Simulation of the Multifactorial Cellular Environment within the Intervertebral Disc to better understand Microtrauma Emergence

Laura Baumgartner, Miguel Ángel González Ballester, Jérôme Noailly

I. INTRODUCTION

Intervertebral disc (IVD) failure, reflected by degeneration and/or herniation phenotypes, is closely related to low back pain, i.e., one of the largest global burdens [1]. Despite considerable amount of research into IVD failure aetiology, the underlying mechanisms remain unclear. Generally, it is assumed that repetitive, physiological loads over long periods of time are responsible for microtrauma accumulation within the IVD tissues, pointing out interactions between the loads acting on the IVD and the weakening of the disc tissue. Hence, improved understanding of such long-term interactions may be crucial to develop new injury criteria for IVD failure. Tissue strength is closely related to cellular activity, since cells dynamically build and degrade the IVD's extracellular matrix (ECM). However, disc cells are sensitive and respond to intricate combinations of mechanical and biochemical stimuli that are difficult to measure or estimate with the current technologies used in IVD research. In order to cope with such limitation, the present research aims at introducing Agent-based modelling (ABM) in IVD research, to capture the dynamics of disc cell response to multifactorial stimulations, in combination with more classical methods in biomechanics, i.e., finite element (FE) modelling. In a first step, indirect mechano-transduction (i-mech) was simulated in a 3D ABM [2]. Now, the model has been extended to include direct mechano-transduction (d-mech) effects, i.e., the influence of load magnitude (mag) and frequency (freq) on cell activity.

II. METHODS

The ABM simulates 1 mm³ of Nucleus Pulposus (NP) environment, consisting of 4000 NP cells. Biochemical stimuli were defined by the levels of glucose (glc) and lactate (lac) that ranged from 0 mM to 5 mM, and from 0 mM (pH 7.4) to 10 mM (pH 6.5), respectively [2]. To implement mag and freq, two generic functions were built, reflecting cell mRNA expression for the ECM proteins Aggrecan (Agg) and Collagen Type II (Coll-II) and for the proteases MMP3 and ADAMTS. Mag could be chosen within a physiological range from 0.1 MPa to 3.5 MPa [3-4]. For freq, values between 0.1 Hz and 40 Hz could be selected. Anabolic and catabolic ranges of mag and freq were estimated based on [3][5-7]. Each value for mag and freq was then assigned to a cellular activity for each mRNA production, ranging from 0 (lowest) to 1 (highest). Finally, calculated cell activation levels derived from each stimulus were weighted and integrated through a systems biology approach [8] to estimate an overall cellular activity related with each of the targeted mRNA expressions. Subsequently, first plausibility cellular activity scenarios were simulated, for non-degenerated (non-deg) i-mech conditions (1.0313 mM glc; 4.9698 mM lac (pH 6.95)) exposed to different loading conditions. These input data were derived from a mechanotransport FE Model (mFEM) [9] able to estimate local glc and lac concentrations (Fig. 1). Mag and freq were chosen according to values used in experimental setups [10-11] (1 MPa, 1 Hz; 2.5 MPa, 0.1 Hz) and based on in vivo measurements and estimations [3][6][12] for daily activities, i.e., walking (0.6 MPa, 1.8 Hz), walking with an additional load of 20kg (1.1 MPa, 1.8 Hz) and jogging (0.6 MPa, 2.8 Hz). To evaluate the influence of i-mech, an early degeneration (early-deg) environment (0.8969 mM glc; 5.1633 mM lac (pH 6.94)) was simulated and cell Agg and Col-II mRNA expressions were calculated under 1 MPa, 1 Hz. Instantaneous mRNA expression was estimated, thus, a momentary insight of cellular activity during a certain loading condition was captured.
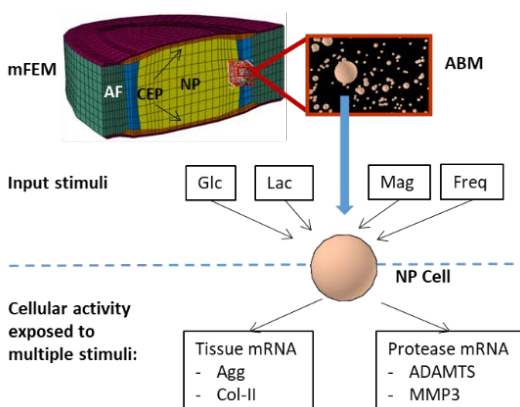

Fig. 1. overview over the region of captured i-mech conditions, ABM input stimuli and estimated mRNA expression. AF: Annulus Fibrosus, CEP: Cartilage Endplate

L. Baumgartner (e-mail: laura.baumgartner@upf.edu; tel: +3493 542 13 46) is a PhD student in Biomechanics and Mechanobiology at the Universitat Pompeu Fabra (UPF), Barcelona, Spain. M. A. González Ballester is ICREA (Barcelona, Spain) research Professor and the head of BCN MedTech at UPF. J. Noailly is Ramon y Cajal senior Researcher and the head of the Biomechanics and Mechanobiology research area of BCN MedTech at UPF.

