Laboratory Enhanced Education in Biotransport Phenomena through COMSOL Multiphysics

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Abstract

Biotransport Phenomena, that is, the transfer of Fluids, Mass and Heat in physiological systems, is fundamental to Biomedical Engineering (BME). As a consequence, undergraduate and graduate BME curricula contain key courses in this area but, these courses tend to be mathematically intensive, and therefore it is difficult for students to visualize phenomena to gain the desired Engineering intuition necessary for design and problem solving. The logical solution to this educational gap is to include experimental laboratories; however, key aspects of Biotransport Phenomena, e.g., wall shear stress and diffusive processes, are difficult (or too time-prohibitive) to incorporate into a hands-on laboratory experience.

In the Cal Poly San Luis Obispo BME curriculum, a set of in-silico laboratory activities have been developed using an easy to use multi-physics Finite Element Package (FEA), COMSOL Multiphysics, to augment teaching Biotransport Phenomena. More specifically, in this upper division Biotransport course, there are six required FEA laboratories and one extra credit FEA laboratory. These laboratory exercises are designed to enable students to simulate and visualize key aspects of physiological Transport Phenomena. In this paper, the course laboratories are presented and explained in the context of the course goals and expected outcomes, and selected laboratories are presented in sufficient detail to demonstrate how students are able to perform in-silico experiments in a timely fashion and develop valuable experience and Engineering intuition in Biotransport Phenomena. In addition to gaining valuable Engineering intuition, the students develop some skills and gain experience in using COMSOL Multiphysics. Owing to the ease at which COMSOL Multiphysics permits coupled multi-physics in computations and simulations, this FEA package is gaining use in industry. Aspects of COMSOL Multiphysics relevant to education in the BME department at Cal Poly San Luis Obispo are also discussed.

IntroductionBiotransport Phenomena can be a difficult subject to teach. The subject matter, bio-fluid mechanics and bio-mass transfer, in a physiological context adds extra difficulty to these already mathematically intensive courses. Prior to delving into these subject areas students require sufficient depth to acquire relevant Engineering skills and intuition. As a consequence, many Universities teach the various forms of Transport as individual, separate courses. At Cal Poly San Luis Obispo, however, we have developed a single, one quarter, 10 week, course that covers introductory bio-fluid mechanics and bio-mass transfer, both convective and diffusive transport, in the context of human physiologic processes. Given that Transport Phenomena is mathematically rigorous, a single quarter presents added time constraints to learn the necessary mathematical methods, and furthermore, based on pure mathematical results, it is difficult to visualize transport processes. With such limited time and challenges, it is challenging to achieve the ultimate learning objective of properly equipping students for design problems that involve Biotransport Phenomena.

An obvious approach to meet learning objectives is to develop a set of hands-on laboratories. At Cal Poly over the past 5 years, hands-on experimental laboratories have been utilized in the Biotransport Phenomena course; however, key laboratory exercises involving Diffusive processes, which were inherently slow and time prohibitive, extended beyond the allotted laboratory time limit. Additionally, finding and designing wet, hands-on laboratories to complement the flow of the lecture proved to be very difficult. So Cal Poly BME was faced with the dilemma of a) developing a set of complementary laboratories, b) compressing the Mathematical learning curve associated with Biotransport Phenomena, and c) helping students develop valuable Engineering skills and intuition in this key area of the curriculum. At Cal Poly, a set of Finite Element Analysis (FEA) laboratories were created to meet these constraints and challenges.

Before designing the FEA laboratories, it was necessary to select a suitable FEA package. The requirements set for such an FEA package include:

- Commercial availability
- Ease of use
- Ability to handle coupled physics
- Good visualization tools
- Compatibility with other Computer Aided Design (CAD) programs
- Industry relevance

There are only a few packages available commercially that meet these criteria, e.g., CFDRC ACE+ and COMSOL Multiphysics to name a few. Cal Poly selected COMSOL Multiphysics. This choice was based on the popularity of this package in the microfluidics community and the growing interest in the medical device industry. Additionally, COMSOL Multiphysics is very user friendly, and it has innate CAD tools that are sufficient for many relevant problems. For the purposes of the Cal Poly Biotransport Phenomena course, COMSOL Multiphysics provides an excellent approach to forming complementary laboratories to a rigorous lecture course. In the sections to follow the set of FEA laboratories are briefly described, selected results are presented and when appropriate, COMSOL Multiphysics results are compared with theory.

