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Review

A multi-agent cell-based model for wound contraction

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ABSTRACT

A mathematical model for wound contraction is presented. The model is based on a cell-based formalism where fibroblasts, myofibroblasts and the immune reaction are taken into account. The model is used to simulate contraction of a wound using point forces on the cell boundary and it also determines the orientation of collagen after restoration of the damage. The paper presents the mathematical model in terms of the equations and assumptions, as well as some implications of the modelling. The present model predicts that the amount of final contraction is larger if the migration velocity of the leukocytes is larger and hence it is important that the immune system functions well to prevent contractures. Further, the present model is the first cell-based model that combines the immune system to final contractions.

Contents

1. Introduction

An important subprocess during wound healing is wound contraction. During this process, the damaged tissue gets pulled together in order to close the wound rapidly and minimise the

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chance of infection. Naturally, this is a desirable effect for wounds, but when the contraction is too large, it can become a negative side-effect. In that case, a permanent contraction known as a contracture can be the result. This may lead to problems such as functional restrictions (Enoch and Leaper, 2008). A major difference between scar tissue and undamaged tissue lies in the alignment of its fibers (Cumming et al., 2010). While undamaged tissue has an isotropic pattern of interwoven collagen bundles, scar tissue is characterised by fibers aligned in only a few directions. This anisotropy causes the tissue to have inferior strength and flexibility. Clark et al. (2014) and Murphy et al. (2012) state that the regenerated tissue has only 70% of the normal dermal strength. Furthermore, the reduction in flexibility can cause major problems for the affected patient (Hinz, 2006).

Because of the great implications that contraction has on the final stages of skin repair, it serves as an interesting component in a wound healing model. By combining the mechanical implications due to contraction with some of the biological processes of dermal wound healing, we aim at creating a more complete view of the entire wound healing process. Such a model may lead to a better understanding of the wound healing process which is essential for the development of new procedures to reduce contracture formation in the resulting scar tissue. Fibroblasts and myofibroblasts are the primary factors involved in the process of contraction. In this process, the cells adhere to the extracellular matrix (or ECM). The ECM is comprised mostly of collagen fibrils (Enoch and Leaper, 2008). They then pull together these collagen fibrils and consequently compact the connective tissue (Clark et al., 2014). The difference between the cells is that myofibroblasts will exert stronger contractile forces than fibroblasts (Hinz, 2006). An abundance of contraction may result in the permanent contraction (i.e. the contracture) of the wound which remains after all fibroblasts and myofibroblasts have either died or left the wound area. Furthermore, both fibroblasts and myofibroblasts will initiate the synthesis of the oriented collagen fibrils in the wound. These form the building blocks for the new ECM which replaces the fibrin clot. These collagen fibrils themselves act as a guidance cue for subsequently arriving fibroblasts. Hence, there is a constant interaction where fibroblasts affect the orientation of the collagen matrix and the orientation of this collagen matrix influences the movement of fibroblasts (McDougall et al., 2006).

Since there is an extensive amount of literature available on the mathematical modelling of dermal wound healing, we will limit our review to the most relevant articles for the present work. Hence we focus on articles concerning the mathematical modelling of the contraction process and the orientation of the collagen bundles in the dermis during dermal wound healing. In the field of wound contraction modelling, Tranquillo and Murray (1992) were one of the first to propose a mathematical model for wound healing that takes the contraction process into account. The model presented in this work offered a general framework for understanding how traction exerted by wound fibroblast eventually results in wound contraction. The equations described here formed the basis for much of the computational research in this field. From this model, the model by Olsen et al. (1995, 1996) is based on a deterministic formalism to investigate key clinical problems in wound healing disorders. The focus was on contraction and simplifications were made such that only the essential roles of fibroblasts and myofibroblasts were described along with a single chemical growth factor and the ECM. The results showed that a distinction needed to be made between contraction during the proliferation stage and the prolonged remodeling of collagen during the remodeling stage. Later models for wound contraction were developed by Javierre et al. (2009) and Valero et al. (2014, 2015), where in the latter study, non-isotropies were dealt with via a neo-Hookean formulation for the strain energy density. The last-mentioned work does not consider contact guidance of the cells according to the fibre orientation, but it is very useful in linking fiber orientation to mechanical properties.

Another significant contribution to this field was the model by Murphy et al. (2012). This model incorporated the interaction between fibroblasts and the ECM combined with a more realistic modelling of cytokines. Contraction was investigated in a one-dimensional model activated by TGF-β. Here, the cytokine and mechanical tension were assumed to be responsible for the differentiation from fibroblast to myofibroblast. The model then showed that the removal of TGF-β and reduction of tension resulted in a decrease in the number of myofibroblasts and therewith a reduction in contraction. A major shortcoming of these early works, however, is that a contracture is not a stable solution within these models. With respect to the dynamics of fiber bundle orientation, one of the most important mathematical theories was formulated by Barocas and Tranquillo (1997). In this work, an anisotropic biphasic theory for tissue-equivalent mechanics was presented. This theory can account for fibril alignment during wound healing and introduced cell contact guidance. Although the theory was formulated in a general sense, it was speculated that it may be valid for physiological processes such as wound contraction (Barocas and Tranquillo, 1997). Later, the dynamics of fiber bundle orientation was incorporated into a dermal wound healing model by Olsen et al. (1999). Here, two approaches were proposed for modelling the cell populations. First, the cell densities were modeled as continua. This continuum approach resulted in a system of partial differential equation on a macroscopic scale. However, patterns of alignment on microscopic length scales were lost in this approach. Therefore, a novel approach was introduced in which cells are presented as discrete individuals and the ECM as a continuum. This hybrid model produced the desired results on both scales.

The modeling of the interaction between cells and the ECM alignment was developed further by Dallon et al. (2000, 1999, 2001) by including ECM production and decay. In all cases, the cells were considered as discrete objects while the matrix was modeled as a continuum. In Dallon et al. (1999), various aspects of the cell interactions with collagen and fibrin were investigated first in order to find which alignment properties arise in different cases. These aspects included cell speed, flux, polarisation, density, initial matrix orientation and the influence of cells on the matrix. The results showed that all of these factors had a certain effect on the alignment of collagen. It was shown next by Dallon et al. (2000) that of these factors, cell speed and the positions where fibroblasts enter the wound area are the most influential on fiber alignment. Within the model, the matrix orientation was modeled using a vector field. This implied that the orientation of the bundles was unidirectional. In a third article, Dallon et al. (2001) incorporated a time-variant concentration field for the cytokine TGF-β to the model and the effects of different profiles of this cytokine were investigated. It was found that the influence TGF-β has on changes in cell motility, proliferation and collagen production had little effect on collagen matrix alignment. Furthermore, it was shown that the alignment of the new tissue depends highly on the fibroblast reorientation rate.

A couple of years later, a further investigation was conducted by McDougall et al. (2006) on the effects of different cytokine concentrations. They made an important distinction between the degree of scarring and wound integrity. It was shown that a large chemoattractant diffusion coefficient results in an optimised wound integrity while the degree of scarring is decreased when a competitive inhibitor to TGF-β is introduced. From the vector-based representations of collagen bundles and fibrin fibers used by Dallon et al. (1999) and McDougall et al. (2006), a few drawbacks can easily be deduced. First, there is no measure available for the