Modeling the development of tissue engineered cartilage

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Introduction

The composition of tissue engineered (TE) cartilage depends to a large extent on the bioreactor configuration, see figure 1. The EU project IMBIOTOR aims at realizing an intelligent bioreactor in which the properties of the TE construct can be tailored using model based control of the complete bioreactor environment. Manipulating global input parameters: Nutrients, growth factors, O_2, pH, temperature, time and mechanical stimulation, will yield the local output: Collagen II, proteoglycans, cells, permeability and stiffness.

Objective

- A numerical model that can predict local construct properties as a function of the global input.

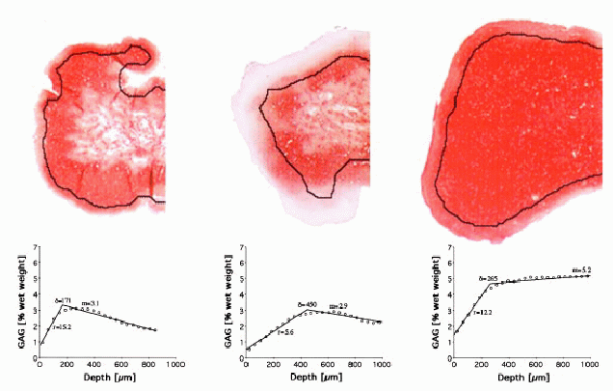

Figure 1 *GAG (Matrix) distribution for constructs cultured in static flasks, mixed flasks and rotating bioreactors [1].*

Methods

A description of highly coupled phenomena, like mechanical adaptation, solute transport, cell growth and biosynthesis is required, which has to deal with quantitatively ill-defined chondrocyte responses. Figure 2 shows the proposed model.

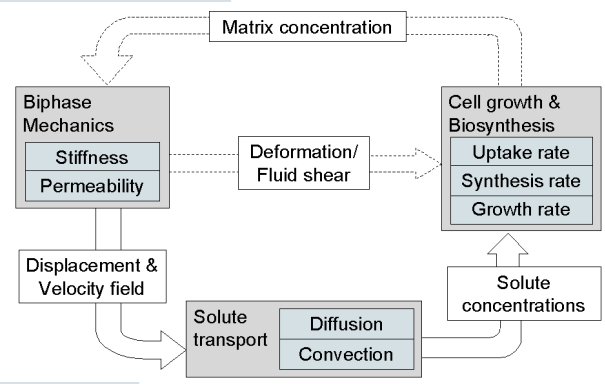

Figure 2 *Proposed model.*

A biphase description captures deformation and mechanically induced convection, ignoring electro-osmotic effects. Simple unstructured kinetics for nutrient uptake, cell growth and biosynthesis will be used [2, 3]. Kinetic rates are influenced by cell and matrix content and nutrient availability. A deformation measure can be used to account for direct mechanical stimulation. The resulting matrix concentration will determine the permeability and stiffness.

Results

Figure 3 shows examples of the model's possibilities.

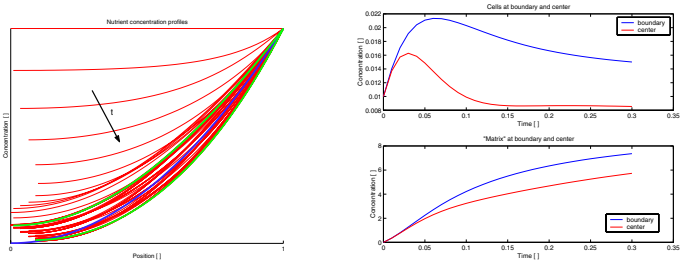

Figure 3 *Left: Nutrient concentration profiles for cyclic deformation in confined compression and constant nutrient uptake. Green are the constant limits reached after a number of cycles. Blue is the steady state profile without deformation. Right: Cell and matrix concentrations in the center and at the boundary (no deformation).*

Conclusions

- Further integration of models for mechanical adaptation, solute transport, cell growth and biosynthesis will lead to significant progress in controlling the development of tissue engineered constructs in bioreactor culture.
- A biphase model is proposed with local permeability and stiffness depending on matrix synthesis and cell growth, which are influenced by deformation and nutrient transport.
- The present model gives a qualitative picture that has to be quantified and validated using experimental data.

References:

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[2] B. Obradovic, J.H. Meldon, L.E.Freed, G. Vunjak-Novakovic: *Glycosaminoglycan deposition in engineered cartilage: Experiments and mathematical model* (AIChE Journal, 2000, 46-9, 1860-1871)

[3] C.J. Galban, B.R. Locke: *Effects of spatial variation of cells and nutrient and product concentrations coupled with product inhibition on cell growth in a polymer scaffold* (Biotechnology and Bioengineering, 1999, 64, 633-643)

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