# DYNAMIC PERMEATION AS A CANDIDATE BIOREACTOR FOR ENGINEERING AN INHOMOGENEOUS ARTICULAR CARTILAGE

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## INTRODUCTION

The distinctive biomechanical functions of articular cartilage, such as load bearing properties and lubrication properties, are derived from the multi-phasic composition and unique structure of the extracellular matrix (ECM) of this tissue [1]. The composition and structure inhomogeneity, thus material property inhomogeneity of normal articular cartilage, may be physiologically necessary and significant for the chondrocytes inside the tissue to respond to the temporally and spatially distributed signals within the ECM [2] under joint loading to maintain the cartilage. This indicates that a spatially inhomogeneous mechano-electrochemical (MEC) signal distribution in the tissue-engineered construct may be employed as a means to engineer an inhomogeneous cartilage.

Permeation loading configuration has been used for determining the fluid transport properties of tissue explants or the engineered tissues [3], and recently has begun to be used for tissue engineering purpose [4, 5]. In this study, a triphasic theory [6] is employed to analyze this configuration, aiming at (1) providing a picture of the MEC signal distributions inside the tissue (or construct), i.e., the temporal dependence and the spatial inhomogeneity, and therefore (2) exploring the feasibility and controllability of this configuration for the inhomogeneous cartilage generation.

## METHODS

A schematic representation of the permeation problem under consideration is shown in Fig. 1a. A tissue sample or an engineered tissue construct with thickness $h$ is subjected to an applied pressure differential $\Delta p^*$ ($=p_u^* - p_d^* >0$), and supported by a rigid, porous-permeable platen at the downstream side. Here the subscripts u and d denote upstream and downstream pressures in the permeation apparatus. The sample under permeation is bathed in a NaCl solution with the same concentration c* on *both* upstream and downstream sides. The pressure in the bath at the downstream side, $p_d^*$, is held constant, while the pressure at the upstream, $p_u^*$, varies with time in a steady sinusoidal fashion, Fig. 1b. Thus, the pressure differential across the sample, $\Delta p^* = p_u^* - p_d^*$, varies sinusoidally with time.

### Governing Equations

Assuming that initially the material property is uniform inside the tissue (or construct), the one-dimensional triphasic governing equations for the described permeation configurations are listed below,

$$\frac{\partial e}{\partial t} = \frac{\partial}{\partial z}\{[\frac{f^w}{K} - \frac{RTf^w(c^F)^2/K^2}{a}]\frac{\partial}{\partial z}(H_a e) + \frac{RTf^w c^F}{K}\frac{D^-\frac{\partial c^-}{\partial z} - D^+\frac{\partial c^+}{\partial z}}{a}\}, \quad (1)$$

$$f^w\ (\frac{\partial c^+}{\partial t} + \mathbf{v}^w\frac{\partial c^+}{\partial z}) = \frac{\partial}{\partial z}\{[f^w D^+ + \frac{f^w c^+ D^+(D^- - D^+)}{a}]\frac{\partial c^+}{\partial z} - f^w c^+ D^+\frac{D^-\frac{\partial c^F}{\partial z} + \frac{c^F}{K}\frac{\partial}{\partial z}[H_a e + p_0]}{a}\}, \quad (2)$$

$$f^w(\frac{\partial c^-}{\partial t} + \mathbf{v}^w\frac{\partial c^-}{\partial z}) = \frac{\partial}{\partial z}\{[f^w D^- - \frac{f^w c^- D^-(D^- - D^+)}{a}]\frac{\partial c^-}{\partial z} + f^w c^- D^-\frac{D^+\frac{\partial c^F}{\partial z} + \frac{c^F}{K}\frac{\partial}{\partial z}[H_a e + p_0]}{a}\}, \quad (3)$$

where $e$ is the strain of the tissue, and the cation concentration $c^+$, the anion concentration $c^-$ and the fixed charge density (FCD) $c^F$ are related by the electroneutrality condition $c^+=c^-+c^F$; the aggregate modulus is defined as $H_a=l_s+2m_s$ and the coefficient $a$ is defined as $a=c^+D^+ + c^-D^- + RT(c^F)^2/K$. Here, $f^w$ is the water porosity, $D^+$ and $D^-$ are the diffusivities for cation and anion, $R$ is the gas constant, $T$ is absolute temperature, and $K$ is the drag coefficient between the solid and the interstitial water.

### Boundary and Initial Conditions

On the upstream boundary where the sinusoidal pressure is applied, the stress boundary condition $s=-(p_u-p_d)$ is applied, and on the downstream boundary, the solid displacement is zero. On both boundaries, the water chemical potential, cation and anion electro-chemical potentials are continuous.

Before the pressure difference is applied, the tissue is assumed to be in equilibrium with the external solution without external loading. Thus, the tissue is in a swollen state relative to the hypertonic reference configuration [6].

