

# THE RATIO BETWEEN LACUNAR AND CANALICULAR GAP SIZE DOMINATES PREDICTIONS OF PERMEABILITY IN THE PERICELLULAR FLUID SPACE OF BONE

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## INTRODUCTION

Bone is a functionally adaptive porous tissue responsible for both mechanical support and metabolic function. It has been postulated that interstitial fluid flow through the lacunocanalicular system plays a critical role in the regulation of bone adaptation through the transfer of both endogenous and exogenous signals [1]. Despite the putative role of fluid flow in osteocyte mechanobiology, fluid flow regimes in the pericellular (lacunocanalicular) space are poorly understood. This is due, in part, to experimental limitations arising from the remoteness and scale of the lacunocanalicular system. Fluid flows through the annular gap around the cell process (in the canaliculi) and the cell body (in the lacuna) of the osteocyte, thereby imparting forces at the interface between the fluid and the cell. Drag forces imparted via the pericellular mesh surrounding the process have been postulated to amplify cellular strain magnitudes to levels approximating those thought to trigger a metabolic response *in vivo* [2]. Similarly, a parallel finite element analyses of an idealized osteocyte cell body and *in vivo* experimental study has demonstrated a relationship between deformation and cell response including NO and PGE<sub>2</sub> production at identical flow rates [3]. Recent studies demonstrate domain specific flow regimes in which hydrodynamic pressure dominates in the vicinity of the cell body (where organelles are housed) and shear stress dominates in the vicinity of the cell process, where hemidesmosomes are prevalent [4].

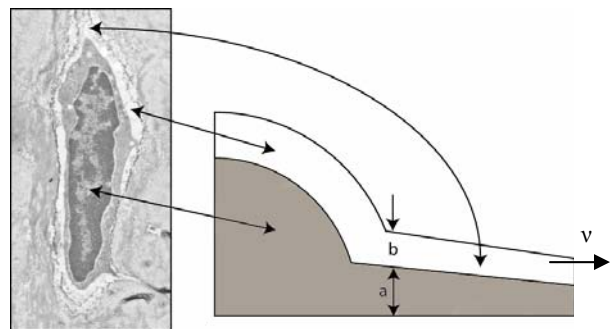
Computational models provide a means to understand cellular and subcellular flow regimes in areas where *in situ* and *in vivo* measurements are not currently feasible. Some current paradigms emphasize the need to include cellular substructures, including tethers and a molecular meshwork, in the pericellular space for development of fluid on the order of magnitude of that required to induce a mechanotransduction response *in vivo*. In this study, we apply a parametric approach to study how resistance to flow, measured as *intrinsic axial permeability*, is modulated through addition of hierarchical sub-/cellular structures including the presence of the osteocyte and its processes as well as the presence of a molecular mesh that is imbedded with fluid within the pericellular space.

## METHODS

An idealized model of the lacunocanalicular system, based on [4] (Fig. 1), was analyzed for mass flow rate using a computational fluid dynamics package, *CFD-ACE* (CFD Research Corporation, Huntsville AL). Intrinsic permeability,  $\kappa$ , was calculated using Darcy's equation for a given applied pressure:

$$\frac{\mu}{\kappa} v = -\nabla p \quad (1)$$

Interstitial fluid properties were  $\mu = 8.55E^{-4}$  kg/ms and  $\rho = 997$  kg/m<sup>3</sup>; the longitudinal dimension of the idealized model was 32  $\mu$ m and process radius at its divergence from the cell body was set to be 150 nm.



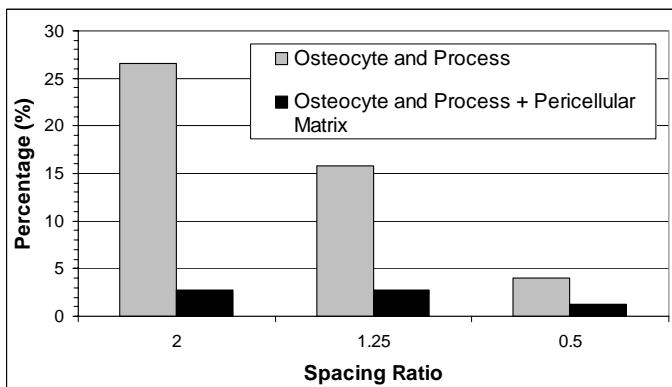
**Figure 1. (left) Transmission Electron Micrograph of an osteocyte in its lacuna, with cell processes emanating in the plane at 12 and 5 o'clock [1] and (right) idealized model of lacunocanalicular system, after [4].**

