Journal of the Mechanics and Physics of Solids 79 (2015) 80–91

Contents lists available at ScienceDirect

Journal of the Mechanics and Physics of Solids

journal homepage: www.elsevier.com/locate/jmps

Modeling of anisotropic wound healing

C. Valero [a,*], E. Javierre [b], J.M. García-Aznar [a], M.J. Gómez-Benito [a], A. Menzel [c,d]

[a] Multiscale in Mechanical and Biological Engineering (M2BE), Aragón Institute of Engineering Research (I3A), University of Zaragoza, Zaragoza, Spain
[b] Centro Universitario de la Defensa, Academia General Militar, Zaragoza, Spain
[c] Institute of Mechanics, TU Dortmund, Germany
[d] Division of Solid Mechanics, Lund University, Sweden

ARTICLE INFO

Article history:
Received 1 August 2014
Received in revised form
6 February 2015
Accepted 29 March 2015
Available online 31 March 2015

Keywords:
Wound healing
Angiogenesis
Collagen fibers
Finite element analysis
Anisotropic hyperelastic

ABSTRACT

Biological soft tissues exhibit non-linear complex properties, the quantification of which presents a challenge. Nevertheless, these properties, such as skin anisotropy, highly influence different processes that occur in soft tissues, for instance wound healing, and thus its correct identification and quantification is crucial to understand them. Experimental and computational works are required in order to find the most precise model to replicate the tissues' properties. In this work, we present a wound healing model focused on the proliferative stage that includes angiogenesis and wound contraction in three dimensions and which relies on the accurate representation of the mechanical behavior of the skin. Thus, an anisotropic hyperelastic model has been considered to analyze the effect of collagen fibers on the healing evolution of an ellipsoidal wound. The implemented model accounts for the contribution of the ground matrix and two mechanically equivalent families of fibers. Simulation results show the evolution of the cellular and chemical species in the wound and the wound volume evolution. Moreover, the local strain directions depend on the relative wound orientation with respect to the fibers.

1. Introduction

Skin covers the entire human body and, therefore, keeping its integrity is crucial for human life. The two most external layers of the skin are the epidermis and the dermis which both consist of a ground substance and embedded collagen fibers. These collagen fibers are the components that support most of the mechanical loads acting on the skin. The mechanical properties of the skin decrease when an injury occurs and a wound appears. The regeneration of the skin properties takes place during wound healing, a physiological process that is usually divided into three overlapped stages: inflammation, epithelialization and remodeling.

During the inflammatory stage, inflammatory factors that stimulate cell activity are released, and inflammatory cells such as macrophages eliminate foreign particles (Singer and Clark, 1999). During this stage the normal oxygen supply is not possible due to the capillaries disrupted during injury and which have not yet been repaired (Gurtner et al., 2008). The formation of new blood vessels from the pre-existing ones is known as angiogenesis and occurs during the epithelialization stage. Angiogenesis is responsible for the re-establishment of the oxygen supply, which is necessary for cell activity. The epithelialization stage is characterized by the contraction of the wound due to the stress generated by cells, mainly

* Corresponding author.
E-mail address: claraval@unizar.es (C. Valero).

http://dx.doi.org/10.1016/j.jmps.2015.03.009
0022-5096/

fibroblasts and myofibroblasts (Valero et al., 2014). These cellular species are responsible for the new collagen secretion. As long as healing advances, the collagen forms fibers (initially dispersed) that align with the so-called skin stress lines. Protein fibers are embedded on the ground substance, made of proteoglicans and fibronectins (Gray et al., 1995), which helps cells to move through the fibers. Collagen fibers align in the skin following the stress lines, also established as Langer lines, which are present on the body's surface and which were discovered by Langer (1861). Langer (1861) performed circular cuts in the skin on all body surfaces, finding that these cuts turned into ellipses aligned with tension lines when the skin relaxed. The orientation of these cuts defined the natural orientation of collagen fibers, usually parallel to the underlying muscles. As an application example for the model proposed here we have simulated a semiellipsoidal wound which is oriented along one of the fibers symmetry axis.

