the behavior of immune cells, fibroblasts and endothelial cells. Subsequently, the immune cells enter the wound, and then the inflammatory phase commences. The immune cells clear up the contaminants and neutralize harmful pathogens. Shortly after this partial process, the proliferative phase sets in, where wound closure, wound contraction, angiogenesis are important

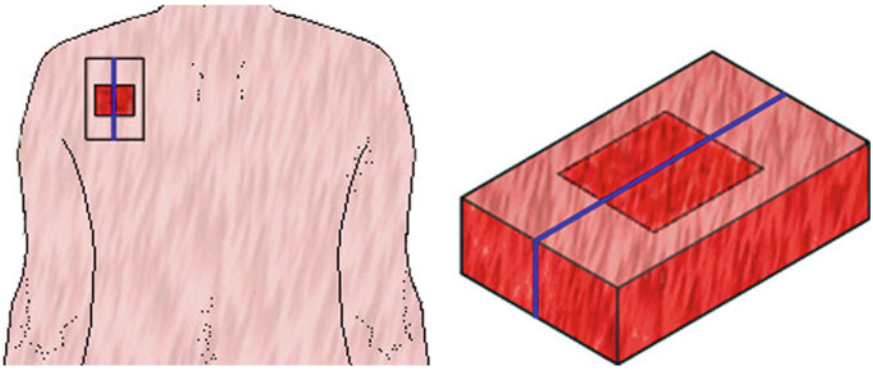

Fig. 1 Schematic of a burn injury on the shoulder (*left*), and a simplification of the geometry (*right*)

sub-processes. The epidermis is regenerated in the epithelialization process. Herewith, a protective layer over the wound is reconstructed. Furthermore, the dermis is reconstructed under the epidermis, where the dermis has a different texture than the epidermis and the texture of the dermis differs from an embryonic skin pattern. An important difference is the isotropy of the skin. Embryonic skin contains collagen molecules that are ordered more or less randomly, which allow an isotropic treatment of the skin. However, newly generated skin possesses an orientation that is linked to the migration pathways of fibroblasts. Herewith, the new extracellular material no longer contains an isotropic structure.

Finally, the remodeling phase takes place. During this phase, which in general lasts much longer than the other phases, the structure of the extracellular material changes. This leads to changes of the chemical composition and in the orientation of the collagen. Further, the number of fibroblasts and endothelial cells decrease during this phase.

First the tissue that is considered is simplified. We assume that the tissue that contains the damaged and undamaged part is represented correctly in a domain of computation. Such a domain of computation consists of the wound and a considerable portion of undamaged tissue, see Fig. 1, where we show a model for a burn injury near the shoulder of the patient.

Mathematical models are always simplifications of reality, since it is impossible to incorporate all the biological processes in detail. There exist several reasons for this, first, not all biological mechanisms regarding the formation of hypertrophic scars and contractures are known. The behavior of all cells is not known. Second, the more biological information we take into account, the more parameters have to be known. However, most of these parameters have never been measured and hence it is very hard, or even impossible to attain their values. This implies that more unknowns are introduced into the more complex models.

In the present models, we incorporate the behavior of the phenotypes fibroblasts and myo-fibroblasts. These cells consume and secrete a chemical signal, which is

incorporated in the current models. Furthermore, collagen is incorporated in the models. Since we are interested in the behavior of the dermis in the vicinity of the burn injury, the domain of computation is too large to deal with individual cells and collagen, and therefore we use the cell densities and the density of collagen. As cellular processes, we incorporate migration (by random walk or diffusion and by haptotaxis, which is migration towards the gradient of a chemical through the extracellular material), proliferation, apoptosis and cell differentiation. Fibroblasts differentiate to myo-fibroblasts, which pull with larger forces the extracellular material, and which also produce more collagen than fibroblasts do, under particular circumstances. Since the pulling forces of myo-fibroblasts are much larger than the forces that are exerted by the fibroblasts, we neglect the forces that are exerted by the fibroblasts.

The signaling molecule (chemokine) is supposed to diffuse through the tissue. Furthermore, this molecule is secreted by the fibroblasts and myo-fibroblasts. This molecule, as well as the collagen, is broken down by Matrix Metallo Proteinases (MMPs). This process is taken into consideration in the mathematical model. The production of collagen by fibroblasts and myo-fibroblasts is incorporated into the modeling. Further, we also take into account the orientation of the collagen that is determined according to the migration pattern of the (myo-)fibroblasts.

