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COMSOL CONFERENCE 2020 NORTH AMERICA

Simulation of Oxygen Transport and Cellular Uptake in a Microphysiological System

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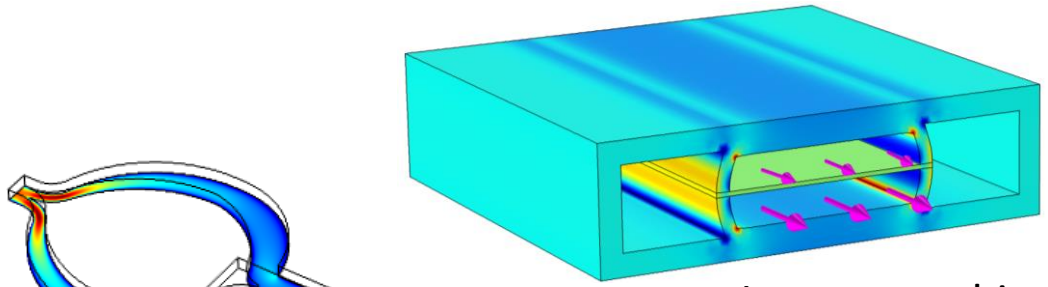
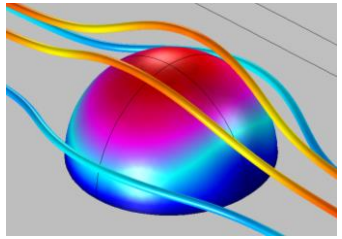
Microphysiological Systems & Simulation

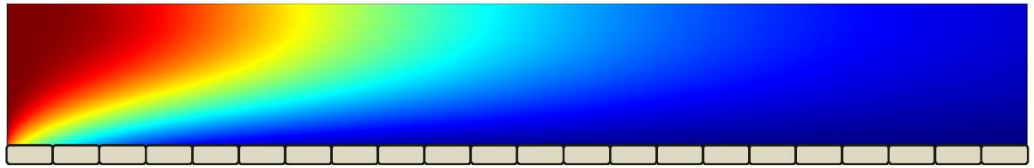
- Microphysiological systems (MPS) combine microfluidics, MEMS, biotechnology to mimic human organ function *in vitro*, including multicellular architectures, tissue-tissue interfaces, physicochemical microenvironments, and vascular perfusion of the body.
- MPSs provide better levels of tissue and organ functionality compared with conventional cell culture systems (e.g. animal models), advancing the study of tissue development, organ physiology, disease etiology, and drug discovery and development.
- Simulation of MPSs is an essential companion to experimental testing and development, reducing cost and saving time, and allowing new ideas to be rapidly tested.



