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Development of an animal-free methodology for mechanical performance assessment of engineered skin substitutes

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Abstract

Functional substitutes for the treatment of skin wounds are nowadays widely available thanks to the progress in skin tissue engineering. However, the performance of the existing substitutes in terms of mechanical behavior, which is a determinant for their success, still does not match the native tissue. Since the mechanical behavior of skin is governed by dermis, an in-depth investigation of human dermis mechanics would be pivotal for integrating the design and validation of skin substitutes. In the perspective of reducing and replacing animal experiments through validated alternative tools, an accurate *in silico* constitutive model describing the human dermis mechanics is presented. Biaxial tests were performed on human dermis samples, and resulting data were used for setting the constitutive parameters of the model, able to reliably describing the mechanical properties of the native tissue, and to be compared with the mechanical behavior of skin substitutes attainable through the same procedure.

Introduction

Progress in skin tissue engineering has led to the development of functional substitutes for the treatment of acute and chronic skin wounds. However, the performance of the existing substitutes in terms of mechanical behavior still does not match native human skin.[1] Since the mechanical behavior of skin strongly depends on dermis, an in-depth investigation of the human dermis mechanics would be essential for supporting the design and the validation of skin substitutes.[2] In the perspective of reducing and replacing animal experiments thanks to validated alternative tools, here we present an accurate *in silico* constitutive model describing the human dermis mechanics. Biaxial tests were performed on human dermis samples, and resulting data were used for setting the constitutive parameters of the model adopted for faithfully describing the mechanical behavior of dermis under load.

Materials and Methods

Dermis samples were harvested from the lower back of a human donor, coherently with the anatomical orientations[3] (craniocaudal-CC and mediolateral-ML). Planar equi-biaxial tests were performed using a purpose-built fixture[4] mounted on a uniaxial testing machine (loading rate = 0.16 mm/s) (Figure 1a). Results were reported in terms of Cauchy stresses *vs* engineering strains, computed by tracking the average distance along the CC and ML directions of four central markers drawn on the sample surface.[4] Since dermis exhibits a highly nonlinear behavior, with anisotropic and heterogeneous responses during loading,[3] the Gasser-Ogden-Holzapfel (GOH) model (Eq. 1, for parameters details see Aldieri *et al.*[5]) was selected. Its constitutive parameters, describing the anisotropic hyperelastic response of dermis, were extracted from experimental data through a minimization procedure.

$$W = \frac{c}{2}(\bar{I}_1 - 3) + \frac{k_1}{2k_2}\left[e^{k_2[\kappa \bar{I}_1 + (1-3\kappa)\bar{I}_4 - 1]^2} - 1\right] + \frac{k_3}{2k_4}\left[e^{k_4[\kappa \bar{I}_1 + (1-3\kappa)\bar{I}_6 - 1]^2} - 1\right] \quad (1)$$

The GOH model was validated by repli-

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Key words: Human dermis; anisotropy; biaxial test; finite element; GOH model.

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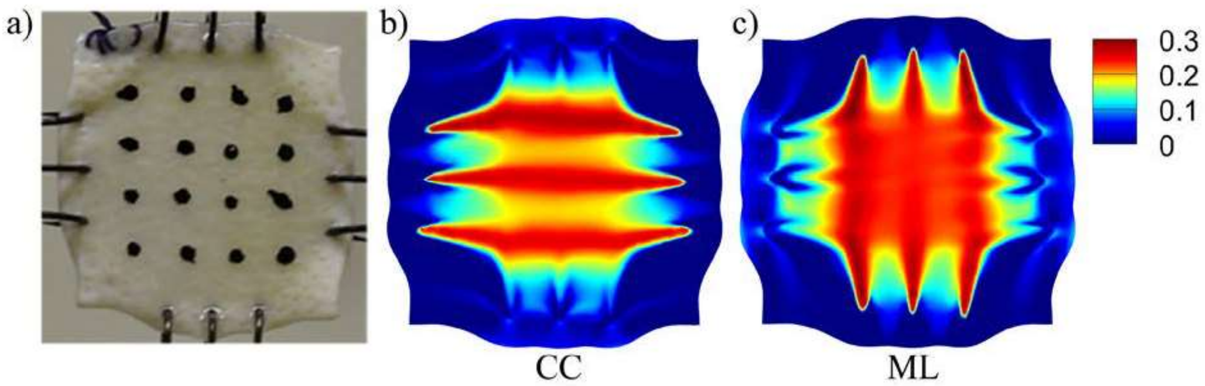

Figure 1. Human dermis sample during equi-biaxial test (a), and contour plots of engineering strains along the CC (b) and ML (c) loading directions.

cating experimental tests through Finite Element (FE) analyses and computing the normalized mean square error (NMSE) between numerical and experimental displacement magnitudes of the central markers.

Results

The obtained GOH constitutive parameters (k_1=90.3 *kPa*, k_3=50.6 kPa, k_2=11.0, k_4=8.0, *c*=1.2 *kPa*, κ=0.0005) were implemented in the FE model. Figure 1b and c shows the contour plots of engineering strains along the CC and ML directions, respectively. The numerical displacement magnitudes of the central markers were in good agreement with the experimental ones (average NMSE = 0.908), and, in accordance with experimental evidences,[3,4] a higher degree of deformation was achieved along the ML direction. This confirmed that the FE model outcomes accurately described the sample biaxial response, mirroring the experimental anisotropy.

Conclusions

In this work biaxial characterization and FE analyses on human dermis samples were combined to identify the GOH constitutive parameters for dermis mechanical description. The proposed animal-free methodology enables to investigate the mechanical performance of engineered skin substitutes with a combined *in vitro/in silico* approach, representing a powerful tool for selecting the optimal engineered substitute to be *in vivo* tested, with consequent reduction of animal testing.

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