Phenomenological modelling tools for orthopaedic tissue engineering

N. I. Nikolaev[1], G. Lemon [2], B. Obradovic[3], H. K.Versteeg[1] and D. J. Williams [1]
[1] Wolfson School of Mechanical and Manufactural Engineering, Loughborough University, Loughborough LE11 3TU, UK
[2] School of Mathematical Sciences, University of Nottingham, Nottingham NG7 2RD, UK
[3]Department of Chemical Engineering, Faculty of Technology and Metallurgy, University of Belgrade Karnegijeva 4, 11000 Beograd, Serbia and Montenegro

INTRODUCTION: Today tissue engineering has to solve challenging task - in vitro growth of different tissues. In specially constructed bioreactors *in-vivo*-like conditions have to be created. Many experiments will be needed first to identify key growth factors/growing conditions and subsequently optimise them. Because many processes are involved, mathematical models may be useful to estimate the impact of each of them and later to improve biological and mechanical functionality of tissue engineered constructs [1]. We analyze the role of the different processes for tissue growth: nutrient transport and consumption, cell population dynamics, extra-cellular matrix (ECM) secretion, stress and strain distribution, construct expansion, tissue degradation, and the role of mechanical stimulation. Our aim is to embed current understanding of processes controlling the seeding of a scaffold, cell and ECM growth and maintenance for engineered spinal disk tissue in to a modelling tool to predict tissue quality metrics and for potential use in the optimisation of processes to create such constructs with a bioreactor.

METHODS: Multiphase theory [2] is used to describe tissue growth. We have incorporated a viscoelastic model [3] and approaches used for wound healing description [4]. Tissue is described as a mixture of four phases – cells, water, scaffold and ECM (at this stage we represent ECM in terms of a single component - GAG due to lack of suitable experimental data for other parts). Scaffold and ECM move together like in [4] and cells are attached to them. This joint movement is caused by cell traction and deformations associated with tissue growth. The scaffold is gradually degraded by hydrolysis. ECM synthesis is modelled as a two-stage process. Initially, cells produce proteoglycan (PG) molecules, which may bind to already existed GAG matrix or diffuse and leak out of the construct. The rate of PG synthesis is proportional to nutrient and cell concentration and is limited by the local concentration of GAG. To simulate expansion of the construct due to the growth a "thermoelastic" model is employed in conjunction with moving boundary conditions [2,3]. The experimental results in [6] have been used to calibrate the model. One of the current challenges is to match the temporal evolution of spatial cell distribution. In this paper we investigate the ability of different mechanisms to explain the experimental trends. Different models for description of the growth of the construct have been tested and compared.

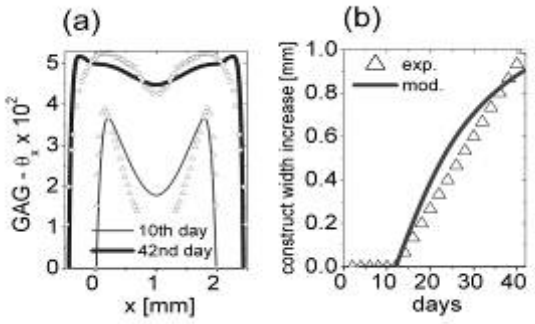

Fig. 1: Comparison between experimental results from [6] (dots or triangles) with simulations (solid lines). (a) GAG distribution - 10th day (thin line), 42nd day thick line; (b) increase of the width of the construct.

RESULTS: The results obtained (Fig. 1) show the satisfactory agreement to those observed experimentally with respect to the time evolution of GAG distribution and increase the size of the construct. Further work is required to verify the model, a recently commissioned experimental system will enable this.

REFERENCES: [1] Sengers B G, Taylor M, Please C P, Oreffo R O C (2007) Computational modeling of cell spreading and tissue regeneration in porous scaffolds , Biomaterials **28**: 1926-1940 [2] Lemon G and King JR. (2007) Multiphase modelling of cell behaviour on artificial scaffolds: effects of nutrient depletion and spatially nonuniform porosity Mathematical Medicine and Biology-a Journal of the Ima **24**: 57-83. [3] Moon, A.G and Tranquillo R T. (1993) Fibroblast-Populated Collagen of Cell Traction Force: Part 1 Microsp here Assay Continuum Model, AIChE Journal, 39: 163-177. [4] Murray J. D. Mathematical biology – Spatial models and biomedical application, Chap. 10. Dermal Wound Healing. [5]Volokh, K.Y (2004) A simple phenomeno-logical theory of tissue growth, Mech Chem Biosyst. **1**:147-160. [6] Obradovic B, Meldon JH, Freed LE, Vunjak-Novakovic G., *Glycosaminoglycan deposition in engineered cartilage: experiments and mathematical model*. AIChE J 2000, 46, 1860-1871.

ACKNOWLEDGEMENTS: This work forms part of the UK EPSRC funded Innovative Manufacturing Grand Challenge in Regenerative Medicine - remedi. Remedi is a partnership of Loughborough, Nottingham, Cambridge, Birmingham, Ulster and Liverpool Universities, Industry and Agency stakeholders.