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TU/e technische universiteit eindhoven

# Multiscale modeling of diffusion hindrance in tissue engineering constructs

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## Introduction

Macroscopic mechanical properties of tissue engineering constructs depend on their composition, which evolves in time following synthesis, transport, binding and degradation of biomolecules. A throughout understanding of these phenomena is relevant to improve the development of artificial tissues. From a purely mechanical point of view, diffusion plays a fundamental role in the transport of newly synthesized material across the tissue.

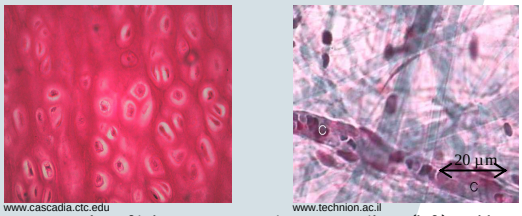


Figure 1: Examples of inhomogeneous tissues: cartilage (left) and loose connective tissue (right).

Diffusion mechanisms are highly inhomogeneous in developing biological tissues, in which large aggregating matrix molecules such as collagen and GAGs are continually synthesized by individual cells. In these systems, diffusivity decreases due to an increase in the tortuosity of the extracellular matrix. This effect has not been considered so far.

## Triggering questions

- What are the effects of diffusion hindrance on global mechanical properties of tissue engineered constructs?
- How do the continuous accumulation of bound material and the developing complexity of the microgeometry of the tissue affect the diffusion of aggregating molecules?

## Methods

The model is based on a continuous formulation for diffusion, binding and a posteriori degradation of matrix components. Diffusion hindrance is modeled in terms of a random walk approximation. The governing equations are solved using finite element methods at tissue and RVE scales.

## Results

### One-dimensional tissue model

The effects of concentration-dependent diffusivity on the binding of matrix components in a 1D tissue engineered cartilage are shown in Figure 2.

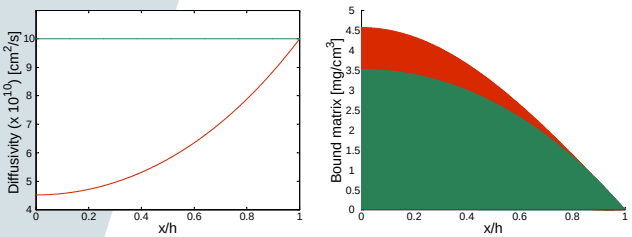


Figure 2: Diffusivity profile (left) and bound matrix distribution (right) in a 1D cartilage tissue construct. x/h represents the normalized position with respect to the center of the tissue, h is the length of the tissue.

### Two-dimensional RVE computations

At the RVE level, 2D calculations show a significant localization of bound material when diffusion hindrance is considered. Matrix accumulation hampers the transport of newly synthesized mobile material.

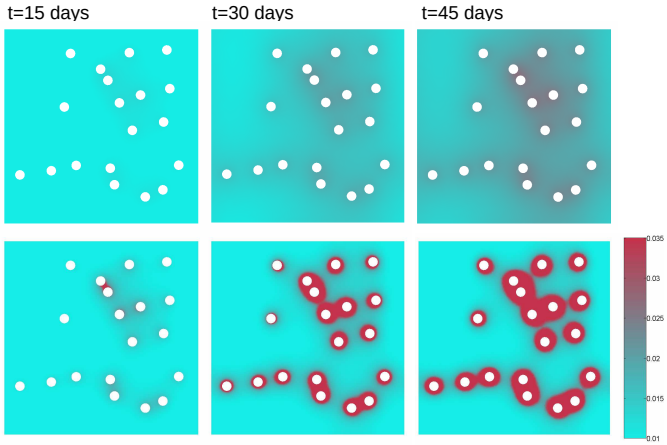


Figure 3: Temporal evolution of the concentration distribution of immobilized GAG in a 2D RVE of a tissue engineered cartilage. On top, a constant diffusivity is considered, below the effects of tortuosity are taken into account. Cells are shown in white.

## Macroscopic mechanical properties

The development of the bulk modulus of the tissue engineered construct, as a function of time during culturing is depicted in Figure 4. The stiffness of the material increases monotonically with time and is considerably affected by the deposition of immobilized material after 20 days of culture. Considering diffusion hindrance yields an important softening of the construct and also contributes to flatten the bulk modulus, which has been observed experimentally.

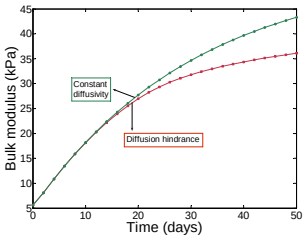


Figure 4: Time-dependent bulk modulus of a tissue engineered cartilage. The influence of diffusion hindrance is considered (red line).

## Conclusions

- Diffusion hindrance significantly impedes the transport of aggregating molecules in the construct, yielding zones of high concentration of immobilized material.
- The global stiffness of the construct lowers due to local diffusion hindrance as much as 17 % at 50 days of culturing.

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