IX International Conference on Computational Bioengineering
ICCB 2022
P. R. Fernandes and J. Folgado (Editors)

Abstract ID 67

INTEGRATION OF MECHANICAL STIMULI INTO AGENT-BASED SIMULATIONS OF INTERVERTEBRAL DISC CELL ACTIVITY

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Keywords: Intervertebral disc; Agent-based modelling; Network modelling; Mechanoregulation; Computational systems biology

Summary: Intervertebral disc (IVD) degeneration is a slow process, presumably affected by small persisting changes in cell activity (CA) that is assumed to be influenced by physiological activities. Microscale modelling can help to understand important processes that lead to micro injuries and therefore to tissue disorders over time. In previous work [1,2] we presented a 3D agent-based model representing Nucleus Pulposus (NP) cells within their mechanobiological microenvironment. CA was estimated based on experimental findings, integrated through parallel network methodology [2]. We addressed the effects of nutritional (glucose, pH) and inflammatory microenvironments, and hereby we tackle further coupling with key mechanical cues. Mechanical load magnitude (mag) and frequency (freq) were described as continuous, sigmoid-shaped functions, covering physiological ranges of mag (0.1-3.5MPa) and physiologically relevant ranges of freq (0Hz-40Hz). Functions were determined based on the literature (e.g. [3]). Normalized cell mRNA expressions were calculated for important mechanoregulated Extracellular Matrix proteins, i.e. Aggrecan, Collagen I and II, and the proteases MMP3 and ADAMTS4. Mathematical formulations were developed to approximate the sensitivity to chronic stimulus exposure, individual for each CA, based on experimental knowledge [4]. Eventually, the effect of load duration depended on the current load intensity and on the regulated protein considered. To evaluate the model, the effects of different physical activities (e.g. walking, sitting with active/round back, jogging) were simulated. Results predict sitting with an active back and walking as highly anabolic, whilst the anabolism of sitting with a round back and jogging was predicted to be highly time-sensitive. Thanks to the ability of this model to capture individual, time-sensitive responses of various mRNA expressions, the effect of different physical activities on NP cell responses could be observed for the first time. Findings were consistent with general expectations about the anabolic/catabolic cell stimulation induced by each physical activity. As a novelty, we could thereby show that cell responses were highly sensitive to the stimulus environment; whilst negative effects of jogging were related with a high activation of MMP3, sitting with a round back led to an activation of Col-I and ADAMTS4 mRNA expression, with minimal MMP3 alteration. Hence, the strength of this method is the possibility to compare physical activities by quantifying complex load combinations and considering loading duration, which aims to provide further insight in crucial factors contributing to tissue breakdown during normal life. This is the first IVD cell model, to our knowledge, able to integrate experimental findings, to estimate IVD cell activity within a mechanobiological, multifactorial environment.