The human skin's mechanical properties vary depending on different factors. This variation considerably influences healing when a wound occurs. One of the factors governing wound healing is collagen density and organization. Most of the mechanical properties of the skin are due to the fibers, which have an elastic modulus of 150–300 kPa (Wilkes et al., 1973), and which make up the extracellular matrix (ECM).

A number of experimental works focus on the determination of the mechanical properties of the skin. It is clear that this behavior is non-linear and that the skin has been considered as a viscoelastic or hyperelastic material. Experimental works that characterize skin as a viscoelastic material are, e.g., Boyer et al. (2007) and Silver and Siperko (2003). A large number of experimental works have demonstrated that the hyperelastic approach is suitable to reproduce the long term equilibrium behavior of skin.

Flynn et al. (2011) measured in vivo the force–displacement response of the forearm skin under consideration of three-dimensional deformations. Later, they found the material parameters that fit the Ogden hyperelastic model and the Tong and Fung (1976) model. Gahagnon et al. (2012) studied the anisotropy of forearm skin in vivo by using elastographic tests. They stretched the skin parallel and perpendicularly to the Langers lines and found anisotropic behavior.

In vivo assays carried out in order to determine the skin properties are difficult to perform and show a high variability between experimental subjects. The wide range of values obtained comes from the different anatomical locations of the skin, the attachment of the dermis to the underlying tissue and from patient specific characteristics, which makes it difficult to find a unique characterization valid for every kind of skin.

In vitro experiments are a useful alternative to in vivo assays. In vivo studies provide information on the skin in its natural environment, without eliminating natural processes, while in vitro studies allow the performance of more controlled experiments where different aspects can be isolated and where more destructive assays can be performed.

Hyperelastic characterization of the skin has also been obtained from in vitro studies. Annaidh et al. (2012a) investigated the influence of location and orientation of the skin on its properties by focusing on skin anisotropy. They performed in vitro tensile tests on human skin samples obtained from different parts of the back, finding a correlation between the orientation of Langer lines and collagen fibers (Annaidh et al., 2012b). They matched their results with the hyperelastic model developed by Gasser et al. (2006). Groves et al. (2013) carried out tensile tests on circular human skin specimens to measure the skin properties. To find skin anisotropy they performed tests along three different load axes. They found out that skin has anisotropic hyperelastic behavior and used the model introduced by Weiss et al. (1996) to simulate it. Moreover, it must be noted that the mechanical properties of the skin vary depending on the anatomical location, orientation and depth but also on age; skin turns to be less elastic with time, respectively age, and loses its recovery capacity (Escoffier et al., 1989).

Having accurate skin properties is highly important for the study of processes like wound healing, both experimentally and computationally. Wound healing models have been widely proposed during the last decades. One of the first wound healing models was developed by Sherratt and Murray (1990) and only included the effect of cells guided by a chemical attractant factor. It was later extended by Tranquillo and Murray (1992) who included the mechanical behavior of the skin, being the first work to simulate wound contraction. This model has been extended and modified by several authors (Olsen et al., 1995; Javierre et al., 2009; Murphy et al., 2011, 2012; Valero et al., 2014). On the other hand, a number of angiogenesis models in wound healing have been developed (Pettet et al., 1996; Maggelakis, 2003; Javierre et al., 2008; Schugart et al., 2008; Flegg et al., 2009, 2010; Vermolen and Javierre, 2010, 2012; Valero et al., 2013). In this work we extend a model previously developed which considers angiogenesis and wound contraction (Valero et al., 2013), by adding the effect of collagen fibers to properly reproduce the simulation of three dimensional wounds.

It is a well established fact that wound healing is highly influenced by the mechanical properties of the surrounding skin. Although different mechanochemical models have been proposed to simulate wound healing, these have mainly focused on the interaction between biochemical species and the deformation of a linear elastic extracellular matrix, and little (or no) attention has yet been paid to the role that the mechanical properties of the surrounding undamaged skin may have on the outcome of healing. Thus, this work focuses on the coupling of an anisotropic hyperelastic model for the skin with a previously developed mechanobiological model of healing that includes angiogenesis and wound contraction (Valero et al., 2013). The model is implemented in three dimensions and eliminates previously considered simplifications on the wound morphology or the mechanical behavior of the tissues, and it is used to determine the influence of wound orientation with respect to the skin collagen fibers in a semiellipsoidal wound.