INFLUENCE OF OSTEOCYTE DENSITY ON BONE TISSUE PERMEABILITY: INSIGHTS FROM A STOCHASTIC NETWORK MODEL

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INTRODUCTION

Osteocyte density and connectivity are profoundly affected by the presence of underlying bone disease [1,2]. These changes in the lacunocanalicular network are likely to change cellular communication directly through interruption of the communications network and indirectly though changes in tissue permeability. Change in local and tissue level permeability will influence transport of nutrients and waste products to and from osteocytes as well as the transport of signaling molecules by the pericellular fluid that acts as a coupling medium throughout the bone cell syncytium which serves as a network connecting osteocytes, osteoblasts, and osteoclasts [3].

Previously, we developed a continuum-level, poroelastic finite element model to study load-induced fluid flow through cortical bone [4]. The permeability of bone tissue is an important parameter for this model and is estimated and defined on a continuum level [5]. In order to determine the influence micropathoanatomic changes in the lacunocanalicular network on the permeability of bone tissue, continuum assumptions no longer apply, necessitating an alternative approach.

Stochastic network models lend themselves to study effects of structural and compositional changes on the flow through the lacunocanalicular network. They have been used extensively in chemical engineering to model the flow through chromatographic columns (*e.g.* [6]). We now have developed a stochastic network model to simulate the flow through the lacunocanalicular network, as well as through the matrix microporosity. This study represents a first application of this model, where we determine the influence of the decreasing osteocyte density on cortical bone permeability.

METHODS

Network modeling involves two steps: First, the random network of nodes and connecting bonds has to be constructed for optimal representation of the structure to be simulated. Second, the flow through this network is calculated. Both steps are repeated several times until statistical significance is achieved.

In the first step, we developed a three-dimensional, cubic lattice network model with the dimensions LxLxL (L=15), based on the methods described in [6], which simulates the properties of the matrix microporosity. Two different bond diameters, representing the pores between the apatite crystals and the collagen fibers, respectively, were distributed randomly with defined probabilities across the network, whereby the overall porosity of the matrix is maintained. Next, osteocytes were distributed randomly across the nodes of the network. For every osteocyte, the distance to the neighboring osteocytes was determined. If the distance was smaller than a predefined threshold value, the osteocytes were connected by a canaliculus. Finally, since the network represents a part of a bigger structure (*i.e.* the tissue), and is not an isolated entity, periodic boundary conditions were implemented for the microporosity bonds and the canaliculi (Fig. 1).

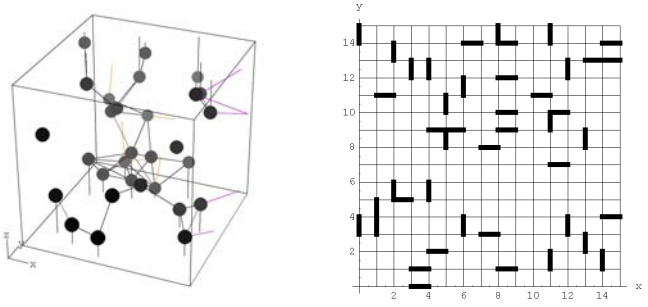

Figure 1: (Left) Example of an osteocyte network with flow direction from top to bottom. The 'loose ends' visible on the right face of the cube represent the periodic boundary conditions. (Right) A planar cut through the network shows the matrix microporosity with a distribution of two different bond diameters.

In the second step, the actual flow through the network was calculated. The driving force for this flow is a pressure gradient $\Delta p = p_{in} - p_{out}$ between the upper and the lower surface of the network. Therefore, all nodes on these surfaces were assigned either p_{in} or p_{out}. The flow rate through the bond between two nodes can be calculated as a function of the pressure gradient between the two nodes [5]

$$Q_{ij} = \frac{(p_i - p_j)d^3}{\left(\left(\frac{128l}{\pi d} + 24\right)\mu\right)}, \quad (1)$$

where d is the bond diameter, l the distance between two nodes, and μ is the fluid viscosity. The pressure at each node can be calculated by solving a system of linear equations for the flow balance at each node. When the pressure at each node is known, the flow through the entire network can be calculated, and by using Darcy's law, the permeability of the network can be determined

$$\kappa = \frac{Q_{tot}}{\Delta p}. \quad (2)$$

In order to demonstrate the effect of osteocyte density on tissue permeability, we applied published data quantifying the change in osteocyte density in trabecular bone of patients between 30 and 60 years old [7].

RESULTS

The permeability was calculated as the mean value from the outcome of 20 calculations of the model for every osteocyte density. The results are shown in Fig. 2. Whereas the osteocyte density is assumed to be declining almost linearly [7], the loss in permeability has to be approximated with a power law (R^2=0.98).

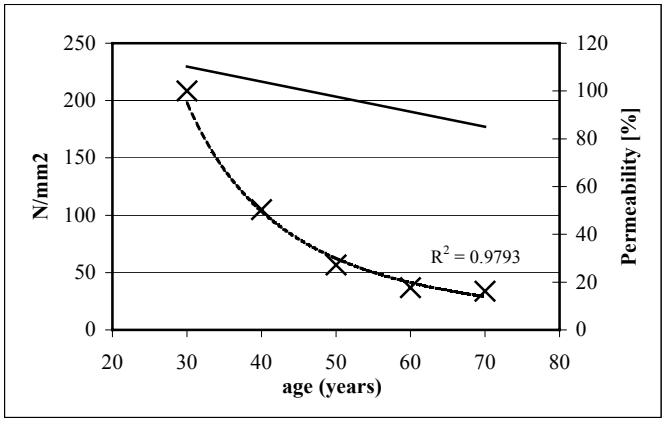

Figure 2: The decline in osteocyte density (solid line, number of osteocyte per area) and its effect on bone tissue permeability (crosses and dashed line, permeability in percent of original permeability at 30 yrs.)

DISCUSSION AND CONCLUSIONS

Using a stochastic network model to simulate interstitial fluid flow through the lacunocanalicular network and the matrix microporosity of bone, we were able to demonstrate the dramatic effect of declining osteocyte density on the tissue permeability. These data predict that a mere 5% decrease in osteocyte density between the ages of 30 and 40 years decreases bone permeability by almost 50%. It is expected that this would exert an enormous effect on tissue perfusion and cell survival, as well as on the transport of signalling molecules to and from the osteocytes.

In this study we used the example of a change in the osteocyte density to demonstrate the power of the method of network modeling. However, there are many more possible applications for this method. Based on the microscopic observations [1,2], a next step will be to determine the influence of osteocyte *connectivity* on tissue permeability. Osteocytes in close proximity to each other are typically connected by canaliculi that decrease in number with increasing distance from the blood supply as well as in the presence of bone disease. Furthermore, by taking into account the preferred spatial orientation of the lacunocanalicular network, it will be possible to detect anisotropic differences in the permeability of bone tissue, which will be important for the development of more accurate, continuum level finite element models. Finally, by excluding pores that are too small to allow the passage of a certain size molecule from the model, we will be able to simulate the molecular sieving properties of bone tissue.

In contrast to applications of network modeling in chemical engineering (e.g. [6]), validation of our physiologic bone models presents unique challenges. At the present, this approach is limited to qualitative comparison studies. Nevertheless, it shows the potential to become an important tool for the study of many aspects of molecular transport through bone.

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