III. INITIAL FINDINGS

Initial findings under non-deg biochemical conditions show a decrease in the instantaneous cellular activity under high mag and low freq, but only a small change under moderate load and freq (Fig. 2, left). As for simulated daily activities, walking resulted in highly anabolic cellular activity with no particular effect of a 20 kg load bearing. Jogging conditions led to less anabolic or moderate catabolic shifts. The effect of d-mech on cells exposed to an early-deg biochemical environment shows a shift of Agg and Col-II mRNA expression of -0.15 % and +0.79 % (Fig. 2, right) compared to an Agg loss of 0.23 % and Col-II augmentation of 0.25 % under non-deg conditions.
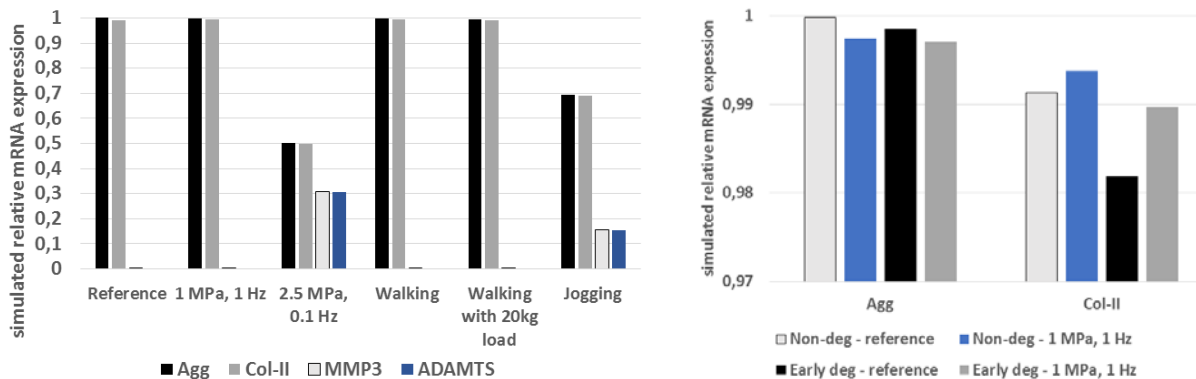

Fig. 2. Left: estimation of the influence of different d-mech conditions in a non-deg biochemical environment. Right: estimation of the influence of d-mech within a non-deg and early-deg biochemical environment.

IV. DISCUSSION

Results are in good agreement with the general understanding of long-term tissue weakening despite natural repair strategies, which could explain microtrauma accumulation in early degeneration. Small changes of instantaneous mRNA expression coincide with the fact that it might take years to show a certain phenotype of tissue breakdown. Additionally, model predictions are backed up by findings from literature, i.e., significantly reduced Agg mRNA expression of human NP cells after exposure of 24 h to 2.5 MPa compared to unstimulated controls [11]. Furthermore, [7] found that walking is less related with IVD degeneration, whereas frequent jogging might be associated with IVD failure over time. However, simulations of 1 MPa and 1 Hz lead to an augmentation of Col-II and a decrease in Agg (Fig. 2, right), which is only partly in agreement with [10], who showed a generally anabolic effect with loading of 1 MPa at 1 Hz for 8 h per day over two weeks. With this regard, it must be taken into account that data of [10] comes from in-vivo rat-tail models, where, apart from differences based on different species, i-mech conditions are unknown and assumingly not constant over time. Hence, calculated reference values obtained under optimal i-mech conditions are likely to be rather optimistic. Current simulations indicate furthermore a tendency towards a more anabolic impact of d-mech for early-deg conditions (Fig 2., right), which would be an interesting finding regarding possible future microtrauma prevention strategies. However, these preliminary results might be affected by some limitations such as the neglection of the influence of inflamed cells on overall mRNA expression or a current insensitivity of d-mech to individual load exposure times. Additionally, weighting parameters of different stimuli must be confirmed in future simulations. Nevertheless, current results reasonably point out the likely complexity of microtrauma occurrence, as an emerging event from the combined i-mech and d-mech phenomena. The heterogeneity of the mechanical and nutritional cell cues within the IVD might explain the variety of phenotypes in IVD failure, and we can conclude that ABM in IVD research provides a, to date, unique, systematic insight in possible changes of the tissue's load bearing capacity due to local cellular activity.

V. REFERENCES

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