## RESULTS

In the calculation, $H_a$ is chosen as 0.3MPa, the initial FCD is set as 0.2mEq/ml, $K$ is set as $10^{15}$Ns/m$^4$, and the sinusoidal amplitude of the pressure is set as 41kPa, and the external solution concentration is 0.15M. With these material parameter, our calculation shows that it takes approximately 500 sec for the system to reach a steady periodic responses, and all the strain, ion concentrations, electrical potential, and water and ion fluxes are time and depth dependent. As an example, the strain distribution is shown in Fig. 2. If the length of the strain boundary layer, δ, is defined as the distance from the supporting boundary (z=0) where maximum strain variation occurs to the point where 1/e (e is the basis of natural logarithm) of the maximum strain variation occurs, δ is affected by the loading frequency (or period), see Fig. 3. The potential response on a pair of Ag/AgCl electrodes during the dynamic permeation is also periodic, and the amplitude of this potential is significantly dependent on the FCD of the tissue, but less significantly on the stiffness of the tissue (Fig. 4).

## DISCUSSION

From this analysis, it is concluded that mechanical, electrical and chemical (ion concentrations) signals within the tissue (or construct) subjected to dynamic permeation are coupled and are both time and depth dependent. Thus, using a dynamic permeation configuration in a bioreactor, and by virtue of the known dependence of chondrocytes to these mechanical and physical stimuli in a dose-dependent manner, it is likely to generate an inhomogeneous engineered tissue, *i.e.*, an engineered tissue with depth-dependent biochemical composition and material properties. Since the electrical potential response is related to tissue FCD and tissue elastic modulus, the electrical potential response can be used as an indicator for the quality of the engineered cartilaginous tissue. This study provides additional insight into the mechanical, electrical and physicochemical environments within the tissue (that chondrocytes must experience) in the dynamic permeation test and may be useful for bioreactor applications for inhomogeneous cartilaginous tissue engineering.


## ACKNOWLEDGMENT

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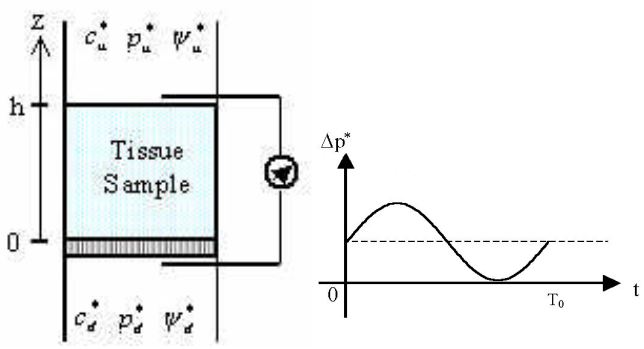


Figure 1. (a) A schematic representation of the permeation problem under consideration (left figure). (b) The periodic sinusoidal pressure difference across the tissue (right figure).

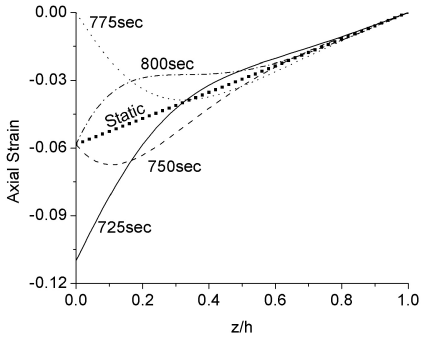


Figure 2. The time variation axial strain distribution throughout the tissue during the 8th pressure differential cycle. Oscillatory compressive strain is seen at the lower portion of the tissue, while steady compression is seen in the top portion. The result is compared with the static pressure application of 41kPa.

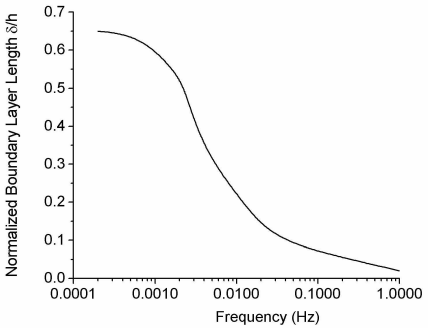


Figure 3. The length of the boundary layer vs. the frequency.

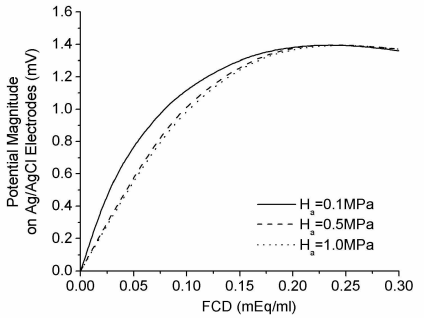


Figure 4. The magnitude of the potential difference across the tissue on Ag/AgCl electrodes vs. the FCD of the tissue with the stiffness of the tissue as a parameter.