# OPTIMIZING AN OSTEOCHONDRAL BIOREACTOR FOR THE SCREENING OF TREATMENTS FOR OSTEOARTHRITIS

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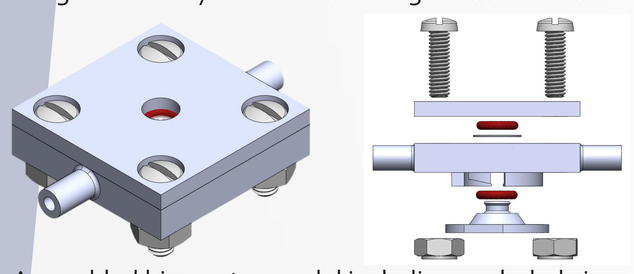
## ABSTRACT

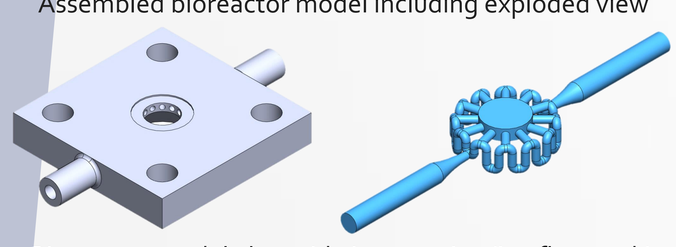
Bioreactors are systems used to monitor the response of tissues and cells to candidate drugs. A previous model of an osteochondral bioreactor was developed at the University of Pittsburgh; however, the cells cannot be observed with a microscope without damaging the construct. A new design was created which allows for optical access to the cells. This design was optimized in order to achieve the maximum possible velocity of fluid through the central chamber which corresponds to the maximum possible drug exposure. This was achieved by minimizing the channel diameter, while maximizing the step height, outer ring diameter, pore diameter, and number of pores. A model with maximized drug exposure was then created and tested in a laboratory setting.

## INTRODUCTION

Bioreactor technologies can be used to monitor the response of tissues and cells to candidate drugs. Specialized microfluidic designs are required to ensure sufficient diffusion of nutrients and delivery of drugs to the target cells [1]. Our bioreactor consists of a central chamber hosting cells suspended in a permeable hydrogel and of a communicating channel around the chamber, which most of the fluid travels through and which allows for the discharge of air bubbles. Maximizing drug exposure can be achieved by maximizing the velocity of the fluid through the central chamber.



Assembled bioreactor model including exploded view



Bioreactor model alongside its negative (i.e. flow path)

## OBJECTIVE

The goal of this project was to develop a bioreactor design that would maximize drug exposure through the test cells, and this can be achieved by maximizing the velocity of the fluid through the central chamber.

## DESIGN OF A SIMPLE CENTRIFUGAL RING BIOREACTOR

The design was inspired from previous work by University of Pittsburgh graduate students, Laura Iannetti and Giovanna D'Urso [2]. They created the model flow path shown below; however, problems arose in that the model did not allow for optical access to the cells – the cells had to be removed from the environment in order to observe them.

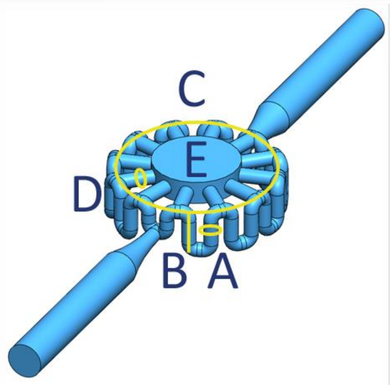


To build off this design, a circular channel surrounding the central chamber was still used, but the dimensions were altered in order to allow for vision into the chamber. This was achieved by limiting the height of the central chamber housing the cells to only 1 mm which allows for optical sectioning.

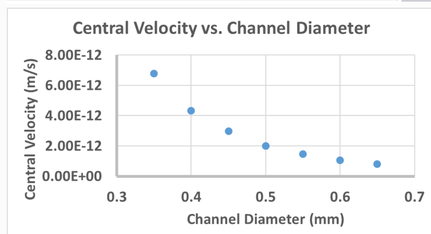
Drug exposure results obtained from this model using similar simulation constraints were not nearly as effective as the previous model used by Laura and Giovanna [2]. Enhancements to the model were required.