Lung-on-a-chip

Liver MPS



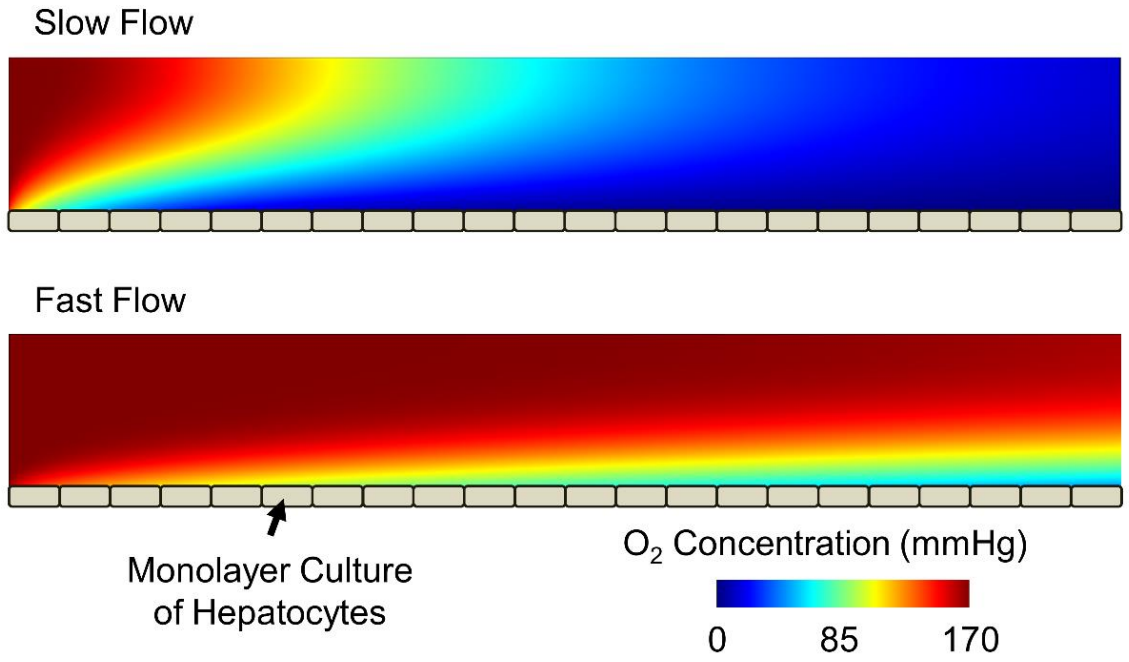


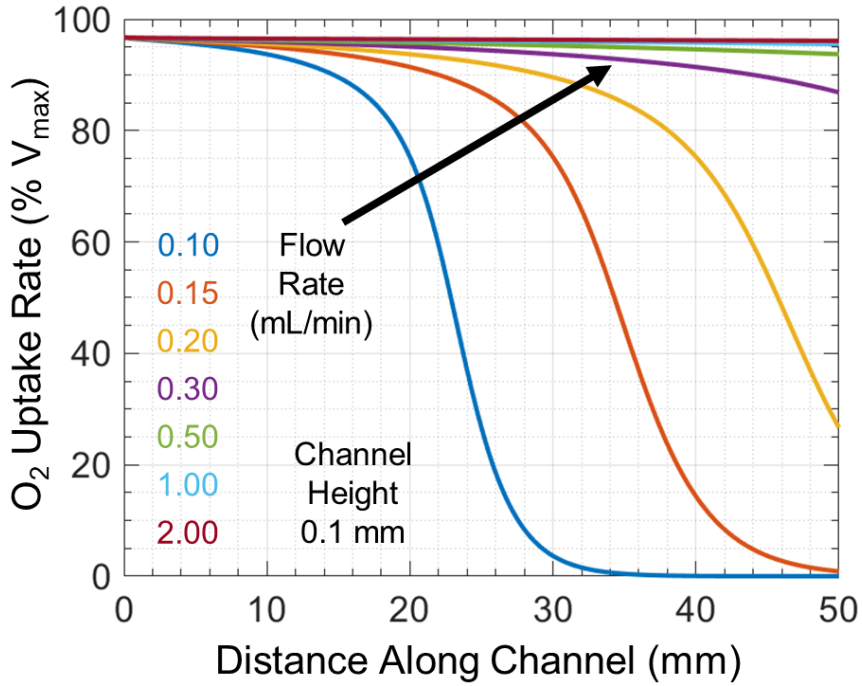
Monolayer of cells in a microchannel

Bhatia & Ingber 2014, Lee-Montiel *et al*. 2020

Oxygen Transport & Cellular Uptake

- Oxygen transport is a key factor in the design of biomedical devices with cells, including microphysiological systems (MPS), lab-on-a-chip systems, and bioreactors. In the system below, oxygen-rich culture media flows over a monolayer of cells in a microchannel. Simulations help determine the flow rate and channel height needed to achieve desired oxygen concentration and uptake gradients, as well as shear stress on cells.

