Revealing Interactions of Load Magnitude, Frequency and Exposure Time in Intervertebral Disc Microtrauma Accumulation

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I. INTRODUCTION

Despite its high prevalence affecting over 70% of the population [1], intervertebral disc (IVD) degeneration remains poorly understood. While it is widely accepted that unique, high-load impacts are unlikely to lead to isolated IVD failure, microtrauma accumulation over time is hypothesised to be the critical mechanism. Factors leading to microtrauma accumulation are assumed to include: (i) emergence of catabolic shift of cell activity along with limited repair capacities; and (ii) a general lowering of the tissue quality and, therefore, of the resistance of the tissue to locally high or permanently acting loads. Since cells are responsible for both aspects, microtrauma accumulation is assumed to reflect a biologically driven injury scenario. For several decades, experimental research focused on exploring the response of cells exposed to a broad variety of load magnitudes (mag) and frequencies (freq) applied over different periods of time, to investigate their activity in terms of tissue building or breakdown. Cell activity is often reflected by cellular messenger RNA (mRNA) expression (expr), i.e. the transcription of sequences of DNA that encode specific proteins that the cell is going to synthesise. Understanding reasons for microtrauma accumulation in the IVD is an indispensable basis for developing prevention strategies or injury criteria, and it requires capturing cellular predisposition for tissue building/maintaining or weakening. This ongoing work focusses on developing an in-silico methodology that systematically uses experimental knowledge to approximate cell activity for user-defined loading parameters, which eventually allows for comparison of the effect of different loading conditions on cell activity.

II. METHODS

An Agent-based model was developed [2], containing 4,000 Nucleus Pulposus (NP) cells that can be virtually exposed to user-defined loading conditions by choosing a physiological load mag between 0.1 and 3.5 MPa [3-4], a freq between 0 and 40 Hz and a user-specified load exposure time [h]. The translation of load mag and freq, respectively, to a normalised cell activity is provided by a generic continuous function (Fig. 1) for each mag and freq. The functions were approximated based on experimental and physiological findings from literature.

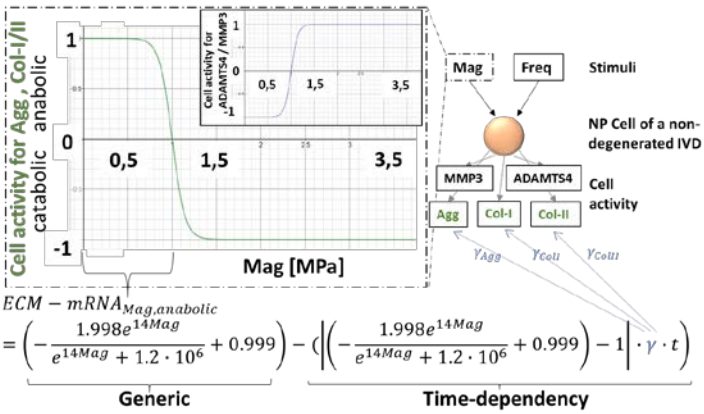

Fig. 1. The effect of load on cell activity, using the example of the influence of mag on tissue mRNA expr. t = time, γ = protein specific sensitivity of load.

Cell activity for the important mechanoregulated tissue proteins Aggrecan (Agg) and Collagen Types I & II and the tissue degrading enzymes (proteases) MMP3 and ADAMTS4 was simulated. Proteases were programmed to behave in an opposite manner to tissue proteins and follow, therefore, a mirrored generic function (Fig. 1). Positive values of the function activated the corresponding mRNA expr with a maximum anabolic effect close to 1, whereas negative values inhibited mRNA expr. The influence of load duration was coupled to the level of mRNA expr and contained a coefficient (γ) that individualised the load sensitivity for different tissue proteins and proteases (see equation, Fig. 1). γ was determined by using experimental data (mainly [5-6]) that quantified the effect of a loading condition on the targeted mRNA expr. To allow the model to combine different load stimuli and consider the activating or inhibiting characteristics thereof, a Boolean mathematical representation of network models [7] was adapted.