## OPTIMIZING THE DESIGN FEATURES OF THE BIOREACTOR

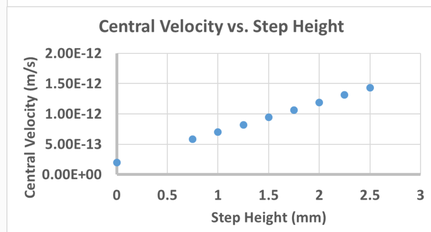
In order to enhance the model, there are different features of the bioreactor flow path that can be altered. These features include changing the channel diameter, the step height, outer ring diameter, pore diameter, and number of pores. These features are pointed out in the figure below.



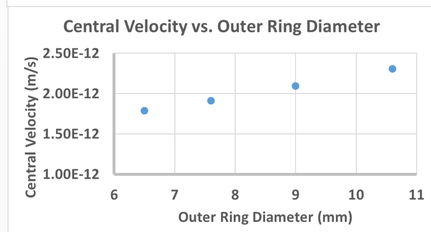

| Location | Feature |
|---|---|
| A | Channel Diameter |
| B | Step Height |
| C | Outer Ring Diameter |
| D | Pore Diameter |
| E | Number of Pores |



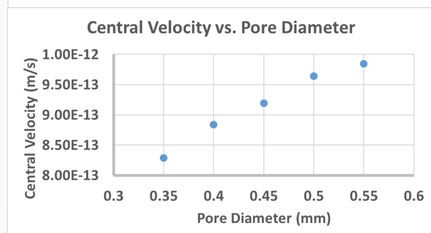

Central velocity is observed to decrease as the channel diameter increases and exhibits a log-log relationship.



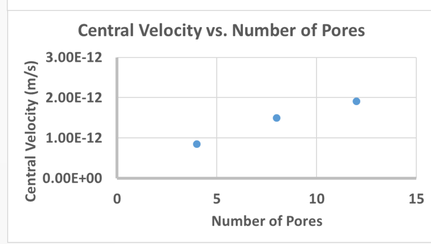

Central velocity is observed to increase as the step height increases and exhibits a linear relationship.




Central velocity is observed to increase as the outer ring diameter increases and exhibits a linear relationship.




Central velocity is observed to increase as the pore diameter increases and exhibits a linear relationship.




Central velocity is observed to increase as the number of pores increases and exhibits a linear relationship.

After the analysis was performed on each feature, it was determined that the channel diameter was to be as small as possible while all other elements were to be as large as possible. The pore diameter can only be as large as the channel diameter, however, and it was determined through testing that the model benefits more from a small channel than large pores.

The maximum resolution of the 3Dsystems Viper (Rock Hill, SC) printer used to print prototypes was 50 µm and the smallest possible void able to be printed is 0.60 mm [3]. In order to eventually be used in a 96 well plate, the entire ring of the design must fit within a 6.8 mm cylinder. To satisfy these requirements, the following dimensions were chosen:

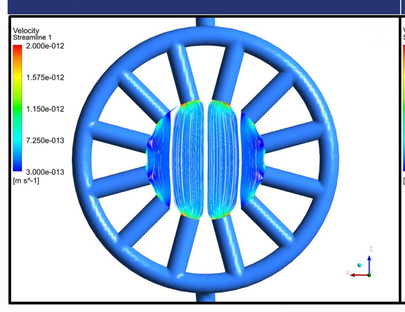
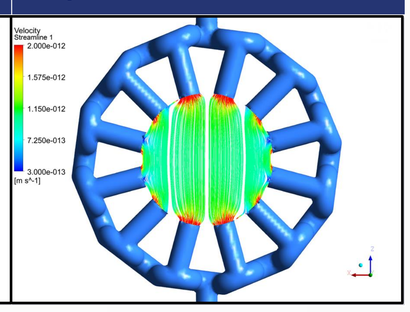
| Feature | Dimension |
|---|---|
| Channel Diameter | 0.60 mm |
| Step Height | 1.75 mm |
| Outer Ring Diameter | 6.75 mm |
| Pore Diameter | 0.60 mm |
| Number of Pores | 12 |

