Quantitative analysis of histological images for the validation of computer models that predict tissue differentiation during fracture healing

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Introduction

Various iterative computational models have been reported in the literature to predict the tissue changes during callus maturation in secondary bone fracture healing (see [1] for a comparison of mechano-regulation algorithms). For the validation of such computer models, the predicted tissue distribution within a fracture callus is usually compared to histological photomicrographs of an animal study, on which the computational model is based. These comparisons are often performed qualitatively, *i.e.* by visual comparison of the shape of the predicted tissue distribution with a typical histological image. In contrast, the goal of this study was to develop a quantitative method for this validation, in order to improve the significance of the computational predictions.

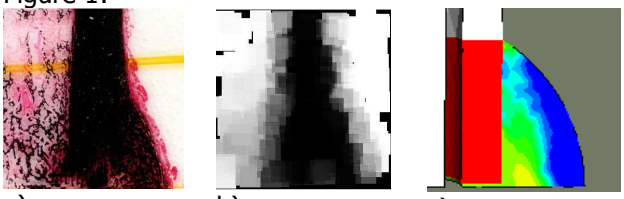
Methods

A custom image analysis algorithm was written in MATLAB (Mathworks, Inc., Natick, MA). This algorithm, which is based on a previously reported program [2], has been adapted for the specific purpose of this study, and is designed to measure the amount of a stained tissue type in histological sections. A random square within the histological image is selected, the desired colour range segmented from the image and the area of this region calculated as percentage of the area of the square. This process is repeated until the entire area of interest on the histological slide is analysed. The results can be used numerically in a direct comparison with computationally predicted tissue distributions, or displayed graphically, as concentration maps for a given tissue type within the histological slide.

Results

The following example demonstrates the effectiveness of the algorithm. Figure 1.a shows a histological section of a transverse ovine tibia fracture (6 weeks after fracture) that has been stabilised with an internal fixator. The mineralised tissue was stained black using the von Kossa protocol. The distribution and density of mineralised tissue for this longitudinal section was calculated and displayed in a density map (Figure 1.b), where increasing grey levels indicate higher degrees of mineralisation.

Figure 1:



a) b) c)

Figure 1.c shows a representative result of a 3D iterative mechano-regulation model from our group (G. Chen, unpublished), from an ovine fracture stabilised with an intramedullary nail, where different colours indicate different degrees of mineralisation.

Discussion

We are presenting a new image analysis method for the quantitative analysis of the distribution of a given tissue type in stained histological sections. In particular, this method can be used to analyse entire series of histological images from an experimental study, so that statistically meaningful results can be produced. This is tremendously valuable for the quantitative comparison with predicted tissue distributions from iterative computational simulations of tissue differentiation during fracture healing, since it goes beyond the standard qualitative comparison with individual, "typical" histological images. In addition, the presented method is useful for the quantification of tissue types that cannot be easily identified with other medical imaging methods, such as CT or MRI.

References

[1] Isaksson, H*, et al.*, *J Biomech*, 2006.
[2] Sidler, H J*, et al.*, *Trans ORS*, 2006.