Next to these issues, a model has been constructed for the mechanical properties of skin. Here, quantities like stiffness and the Poisson ratio play a role. First, a mechanical balance is imposed. Here, one takes into account the pulling forces exerted by the myo-fibroblasts. Further, the orientation of the collagen is taken into account so that the stiffness varies with the collagen orientation. Since a permanent contraction, which can result into a contracture, in which the patient loses mobility, possibly occurs, the model has been adjusted aiming at simulation of permanent deformations. The first simulation results conjecture that a permanent contraction can be modeled, however, rigorous mathematical analysis is needed to formally demonstrate the possibility of simulation of permanent deformations. This issue is incorporated through a morphoelastic description of skin mechanics and this aspect is innovative in our current modeling.

Results

As a first example of simulation results, we show the evolution of a hypertrophic scar over time. Figure 2 shows the distribution of fibroblasts (first row), myo-fibroblasts (second row), signaling chemical (third row) and the collagen density (fourth row) at consecutive times. Next to these profiles, one can see the shape of the skin at these various times. In this simulation, a neo-Hookean description of the mechanical behavior of skin has been used. Shortly after occurrence of the wound, it can be seen that there is an inflow of fibroblasts (see top row). In the early stages myo-fibroblasts are absent, however, in the wound area a

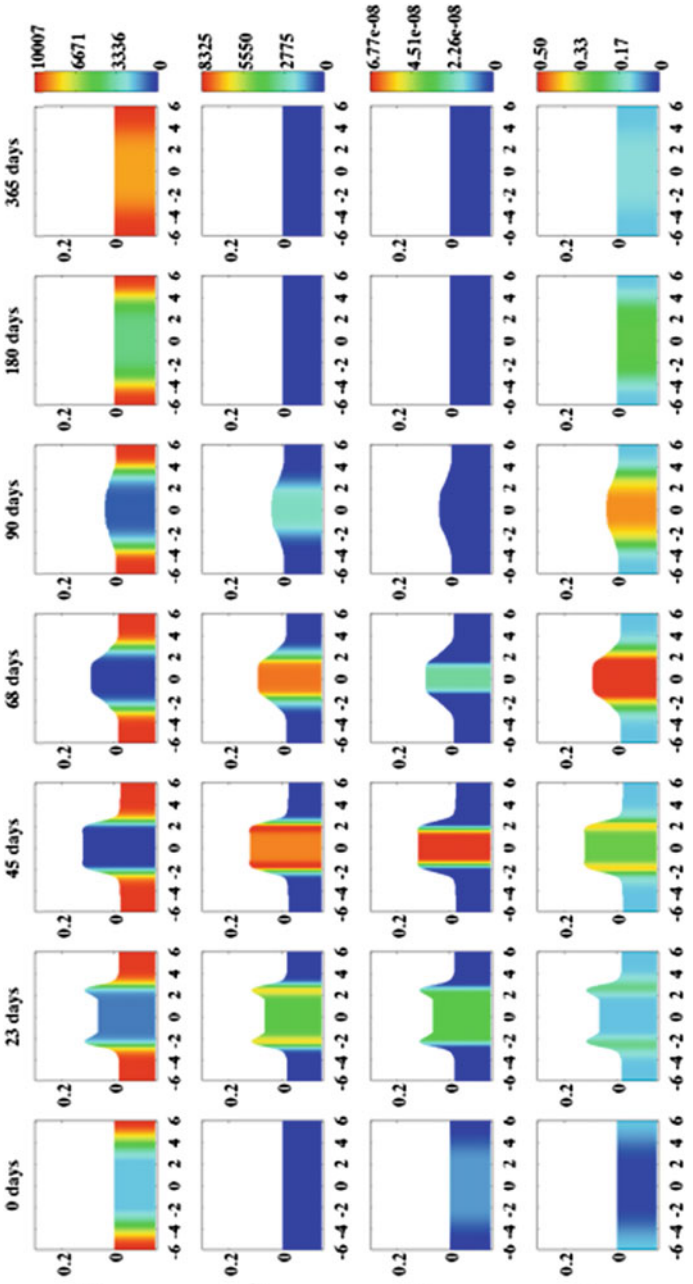

Fig. 2 The distribution of fibroblasts, myo-fibroblasts, chemical signaling molecules, and collagen (from *top* to *bottom* respectively) at consecutive times over a period of half a year (from *left to right* the time increases)

population of fibroblasts develops a bit later as a result of cell differentiation. This has been visualized in row 2. As time proceeds, the number of myo-fibroblasts decreases as a result of apoptosis. Further, it can be seen that the initially present chemical signaling molecules diffuse gradually away from the wound into the rest of the dermal region. Subsequently, these chemical signaling molecules are produced by the (myo-)fibroblasts. Eventually, the concentration of the chemical signal drops down to zero, see the third row in Fig. 2.

