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Micromechanical Modelling of Bone Marrow: Understanding the *in vivo* Mechanical Environment of Mesenchymal Stem Cells

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Introduction

Bone marrow is a cellular soft tissue located within the porous spaces of bone and forms the natural environment for several precursor cell types, including Mesenchymal Stem Cells (MSCs). Several experimental studies have established that mechanical loading directs MSC differentiation [1] and it has been hypothesised that the bone marrow micromechanical environment plays a role in directing the cellular fate of MSCs *in vivo*. Computational fluid dynamics approaches have been used to estimate fluid shear stresses experienced by MSCs by assuming the marrow behaves as homogeneous, Newtonian fluid [2, 3]. However, bone marrow is a complex heterogeneous multi-cellular tissue, whose mechanical behaviour is dictated by the structural properties and physical interactions of its cellular constituents. Furthermore, marrow composition changes with the onset of osteoporosis, where an increase in adipocyte content is accompanied by a decrease in bone mass [4]. Low-Magnitude High Frequency (LMHF) vibration loading has been proposed as a treatment for osteoporosis [5], and it has been proposed that this effect is mediated through mechanical stimulation of the MSCs within the marrow [3], but the precise cellular level stimuli have not been characterised. To understand the effect of marrow composition at the cellular level, we develop a micromechanical finite element model, which discretely represents bone marrow as a cellular structure, and characterise mechanical stimulation of MSCs within their micro-environment under physiological and LMHF loading conditions.

Materials and Methods

A numerical algorithm was created to generate Representative Volume Elements (RVEs) of bone marrow by assuming it was composed of two cell populations, i.e. (i) Adipocytes (E = 0.9kPa, υ = 0.4) and (ii) other cell types, which included MSCs (E = 2.5kPa, υ = 0.4), see Figures 1a and b. This models were representative of (a) healthy bone marrow, where the adipocyte volume fraction (AVF) was 30%, and (b) osteoporosis, which had an AVF = 60%. Finite Element (FE) models were generated to simulate both physiological loading conditions, (i.e. an applied compressive strain of 3,000$\mu\varepsilon$), and LMHF vibration loading (i.e. a sinusoidal loading regime with a maximum acceleration of 1g and a frequency of 10Hz)

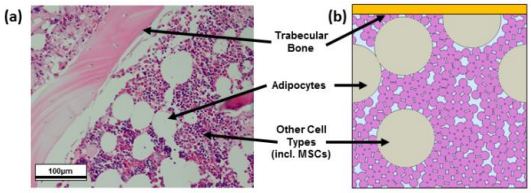

Figure 1: (a) H&E section showing adipocytes and various other cells (including MSCs) and (b) two-dimensional micromechanical model geometry that discretely represents the cellular composition of bone marrow.

Results

The results of this study show that local cell distribution had a distinct effect on how load is transferred throughout the marrow, with strain concentrations observed where cells were adhered directly to one another (Figure 2a). Increasing the AVF in the marrow from 30% (Figure 2a) to 60% (Figure 2b) reduced the magnitudes of maximum principal strain to the MSC cell population by approximately 35% on average due to a shielding effect caused by the more compliant adipocytes. LMHF vibration loading resulted in widespread stimulation of MSC cells throughout the marrow and stimulation magnitudes were in excess of 3,000με and notably within the range to the in vivo loading condition (Figure 2c, d) for the healthy case.

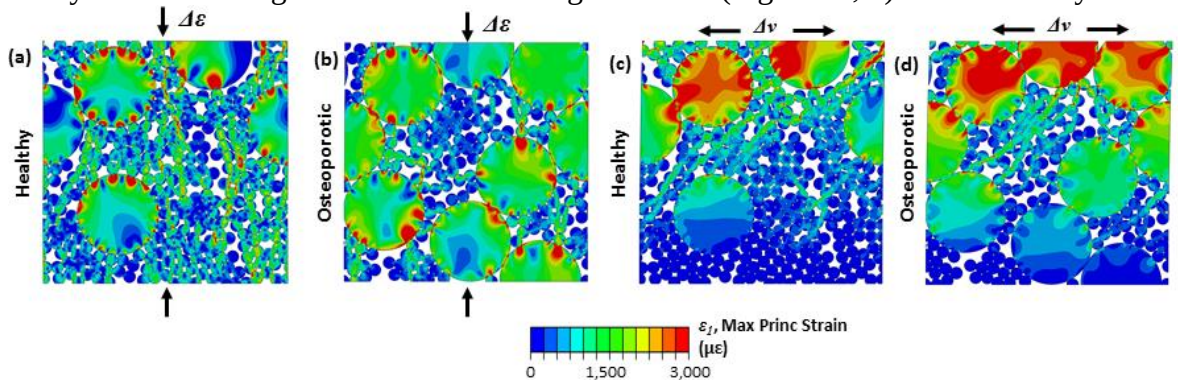

Figure 2: Compressive loading of an RVE having (a) AVF =30 %, (b) AVF = 60% and LMHF vibration loading of an RVE with (c) AVF =30 %, (d) AVF = 60%.

Discussion and Conclusions

The results of this study demonstrate that MSCs cells within bone marrow are highly stimulated at cell-cell attachments, suggesting that adhesion junctions between neighbouring cells may play an important role in mediating the response of MSCs to mechanical stimulation in their native environment. Interestingly it was found that increasing the adipocyte content of the marrow, which coincides with the onset of osteoporosis [4], resulted in lower levels of stimulation within the remaining MSC population. This could have important implications as this lower stimulation might negatively affect bone homeostasis in a similar fashion to disuse or immobilisation and thereby contribute to bone loss during osteoporosis. Finally, LMHF vibration loading was effective in increasing MSC stimulation compared to in vivo loading, which may explain why this treatment has been found to inhibit adipogenesis in vivo [5] and promote bone formation.

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