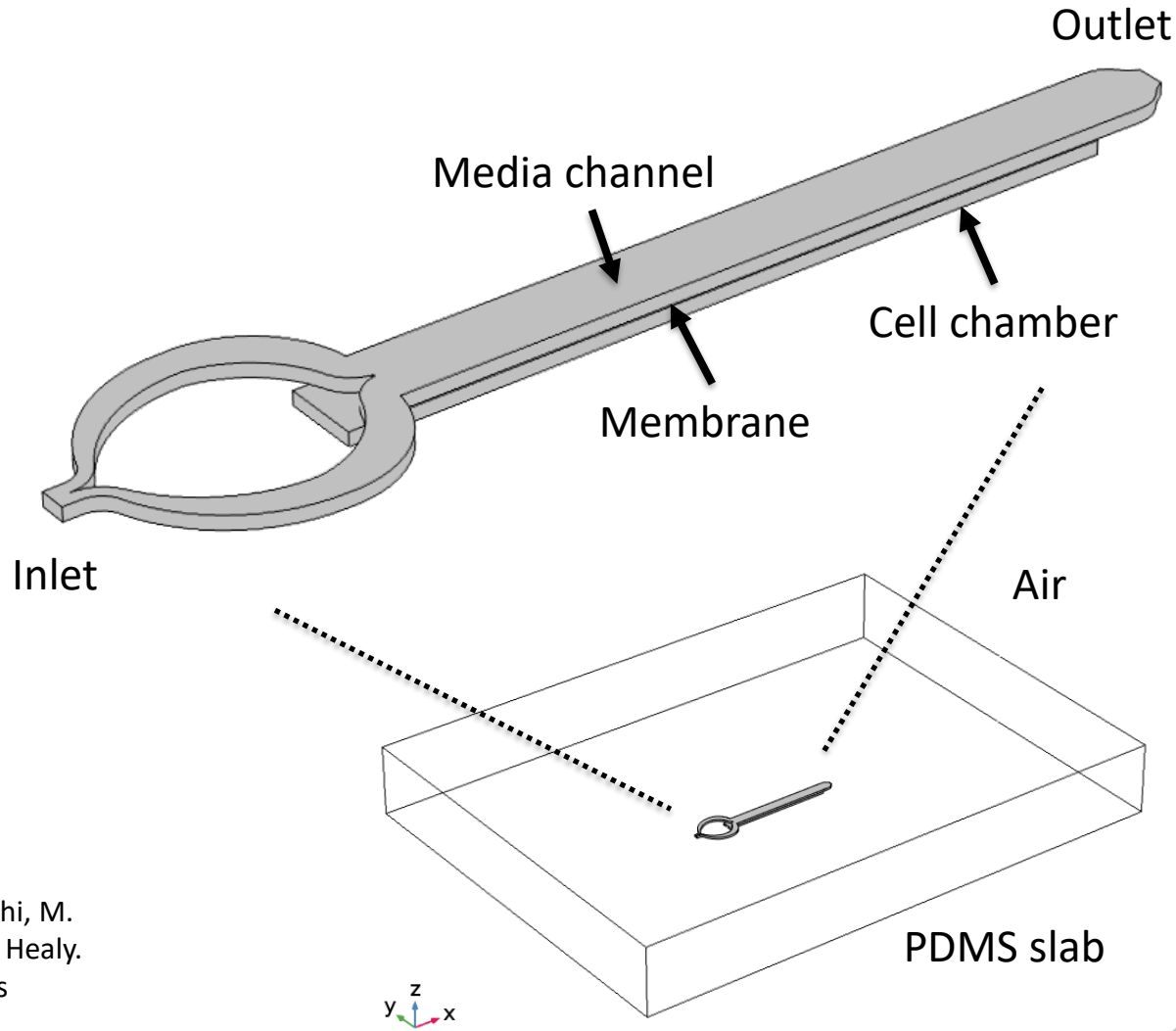




https://www.veryst.com/case-studies/oxygen-transport-and-cellular-uptake-microchannel

Simulating O_2 Transport & Uptake in a Microphysiological System

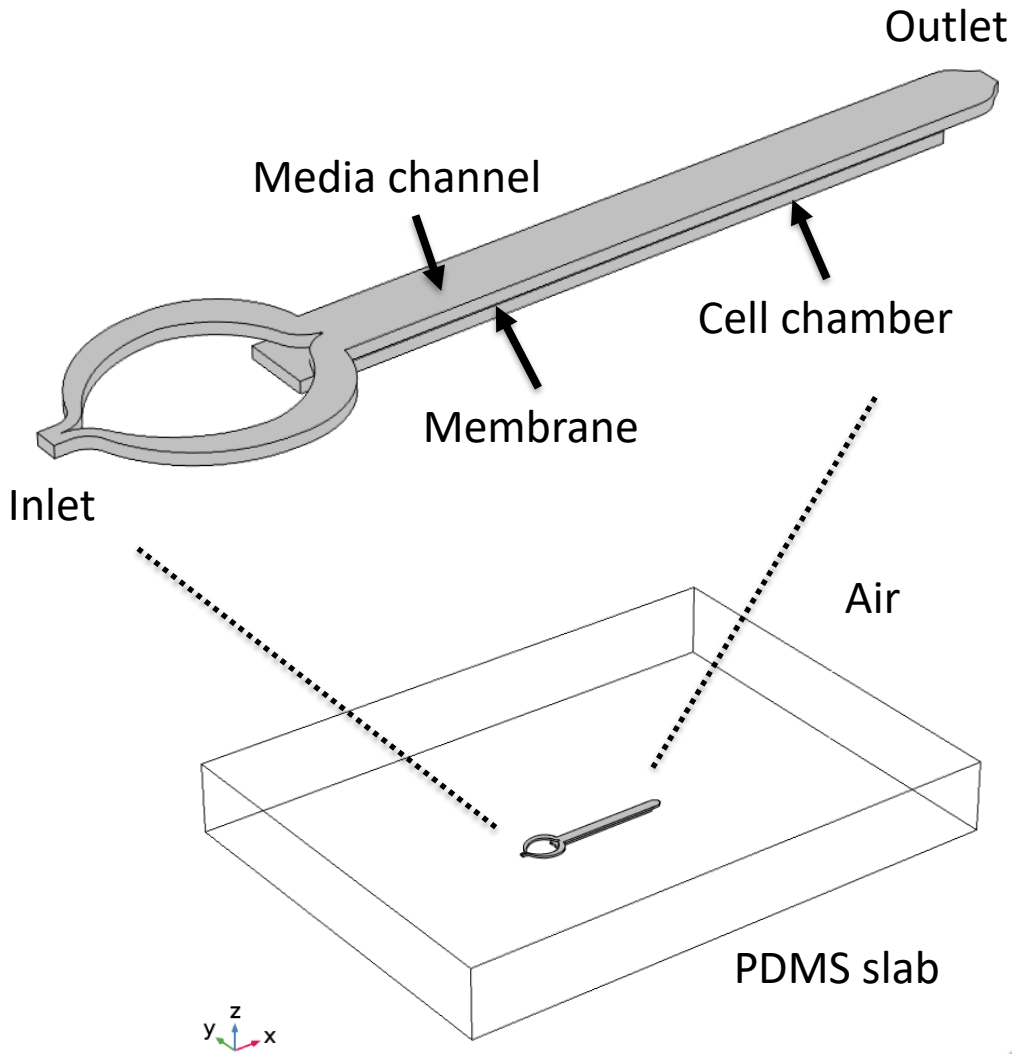
- In more sophisticated devices, such as that reported in Montiel *et al.* 2020, oxygen enters both through gas permeable materials and inflow.
- Montiel *et al.'s* design includes a PDMS slab containing a media channel, cell chamber, and porous membrane separating the media channel from the cells. Oxygen enters the system through inflowing saturated culture media and through the PDMS slab, which is exposed to ambient air.
- In this talk we'll discuss the COMSOL model and simulations supporting the development of said device.



F. T. Lee-Montiel, A. Laemmle, L. Dumont, C. S. Lee, N. Huebsch, V. Charwat, H. Okochi, M. J. Hancock, B. Siemons, S. Bogess, I. Goswami, E. W. Miller, H. Willenbring, and K. E. Healy. An integrated human hiPSC-based liver and heart microphysiological system predicts unsafe drug-drug interactions. https://doi.org/10.1101/2020.05.24.112771

Physics and Boundary Conditions

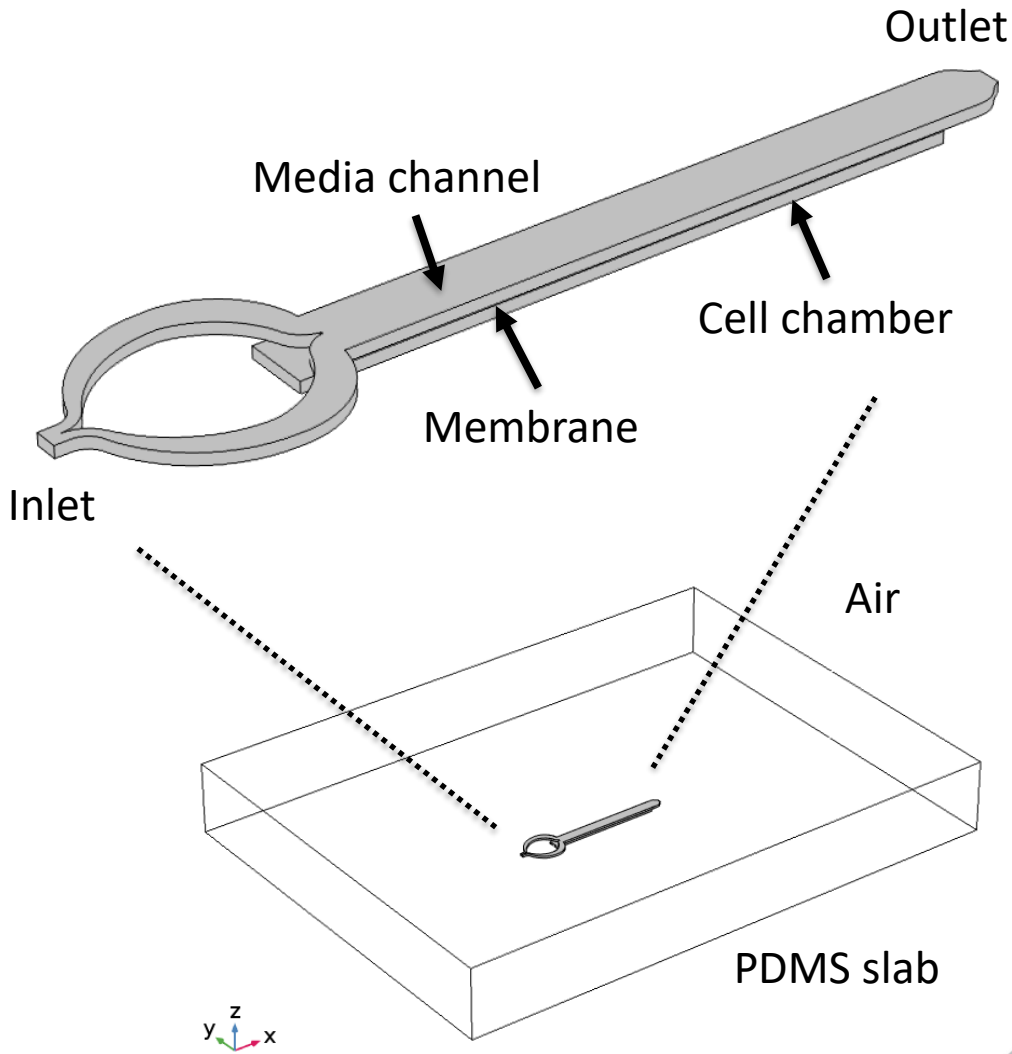
- Physics
  - Laminar flow in the media channel
  - Dilute species transport of oxygen through the PDMS, media channel and cell chamber
- Volumetric oxygen uptake by hepatocytes in the cell chamber is modeled by Michaelis-Menten kinetics with values from literature or measured.
- Oxygen partial pressure continuity is enforced at all interior boundaries, which yields concentration jumps due to discontinuities in solubility (e.g. from PDMS walls to culture media).
- Symmetry conditions (not shown) along vertical center plane allow only half the domain to be simulated.



F. T. Lee-Montiel et. al. 2020 https://doi.org/10.1101/2020.05.24.112771

Physics and Boundary Conditions

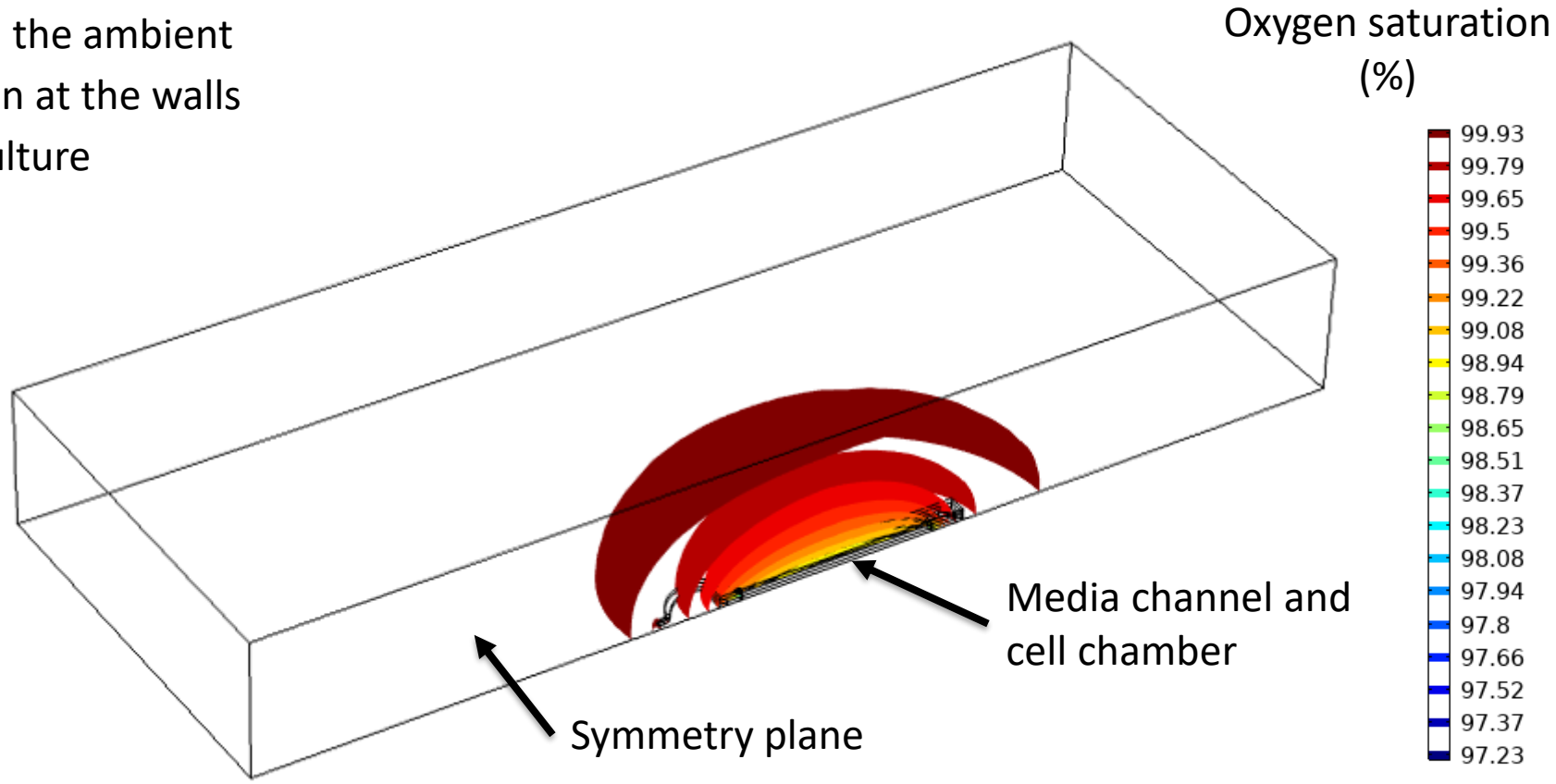
- Thin porous membrane
  - Effective diffusion of oxygen across engineered holes in membrane.
  - Assume no flow across membrane and neglect slip velocity due to low porosity and high resistance. These could be added if needed (e.g. Smith 1987, Pozrikidis 2005 & 2010).
- No-slip at all solid walls.
- Ambient (humid incubator air at 37 °C) oxygen conditions at top of PDMS.
- Flow rate and saturated oxygen concentration at the media channel inlet, outflow conditions at outlet.



F. T. Lee-Montiel et. al. 2020 https://doi.org/10.1101/2020.05.24.112771
S. H. Smith. Stokes flow past slits and holes. *Int. J. Multiphase Flow*, 13, 219 (1987)
C. Pozrikidis. Effect of membrane thickness on the slip and drift velocity in parallel shear flow. *J. Fluids & Structures,* 20, 177 (2005)
C. Pozrikidis. Slip velocity over a perforated or patchy surface. *J. Fluid Mech*., 643, 471 (2010)

Oxygen Concentration in PDMS

- Simulations showed that sufficient oxygen diffuses through the PDMS from the ambient to keep the oxygen concentration at the walls of the media channel and cell culture chamber nearly saturated.



