11th World Congress on Computational Mechanics (WCCM XI)
5th European Conference on Computational Mechanics (ECCM V)
6th European Conference on Computational Fluid Dynamics (ECFD VI)
July 20 - 25, 2014, Barcelona, Spain

MULTISCALE MODELLING OF THE ACTIVATION PATTERN OF NF-KAPPA B IN SKIN AFTER MECHANICAL STRETCH

Kumar Mithrarartne[1] and Vickie B. Shim[2]

[1] The University of Auckland, Private Bag 92019, Auckland, New Zealand, p.mithraratne@auckland.ac.nz
[2] The University of Auckland, Private Bag 92019, Auckland, New Zealand, v.shim@auckland.zc.nz

Key Words: *Non-linear skin mechanics, Multiscale modelling, Mechanobiology.*

Skin is the outermost tissue of the body and the largest organ in terms of surface area. It has a very complex structure that consists of many components. Cells, fibres and other components make up several different layers that give skin a multi-layered structure. Human skin is comprised of three layers: the epidermis, dermis and subcutaneous fat. The melanocyte cells in the basal layer of the epidermis produce melanin. The skin colour is primarily determined by the amount of melanin, which also provides protection against the effects of the sun such as cutaneous melanoma and premature aging.

Melanoma progresses from pigmented lesions. Further progression leads to an in situ melanoma, which grows laterally and is primarily confined to the epidermis. This stage is known as radial growth phase (RGP) of melanoma. If left untreated, it can progress to the vertical growth phase (VGP), which is associated with invasion of the dermis by melanoma cells. The activation of nuclear factor kappa B (NF-κB) has been suggested as an event that triggers melanoma progression [1]. NF-κB is a protein complex found in almost all animal cell types and known to be involved in cellular responses to stress stimuli.

Mechanical behaviour of skin has been extensively studied and a number of computational models to study its constitutive properties and predict deformation under varying load conditions have been reported in the literature. Most mechanical models looked at macro level mechanics employing either theory of linear elasticity or finite deformation (non-linear) elasticity to describe strain-displacement kinematic relationships. However, the relationship between mechanical behaviour and the activation of NF- κB in skin has not been investigated. The aim of this study is to use a multiscale finite element model of the skin to analyse the activation pattern of NF-κB in skin under mechanical stimulation.

In order to investigate the activation pattern of NF-κB in skin, a detailed three-dimensional finite element model of skin was developed using the data derived from very high resolution images. A skin specimen from the forehead of a cadaver was sectioned to obtain 100μm thickness and total 30 slices, which were then stained with Fontana-Mason. These were imaged with a light microscope (Nikon eclipse Ti) using 4x ~ 20x magnification lenses. The images were segmented and the location and size of melanocytes were identified (Fig 1). The three-dimensional finite element model representing the micro-geometric features of the skin specimen was generated (Fig 2).

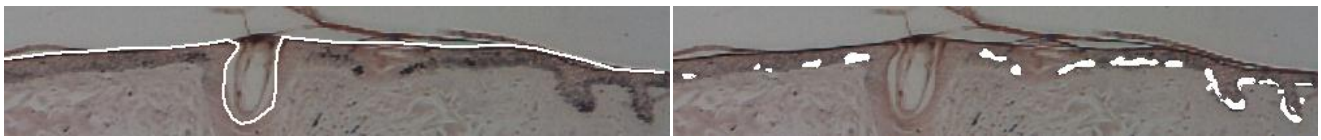

Figure 1 (a) Segmentation of surface topology (b) Identification of melanin granule and masking

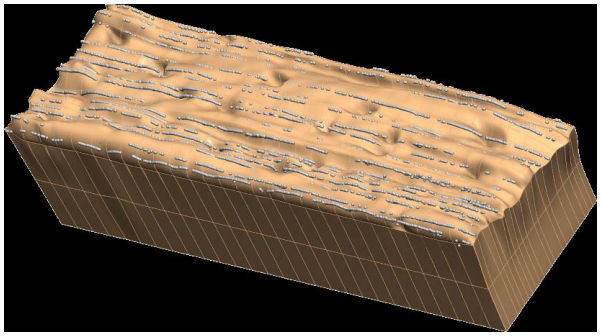

Figure 2 Three-dimensional finite element model of the skin specimen

Once the finite element model representing the detailed surface geometry was created, the identified melanocyte locations were defined with respect to finite element coordinates (body coordinates). The finite element model so developed was then subject to Dirichlet boundary conditions to simulate longitudinal stretch. The deformed state of the tissue block was obtained by solving the weak form of the governing equations, the static Cauchy equations using the Galerkin finite element method with non-linear kinematics. The mechanical behaviour of skin was described with a Neo-Hookean isotropic constitutive model for preliminary simulations. Since the melanocyte locations were defined with respect to finite element body coordinate system, these locations and respective stress/strain tensor at deformed state can be readily determined. This model was linked with a cell model which describes the activation of the NF –κB pathway based on the work of Nam et al [2]. This model quantitatively describes the action of the NF–κB pathway under mechanical stimulation. The cell models were embedded in the skin tissue model via numerical integration points to capture the spatially varying activation pattern of the NF–κB. Therefore, the skin tissue model was stretched longitudinally and maximum principal strain values were calculated at the numerical integration points within the skin FE model. These values were passed onto the cell models as an input, which computed the level of NF–κB activation. An open-source multiscale computational framework was used in our simulation (www.cmiss.org) [3]. Our results indicated that the deformation patterns of skin surface and inner layers were highly non-linear and dependent on topologies of both the skin surface and the dermal-epidermal junction. The resulting NF–κB activation patterns also showed high non-linearity, indicating that the geometry and the internal layer structure may play an important role in activation of this pathway. Future works include a sensitivity analysis to identify parameters most relevant to the activation of NF-κB.

REFERENCES

[1] S. Huang, A. DeGuzman, C.D. Bucana and I.J. Fidler, Clin. Cancer Res., Vol. 6, pp. 2573–2581, 2000.

[2] J. Nam, B. D. Aguda, B. Rath, and S. Agarwal, PLoS One, vol. 4, e5262, pp. 1–10, 2009.

[3] V. Shim, P. Pivonka, P. Hunter and J. Fernandez, IEEE Trans Biomed Eng, Vol. 58(12), pp. 3532–3536, 2011.