## REFERENCES

[1] Lozito T, Alexander P, Lin H, Gottardi R, Cheng A, Taun R. (2013) *Stem Cell Research & Therapy* 4(Suppl 1):S6.
[2] Iannetti L, D'Urso G, Conoscenti G, Cutrì E, Tuan RS, Raimondi MT, Gottardi R, Zunino P. (2016) *PLoS ONE* 11(9): e0162774.
[3] http://www.3dsystems.com/products/datafiles/viper/datasheets/International/viper_si2_uk.qxd.pdf

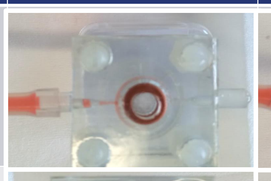
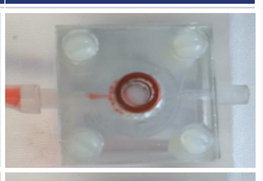
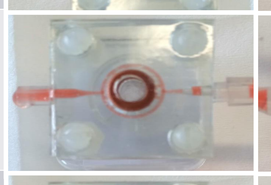
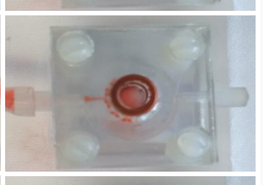
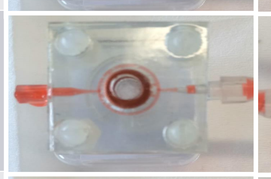
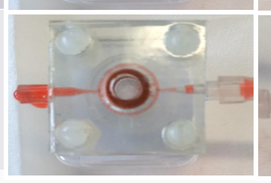
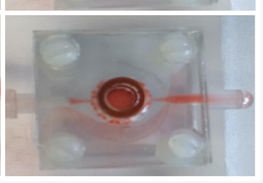
## VALIDATING THE FLOW RESULTS IN A LABORATORY SETTING

Models of the flow path were tested in ANSYS, a finite element analysis software. A 1 mL/day mass flow rate was imposed on the inlet of the model. The following diagrams show the comparison between the fluid flow through the optimized ring model compared to the optimized step model.

| Ring Model | Step Model |
|---|---|
|  |  |



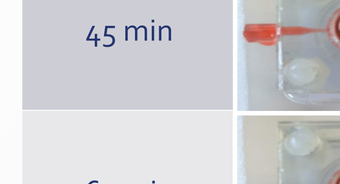
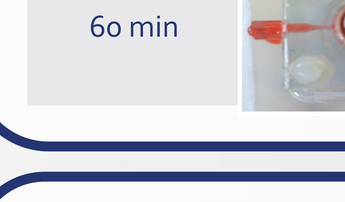
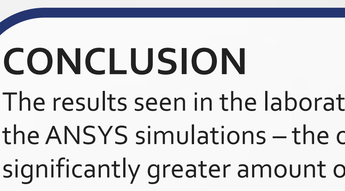
When 3D printed, the physical models were tested to see if the simulations aligned with reality. Using colored dye, the amount of exposure through the central chamber of the model could be observed.

| Time | Ring Model | Step Model |
|---|---|---|
| 15 min |  |  |
| 30 min |  |  |
| 45 min |  |  |
| 60 min |  |  |

## CONCLUSION

The results seen in the laboratory testing confirm what was seen in the ANSYS simulations – the optimized step bioreactor allows for a significantly greater amount of diffusion through the central chamber compared to the simple ring model.

Knowing that the simulation results are verified, different and unique models can be created and tested in ANSYS. These models include a dual inlet model which can be used to test both bone and cartilage simultaneously, and an asymmetric model and non-uniform GelMA model to test the effect of different drug exposures simultaneously.

| Design | Alteration |
|---|---|
|  | Two Inlet Model – two inlets allow for both bone and cartilage differentiation and differing numbers of pores leads to differing exposures |
|  | Asymmetric Model – one inlet, with asymmetric sides of the surrounding ring leading to more exposure on one side of the cell construct |
|  | Non-Uniform GelMA Model – GelMA of two different densities leading to different amounts of drug exposure on the two sides of the cell construct |



## ACKNOWLEDGEMENTS

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