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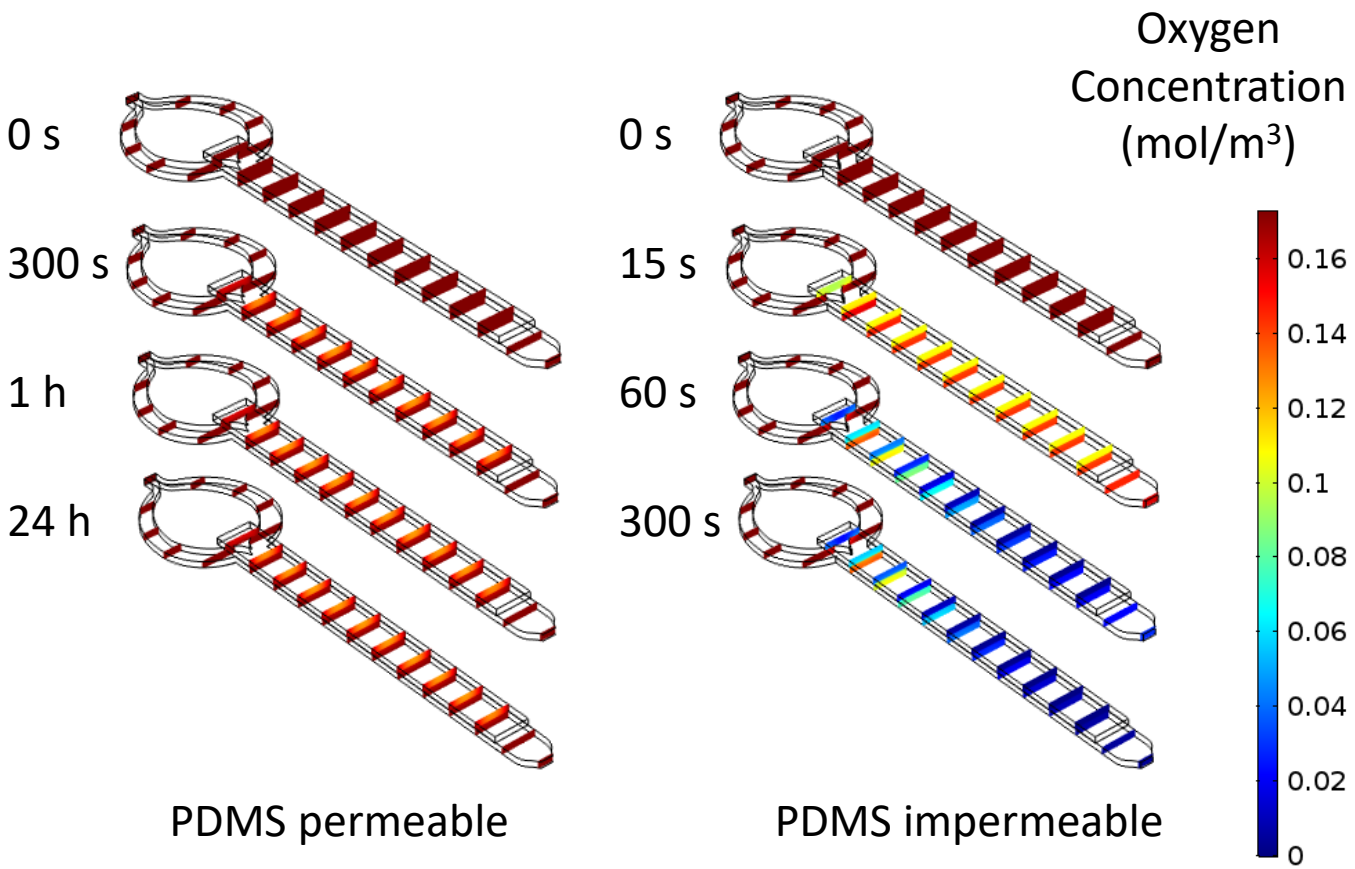
Oxygen Concentration in Media Channel and Cell Chamber

- For a flow rate of 20 µL/h, small concentration gradients with physiologically relevant oxygen levels are observed when cells in the cell chamber consume oxygen and oxygen diffuses from the ambient through the PDMS.
- When oxygen is not allowed to diffuse through the PDMS, cells become hypoxic after 300 seconds, and higher flow rates would be needed to deliver sufficient oxygen to the cells.
- Oxygen concentration jumps between media channel and cell chamber are due to diffusion across the porous membrane.

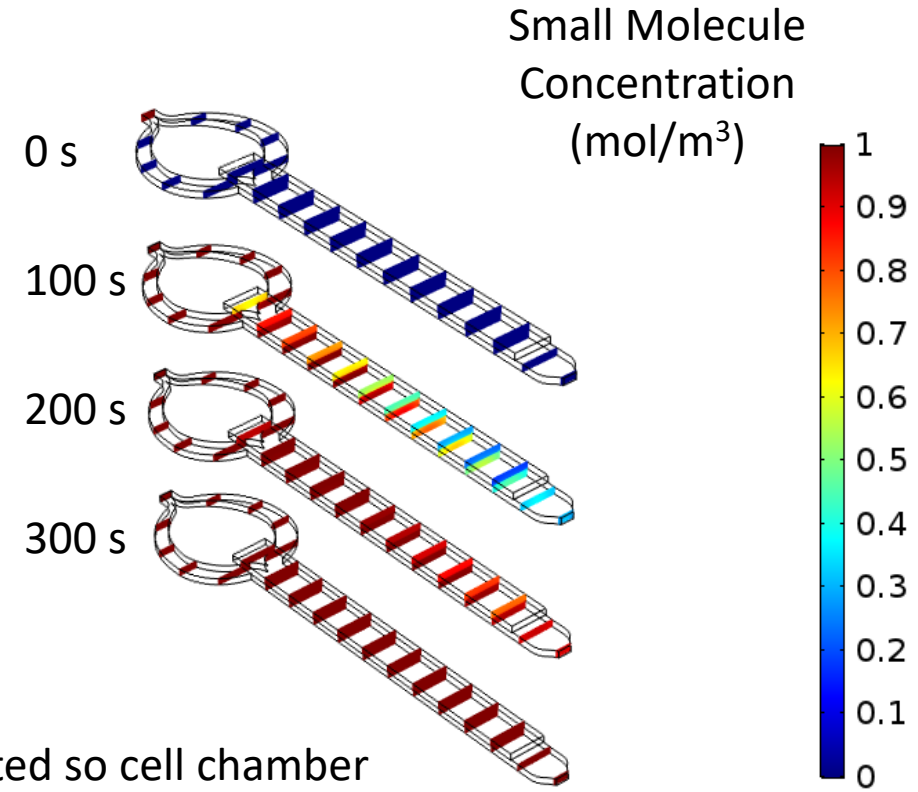


Device rotated so cell chamber is on top, for visualization

F. T. Lee-Montiel et. al. 2020 https://doi.org/10.1101/2020.05.24.112771

Small Molecule Transport in Media Channel and Cell Chamber

- To quantify the transport of chemicals such as drugs and growth factors, we simulated the transport of a dilute solution containing a small molecule entering the media channel at 20 µL/h. We assumed impermeable walls and no cell consumption of said small molecule.
- The small molecule diffuses across the porous membrane and into the cell chamber and reaches a uniform concentration throughout the device within 300 s.



