Simulation of fracture healing of a human tibia in 3D using mechano-regulation algorithm for stem cell differentiation and a random-walk algorithm for cell migration and proliferation

INTRODUCTION:
Understanding the relationship between the local mechanical environment and tissue differentiation in fracture healing has been an aim of many orthopedic researchers. Experimental and clinical studies have shown that insufficient mechanical stimulation delays the initial stages of healing whereas excessive movement inhibits ossification, delays healing and results in lack of stability. Complex fractures often require surgical intervention to re-establish structural integrity of the fractured bone using fracture fixators. The loading on the regenerating tissues at the site of fracture is then determined by the stiffness of the fixator and the physical activity of the patient. Determining the appropriate stimuli to promote optimal bone regeneration in this situation remains a challenge and has been the subject of much research.

The objective of this work is to model fracture healing in a human tibia with an external fixator, under loading conditions that are as physiological as possible and accounting for cellular processes stochastically based on a ‘lattice’ that accounts for cell positions. If this approach proves feasible it offers the possibility of using computer simulation in the clinical treatment of complex fractures, and in other orthopedic applications where bone regeneration occurs.

METHODS:
A three dimensional biphasic finite element model of a tibia was used to determine the biophysical stimuli acting on the regenerating tissue in the fracture callus [1] (Fig. 1a). Both muscle and joint forces were applied to the tibia [2], and a weight bearing ratio (weight bearing of injured leg divided by weight bearing of uninjured leg) was used to relate the increase in loads as healing progresses [3].

Initially the callus was assumed to consist of granulation tissue, into which mesenchymal stem cells could proliferate and migrate from the periosteum, endosteum, and marrow space at the site of the damaged cortical bone tissue. The random-walk algorithm models the cell proliferation and migration in three-dimensions based on a stochastic process consisting of discrete steps of fixed length. Tissue differentiation is regulated by magnitudes of shear strain ($\gamma$) and relative fluid/solid velocity ($v$) [4]. The resulting local stimulus determined from the mechano-regulation algorithm causes: (i) MSCs to differentiate into cell phenotype $i$ (fibroblasts, chondrocytes, or osteoblasts), based on the differentiation rate ($0.3$/iteration) and the number of MSCs that have reached the critical age ($age>7$ iter); (ii) maximal proliferation of the differentiated cell phenotype $i$, and minimal proliferation of all other cell phenotypes; (iii) apoptosis of cell types not under the current stimulus, importantly the possibility of implementing experimentally motivated cell-based rules. Some of the cell rate parameters are not well quantified in the literature and were estimated [6]; however these can be easily implemented when the information becomes available. The model holds therefore the healing time line is patient specific. The lattice approach requires time to synthesize and remodel new tissue and therefore the change in Young’s modulus at a lattice point was described using a rate equation. Since an element contains many lattice points, the element material properties were updated according to the rule of mixtures. Following the experimental protocol of [5] on healing human tibiae, a four-point bend test in the sagittal plane was also simulated at every stage of tissue differentiation to predict the bending stiffness during healing. Once a stiffness of 15Nm/degree was achieved the external fixator was removed. The iterative scheme continues until convergence of the bending stiffness has been achieved.

RESULTS:
In the early stages of healing a significant amount of soft tissue can be seen in the external and interfragmentary callus, while immature bone formation occurs in regions distal to the fracture gap (Fig. 2). As healing progresses much of the cartilage is replaced by bone via endochondral ossification. Bony bridging occurs by week 8; however a small amount of cartilage remains tangent to the cortical surfaces. Resorption is predicted in the external and peristeal callus, and to a lesser extent in the intermedullary canal.

The bending stiffness gradually increases in the early stages of healing, mainly due to the rate equation which models cell maturation (Fig. 3). Both the experimental [5] and simulated bending stiffnesses follow the same trend; however differences between the two may be attributed to patient variability. As ossification is predicted in the callus the bending stiffness is seen to increase significantly from weeks 2 to 6. Thereafter resorption begins to restore the original contour and internal structure of the bone, while further bone maturation leads to a slight increase slight increase in stiffness.

DISCUSSION:
The objective of modeling the 3D fracture healing process with a fixator was achieved; the appearance and disappearance of tissues in the callus is broadly correct even if the callus persists in the medullary cavity. However, the course of change of the bending stiffness is quite similar to experiments. It is important to note that the loads acting on the tibia will vary depending on a number of factors such as, the severity of the fracture, the patient’s age, weight, height, fitness, bone quality etc.; therefore the healing time line is patient specific. The lattice approach using random-walk to account for cell migration/proliferation allows for a more mechanistic approach for the simultaneous dispersal of several cell populations, the explicit modelling of cell proliferation, and more importantly the possibility of implementing experimentally motivated cell-based rules. Some of the cell rate parameters are not well quantified in the literature and were estimated [6]; however these can be easily implemented when the information becomes available. The model holds the potential to be used to non-invasively assess the options for treating fractures in patients.

REFERENCES: