The Effects of 3D Scaffold Dimensions on Chondrocyte Glucose and Oxygen Diffusion

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Introduction

Knee articular cartilage bears much of the weight within the knee. However, over time, the cartilage degrades and eventually develops into osteoarthritis, which limits movement and compounds bone damage. Tissue engineering provides us with a method to artificially produce, maintain, or repair damaged tissue. Chondrocytes, which are the cells that produce the ECM that makes up cartilage, can be grown in a scaffold immersed in a bioreactor to provide nutrients for growth. Because cartilage does not vascularize, diffusion of nutrients is essential for the survival and proliferation of our cells.

Thus, research into the geometries of the scaffold to determine the limits of diffusion necessary for chondrocyte survival is necessary. We examined the effects pore size would have on diffusion rates of glucose and oxygen through a scaffold, with the target of producing a scaffold that would be appropriate for the needs of a knee cartilage transplant.

Methods and Models

We chose a repeating square grid pattern for our scaffold, which was modeled as a cude with three channels cut out between each opposing face. The three dimensions we tested were of faces of length *n* where *n* was either 50 um, 100 um, or 200 um. Based on a literature review, we decided on 68% porosity for each scaffold, resulting in an additional length *w* of 15, 30, and 60 um respectively for each side length.

The total height of our scaffold was 3.2 mm, which is the maximum height a knee cartilage replacement will need to be. We modelled the worst case scenario of the center column, assuming that the nutrients that diffused from the sides of the scaffold would be negligible compared to the amount diffusing from the media on the top and bottom. Our model displays the top 1.6 mm of our system, with the bottom half being symmetrical.

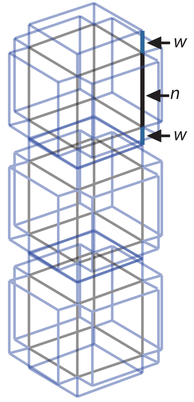

Figure 1: An example of three units of a scaffold column, with length n and w as shown

Metabolic Parameters

From literature, we have found the rate of glucose consumption to be -2.165x10^{-4} mol/m^3, the diffusivity to be 1x10^{-10} cm^2/s, and the initial concentration to be 5.56 mM.[1,2] The diffusivity of oxygen is 3.0x10-5 cm2/s and the initial concentration is held at 20% oxygen tension, which corresponds to 0.205 mM.[3,4]

Oxygen consumption rate is slightly more complicated in that it is affected by the concentration of glucose the cell is in. From a paper studying oxygen consumption by chondroytes, we estimated an equation of best fit from their data, resulting in the equation: y=-3.827x10^{-6} x$^{.492}$,where y is the oxygen consumption rate in mol/m^{3}s and x is the concentration of glucose in mM.[5]

Glucose

Based on our COMSOL models, varying the dimensions of the squares that make up the scaffold does not significantly affect the glucose concentration profile. As seen in Figures 2 and 3, from our initial concentration of 5.56 mM, the concentration in the very center of the scaffold is maintained at between 2 and 2.5 mM.

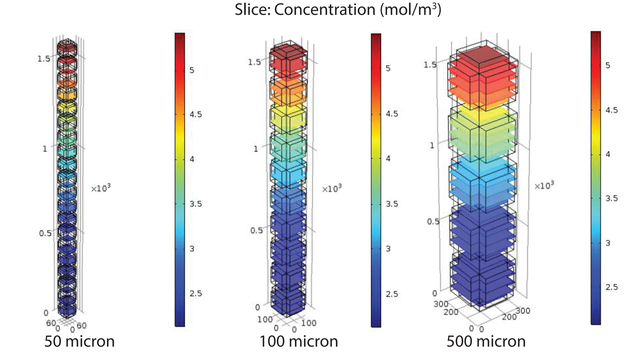

Figure 2: Glucose Concentration slices across our model.

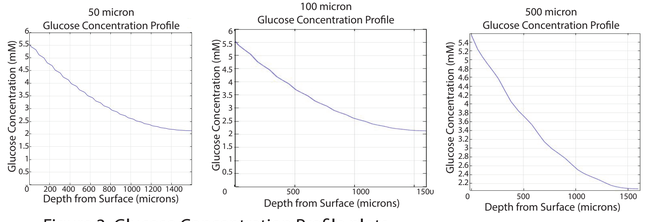

Figure 3: Glucose Concentration Profile plots

Oxygen

Again, our models show that altering pore size has limited effects on the oxygen concentration profile. However, our models predict a negative value for oxygen at depths deeper than 800 microns suggesting that our equation fails at low oxygen concentrations.

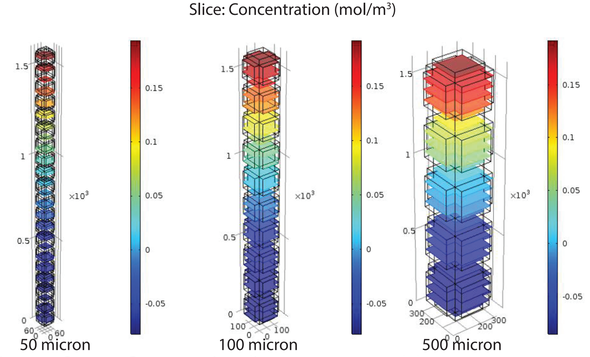

Figure 4: Oxygen Concentration slices across our model.

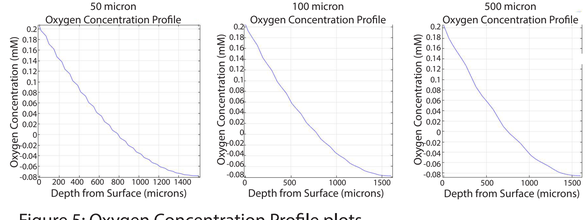

Figure 5: Oxygen Concentration Profile plots

Conclusions

Our model demonstrates that varying the pore size, at least at the levels that we tested, does not result in significant changes in the concentration profiles for either glucose or oxygen. This suggests that for this geometry, diffusion is relatively independent of pore size. One consideration is that our model is based on data and parameters for chondrocytes; other cell types would require their own investigation with different numbers.

The glucose profile shows that glucose concentrations remain above 2 mM at all depths in our 1.6 mm system. Normally, cells require at least 0.5 mM glucose concentration for survival. Furthermore, our model simulates the worst-case scenario where there is only an influx of glucose from the top of the scaffold and none from the sides. It is evident that a scaffold with the pore dimensions as tested allows for sufficient glucose diffusion through the scaffold.

On the other hand, the oxygen profile requires further research. Modeling with an initial oxygen tension of 20% displays a negative oxygen concentration at depths below 800 microns which suggests our model fails at low concentrations. Regardless, it is cause for concern, since if oxygen consumption outpaces its diffusion into the center of our scaffold, the cells will die. Moreover, the solution is not as simple as to increase oxygen concentration at the surface. There is evidence that when grown at 20% oxygen, chondrocytes lose expression of certain key phenotypic markers.[6] Since cartilage is avascular, typical physiological oxygen levels are estimated at 1-7% oxygen.

From these results, we can conclude that for the thickest of cartilage replacements to be grown in a bioreactor, alternate methods of oxygen diffusion are likely to be necessary. This could be achieved by developing methods of facilitated diffusion or delivery such that oxygen levels can be more consistent throughout the scaffold. On the other hand, simple diffusion is probably sufficient for situations where the scaffold doesn't need to be as thick.

References

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