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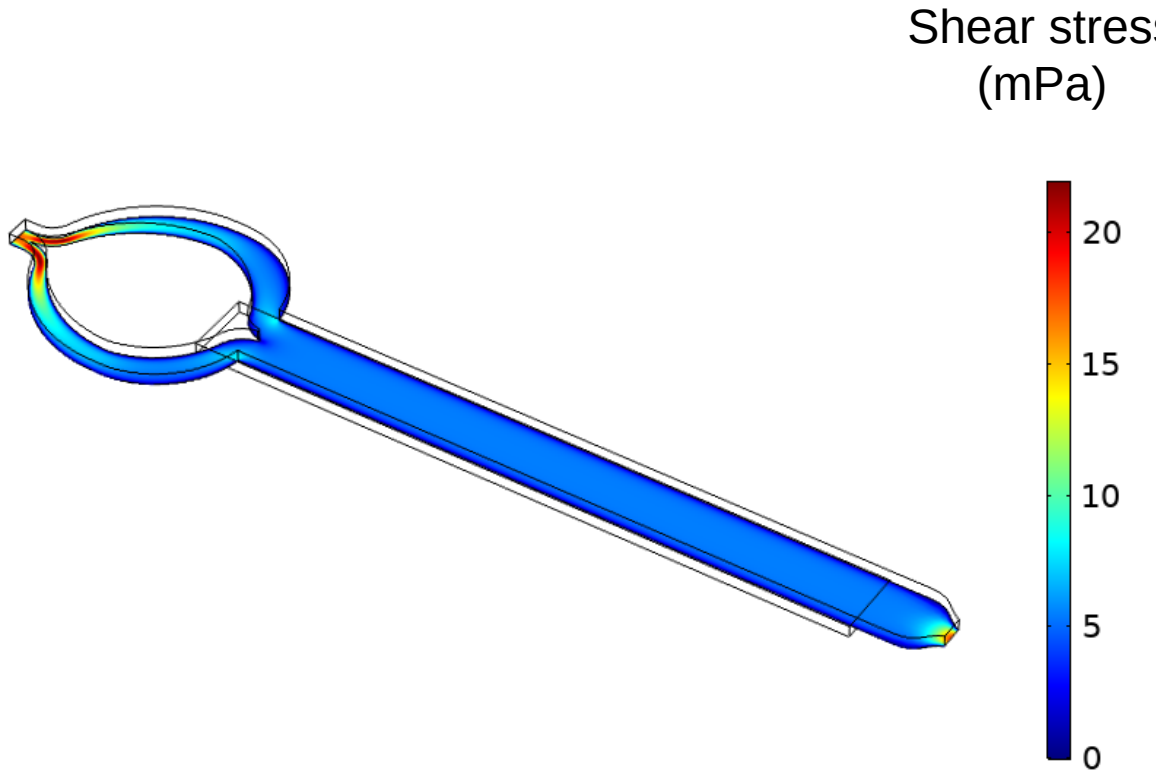
Shear Stress on Cells

- For cases where cells may be cultured along the media channel side of the membrane, shear stresses are well within physiological values for a flow rate of 20 µL/h.