Collagen is produced by the (myo-)fibroblasts and at a certain moment the maximum value exceeds the natural equilibrium value. During the final stages of the healing process, the collagen density will decrease as a result of break-down by MMPs. The collagen density will eventually be equal to the natural density that is coupled to undamaged skin, see the bottom row of Fig. 2. Further, it can be seen that during the early stages, the skin shape becomes bulged, which is reminiscent to a hypertrophic scar. The simulations seem to indicate that if the differentiation rate is higher, and if the apoptosis rate is lower, then the myo-fibroblasts will remain longer there, by which the scar, that is the bulged region, will be present over a larger period of time. In the papers of Koppenol et al. (2016a, b), this situation is described in more detail.

Figure 3 shows the area of a skin graft over time. This result for a skin graft has been obtained with a different model, in which the skin has been treated as a morphoelastic material. It can be seen that the wound contracts at the early stages.

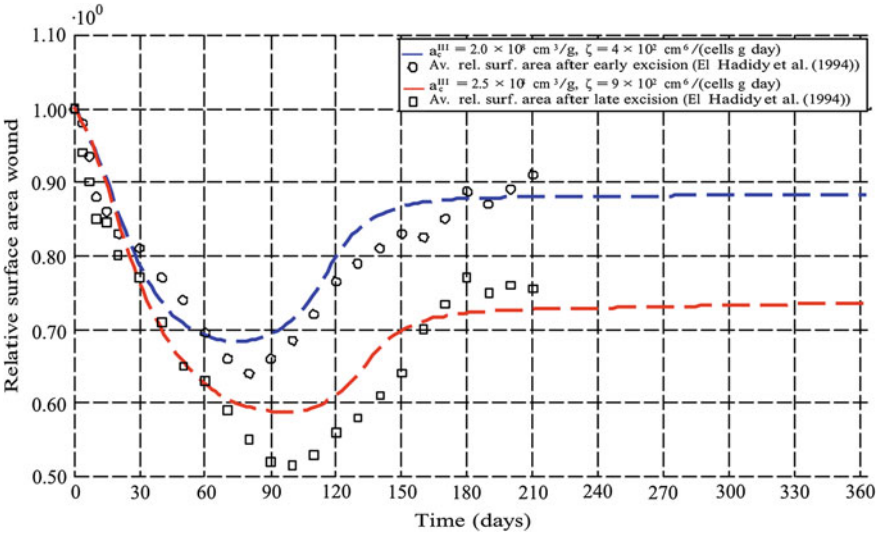

Fig. 3 The area of the skin graft as a function of time. The *circular dots* represent experimental results

This contraction is a result of pulling forces that are exerted by the myo-fibroblasts. In the subsequent stages, the myo-fibroblasts die as a result of apoptosis. Therewith, the pulling forces on the extracellular material disappear. Nevertheless, in Fig. 3, it can be seen that the skin graft no longer deforms back to its original shape. This behavior results since the deformation was so large that this deformation is beyond the elastic region in the stress–strain curve. Now, the skin graft has deformed permanently and this may yield a limitation for the mobility of the patient because of the contracture that may occur. For more information, we refer to Koppenol and Vermolen (2017).

Discussion

The models that we have shown in this manuscript are all based on cell densities and they have a fully continuum-scale character. In order to consider the processes on a very small scale, it could be worth to consider small-scale models like the cellular Potts formulations or semi-continuous cell-based models. However, for larger scales, it is appropriate to use the current partial differential equations-based continuum-scale models since cell-based models would require too many computational resources. Research of interest could be directed to the upscaling of small-scale models to larger scales. The current models further miss the link to the immune system. This link could be investigated more in clinical experiments so that models that couple wound contraction and hypertrophy can be formulated. Of course, a model is a representation of reality, though we try to base the modeling as much as possible on experimental results from several groups. Some caution should be taken since different model formulations may lead to the same results and this may generate some ambiguity in the explanation of experimental results. However, as a tool to forecast the behavior of skin under different circumstances, the models could be helpful in reducing the number of (animal) experiments. It is also believed that cells and skin constitution varies from patient to patient and to this extent, the model results should be subject to a sensitivity analysis. In this sense, a model should not only predict how and whether a contraction or hypertrophic scar develops, but also the likelihood that a scar or contraction develops over time given some initial predefined configuration. This type of information could be of interest to physicians. We believe that regression techniques, stochastic processes, and a statistical evaluation are indispensable in future simulation studies. A first attempt toward this direction has been done in Koppenol et al. (2016). Further, the mentioned models could be combined into one model containing morphoelasticity as well as the ability to predict the occurrence of both hypertrophic scars and contraction by using one single model.

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