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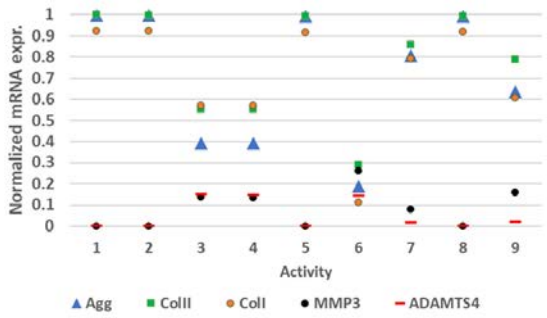
To evaluate the model behaviour, mag, freq and load durations were assumed for different human activities and compared to each other (Fig. 2).

III. INITIAL FINDINGS

Interactions of experimental findings and numerical methods result in a generally higher sensitivity of tissue mRNA than protease mRNA to the considered loading conditions. Long-term exposure of anabolic loads, high freq or additional loading (e.g. activities 3, 4, 6 and, to a lesser extent, activity 9) could cause considerable catabolic shifts in cell activity (Fig. 2).



Activity	Mag [MPa]	Freq [Hz]	Time [h]
1) Sleeping	0.1	-	8
2) Sitting in a car, vibration damped	0.5	-	6
3) Sitting in a car, vibration not damped	0.5	15	6
4) Sitting in a car, vibration not damped, inclined sitting position	0.3	15	6
5) Hiking w/o additional weight	0.6	1	6
6) Hiking with 20kg additional weight	1.1	1	6
7) Jogging	0.65	2.75	4
8) Walking	0.60	1.8	4
9) 90 days in Space	0.1	-	2160

Fig. 2. Predicted cell activity for different loading conditions in non-degenerated human NP cells.

IV. DISCUSSION

In this modelling approach, experimental and observational findings were combined in order to build evidence-based representations of the biological response of IVD cells in multifactorial loading scenarios. The results were consistent with general expectations, e.g. high vibration freq represented a possible risk factor for compromised tissue strengths (2 vs. 3), and walking (8) was more beneficial than jogging (7), which could be associated with IVD degeneration in young adults if practiced frequently [8]. Additionally, as this model is able to capture trade-offs of different ECM proteins and proteases, it uniquely allows weighting the effect of preventive approaches, e.g. damping vibrations (2), rather than inclined sitting positions (4), is suggested to be beneficial for spine health in car passengers and (comfortable) hip belts for heavy backpacks might be essential to relieve the spines of frequent hikers (5 vs. 6). The general trend of such preliminary results could be partly validated against experimental results in a previous model version [9]. However, findings are restricted to the NP tissue of the IVD and, importantly, the effect of inflammation has not yet been considered. Interactions between inflammation and loading are now under investigation. Amongst other findings, the results are expected to provide further insight into reasons for the severe risk of IVD failures shortly after space flights [10]. Arguably, the presented results (9) show a catabolic shift in healthy NP cells after 90 days in space, but a worse effect would be expected. Additionally, calculations related to a stay in space specifically underline the possible negative impact of prolonged exposure of invariant mechanical loads that otherwise would not be considered critical for microtrauma accumulation (1 vs 9). Such results suggest that a change of loading conditions may contribute to the health preservation of the IVD, which might be particularly interesting for preventive strategies for people exposed to prolonged physical inactivity.

To understand and quantify injury risk factors at a tissue/microscale level, the incorporation of biological factors is deemed to be indispensable. Compared to injury scenarios in classical trauma biomechanics, microtrauma accumulation in the IVD progresses over large timescales, pointing out that microtrauma investigation requires the incorporation of injury parameters different from those of classical trauma biomechanics. Furthermore, the prediction of injury emergence and propagation over multiple length and time scales is deemed essential to holistically understand different injury processes associated with IVD failure in different individuals, at a macroscale level.

V. REFERENCES

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