Variation in permeability was calculated as a function of two factors, i) inclusion of the osteocyte and its processes as well as ii) the presence and variation in properties of a pericellular mesh. Permeability was calculated for a range of annular space dimensions

that served to provide insight into the dependence of permeability on relative gap widths at the lacuna and canaliculi. Geometric deviation was accomplished with restructuring of dimensions according to a Spacing Ratio (SR) defined as the dimensionless proportion of annular gap ('b' in Figure 1) to process radius ('a' in Figure 1) at the point where the process merges with the cell body. Spacing ratios, including 2.00, 1.25, and 0.50, were defined based upon physiological values reported in literature [1,5] and were tested for influence on permeability. The influence of the osteocyte and process factor (i) on permeability was determined as a comparison between a hollow state wherein the cell volume was defined using the same parameters as the interstitial fluid (Hollow) and one including the cell wherein properties of that volume were set to solid (Filled). The effect of the pericellular mesh (PCM) (ii) was determined by defining the annular gap of the Filled model as a porous media and systematically altering the porosity and permeability, the two parameters required to define a volume as a porous media in *CFD-ACE*. Results used to examine the effect of the pericellular mesh were taken as the mean of intrinsic permeability across the systematically altered simulations within each spacing ratio.

## RESULTS

Pilot simulations across a range of pressure and viscosity validated the model performance and accuracy while establishing the independence of the intrinsic permeability as a unique material constant subject only to the applied factors.



**Figure 2. Percentage of Hollow Intrinsic Permeability Across Spacing Ratio**

Calculated intrinsic permeability,  $\kappa$ , decreased when the osteocyte and its process were included in the model. Furthermore, permeability decreased with increasing spacing ratios between the lacunar and canalicular gaps. Hollow model values for intrinsic permeability ranged from  $4.24E^{-22} \text{ m}^2$  for the highest SR to  $2.45E^{-23} \text{ m}^2$  for the lowest SR, while Filled values ranged from  $1.13E^{-22} \text{ m}^2$  to  $1.00E^{-24} \text{ m}^2$ . The addition of the PCM likewise reduced  $\kappa$ , on average, to a range from  $1.16E^{-23} \text{ m}^2$  for the highest SR to  $3.01E^{-25} \text{ m}^2$  for the lowest SR, subject to variation in the parameters defining the porous media. The significance of the addition of tested factors was determined as the percentage of Hollow intrinsic permeability as a function of spacing ratio. The effect of the pericellular matrix was determined as a step-wise addition to the model containing the osteocyte and process.

## DISCUSSION

Based on these data, the presence of the osteocyte and process in the Hollow model reduces intrinsic permeability from ~25% to ~4%; this effect is increased as the spacing ratio decreases, underscoring the

importance of a correct definition of the geometric relationships within the lacunocanalicular system. The effect of adding the pericellular mesh to models of the osteocyte and process is to further reduce the mean intrinsic permeability to ~2% of the Hollow model, regardless of spacing ratio. However, the range of parameters defining the porous media of the PCM contributed to varied reduction in intrinsic permeability, with larger spacing ratios permitting a greater deviation and supporting the importance of the spacing ratio as a defined factor. When compared to the effect of the osteocyte and process, the effect of the pericellular mesh becomes less significant when spacing ratio decreases, as the available annular flow volume subjected to PCM effects diminishes as well.

These data further underscore the importance of including the full cellular and pericellular structures in computational model calculations. These results demonstrate that alterations in cellular and extracellular geometries, resulting from *e.g.* osteocyte metabolism or pathophysiology, may dramatically affect the transfer of signals via alteration in pericellular flow regimes. These effects may shed light on possible mechanisms of bone adaptation throughout the course of cell life and death.

Future expansion of this study will include the application of additional physiological geometry with opportunities to quantify effects such as those of multiple canaliculi as well as canalicular wall roughness. Furthermore, the possibility of fixed charge/mobile ion interaction in fluid flow may create subsequent effects on intrinsic permeability. Pending the establishment of well defined interactions of computational parameters, future biological quantification studies may be directed towards more tightly defining those factors found to have the greatest significance on hydraulic conductivity. Additionally these results may provide a tool for the estimation of permeability relationships in scaled up physical models in which cells may be absent [6].

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