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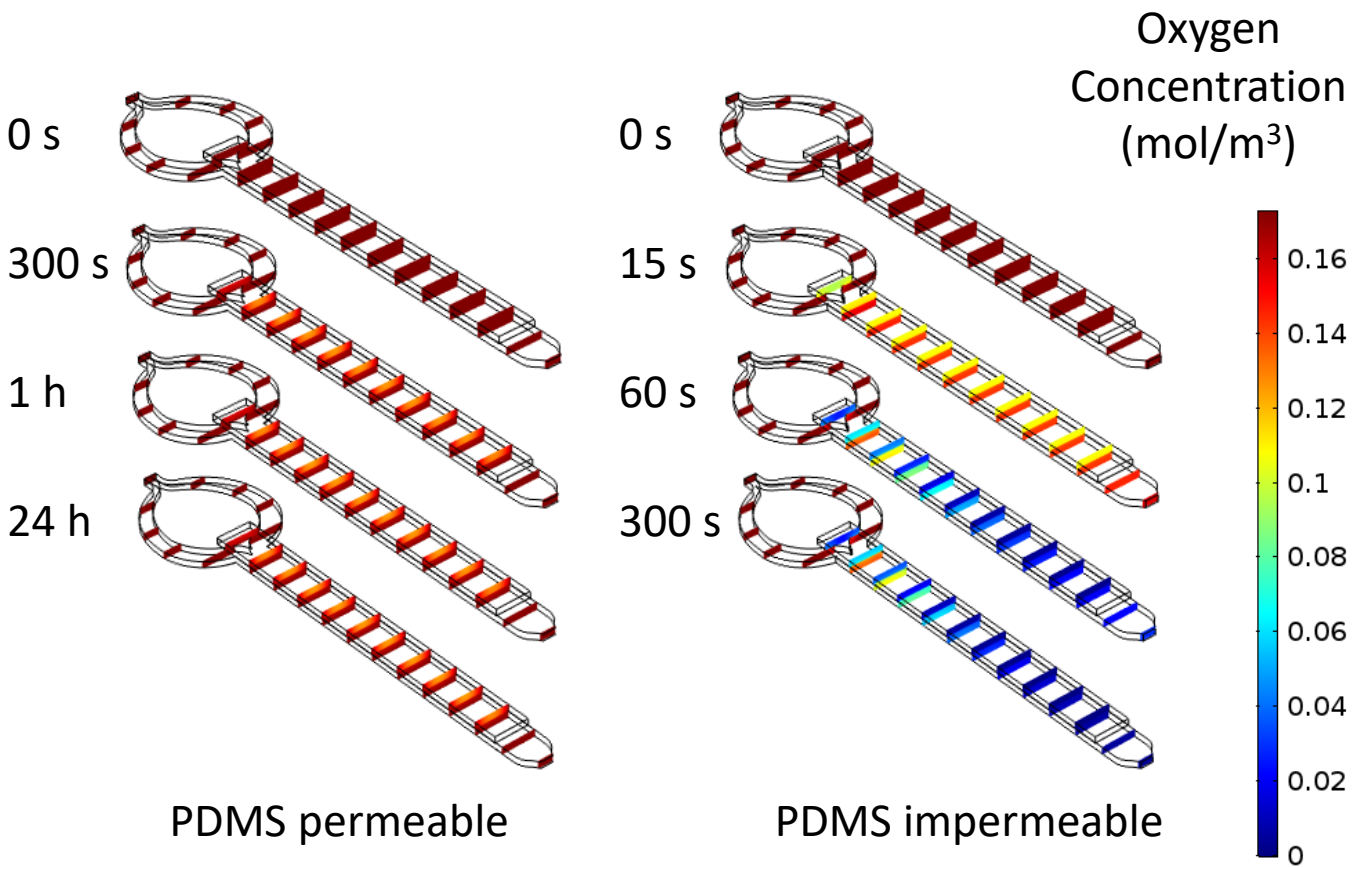
Conclusions

- The oxygen permeability of device materials dramatically affects oxygen concentration within the media channel and cell chamber.
- Depending on the desired oxygen levels and variation in the device, the walls could be coated with an oxygen-impermeable layer.
- Results (not shown) indicate that oxygen levels are insensitive to flow rate when the walls are oxygen permeable, and vice versa. Therefore, devices with oxygen impermeable walls would allow flow rate control of oxygen concentration and variation.



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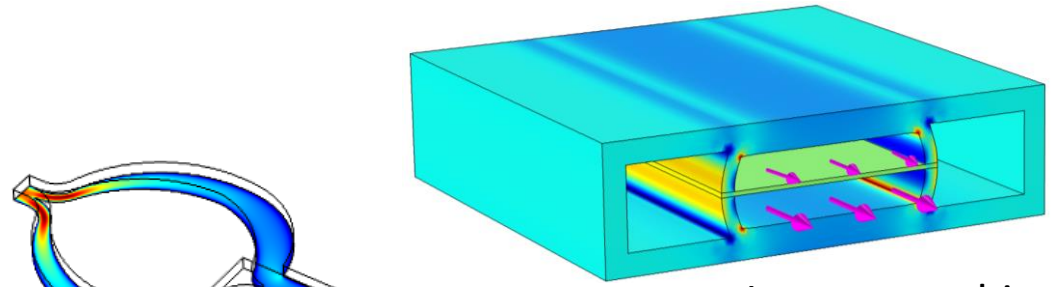
Veryst Engineering Solutions for Biomedical Devices

- Simulating the behavior and performance of biomedical devices is an essential companion to experimental testing and development, reducing cost and saving time, and allowing new ideas to be rapidly tested.
- Please see other Veryst talks where simulations support biomedical product development:
  - **Chemical Mixing and Washing in Fluidic Diagnostic Systems** (Session: Fluid Flow)
  - **Blood Damage Modeling of FDA Benchmark Nozzle** (Session: Fluid Flow)
  - **Simulation of a Piezoelectric Catheter-Based Acoustic Ablation Device** (Session: Structural Mechanics & Acoustics)



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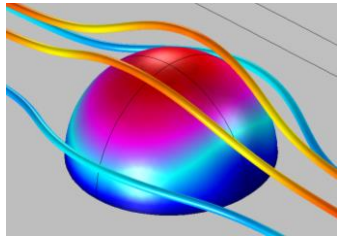

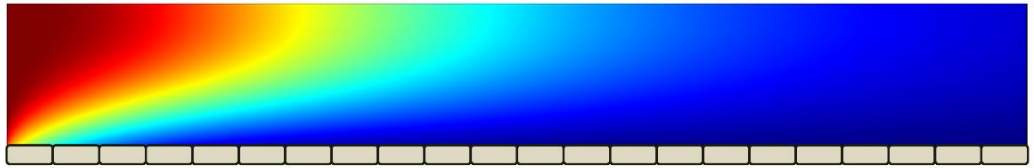

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