The COMSOL Multiphysics Laboratories: An Overview

In the lecture portion of Bio-Transport Phenomena at Cal Poly San Luis Obispo, the following topics are covered: conservation principles, Starling flow, steady-state bio-fluid mechanics, diffusive and convective processes in various physiologic media and mass transfer coefficients, i.e., mass transfer through boundary layers. In parallel with these lecture topics, seven COMSOL Multiphysics laboratories have been developed to complement the lecture. It is important to note that the students typically have no experience with COMSOL Multiphysics when entering the course; hence, the first few laboratories are designed to familiarize students with COMSOL Multiphysics via simple, relevant simulations.

The first three laboratories exclusively cover fluid mechanics. The first lab is simply steady flow of a Newtonian fluid between parallel plates. Before the students perform the numerical experiment, they analytically solve for the average fluid velocity in the gap and for the shear stress at the wall. The second laboratory is used to introduce time-dependent pulsatile flow, using the same parallel-plates model in the first laboratory. While these flow configurations are

not physiologically accurate, the students do gain Engineering intuition, experience and confidence through the basic FEA and learn how to perform the desired post-processing to extract key information. With this foundation, students then characterize steady and pulsatile flow in cylindrical conduits representing blood vessels of various sizes. As with the two-dimensional case, students compare COMSOL Multiphysics results with exact theory.

Following the fluid mechanics laboratories, the students are exposed to pure diffusion and coupled convection-diffusion problems. More specifically, students develop models for a drug-eluting stent in an artery, transdermal drug delivery and tissue oxygenation. In the drug-eluting stent laboratory, students also learn how to perform axisymmetric analysis using COSMOL Multiphysics. Following this laboratory, students setup and study time-dependent transdermal drug delivery problem with a fixed initial drug patch. In this laboratory exercise, the students are able to visualize the depletion of drug in the drug patch, drug transport and concentrations in various layers of tissue as a function of time. Again the students learn how to utilize more advanced features associate with COMSOL Multiphysics. For the final required laboratory, students replicate the Krogh tissue cylinder and explore oxygen transport in tissue surrounding a capillary. This is also performed using an axisymmetric COMSOL Multiphysics model. Toward the end of the course, students are given the opportunity to perform an additional laboratory to recover lost credit and to learn how to apply the software to characterize a bio-reactor for tissue engineering.

For each laboratory, the students report their results by preparing a set of PowerPoint slides that includes a problem statement, system description, computational parameters, mesh description, results answering posed questions, conclusions and future applications. This reporting approach was patterned after how project team members in a National Laboratory setting might report their progress and findings to the project team during a project team meeting.

The COMSOL Multiphysics Laboratories: Selected Examples

To illustrate how COMSOL Multiphysics complements the lecture, selected results from a few of the laboratories are presented below, namely:

1. Two-dimensional, steady-state, pressure-driven flow between parallel plates as compared to theory
2. Two-dimensional, pulsatile flow between parallel plates
3. Three-dimensional steady-state, pressure-driven flow in a cylinder compared to theory and
4. extension to pulsatile arterial flow
5. Two-dimensional axis-symmetric drug-eluting stent
6. Oxygen consumption in a three-dimensional Krogh tissue cylinder

Laboratory Example 1

Pressure-driven flow between parallel plates is a typical, initial computational study in fluid mechanics to compare numerical solutions with theory. In this straightforward flow configuration, students are given the average fluid velocity for an artery, arteriole and a capillary. From theory derived in the laboratory, students predict the necessary pressure drop over the length of each vessel type. The average velocity, (v_x), and resulting expression for the pressure drop, $(P_1 - P_2)$, is given by

$$\langle v_x \rangle = \frac{h^2(P_1 - P_2)}{3\mu L} \quad (1)$$

and therefore

$$(P_1 - P_2) = \frac{\langle v_x \rangle 3\mu L}{h^2} \quad . \quad (2)$$

Here, h is the half-gap between the parallel plates, i.e., the vessel "radius", L is the vessel length and μ is the fluid viscosity. Furthermore, prior to averaging, the magnitude of the fluid shear stress can be found as

$$\|\tau_{yx}\| = \left|\frac{P_1 - P_2}{L} y\right| \quad , \quad (3)$$

where $\|\tau_{yx}\|$ is the magnitude of shear stress acting in the y-direction due to flow in the x-direction[1]. Note also that P_1 is the entrance pressure and P_2 is the exit pressure, that is, $P_1 > P_2$.

After predicting the desired pressure drops and expected results, students set up and perform FEA of pressure-driven flow using COMSOL Multiphysics, specifically flow occurring in the x-direction between parallel plates separated by $2h$. A typical set of COMSOL Multiphysics results is given in Table I below.

Table 1. Comparison of COMSOL Multiphysics with theory for steady-state, pressure-driven flow between parallel plates.

2D Representation	Average Velocity			Wall Shear Stress $y = h$		
	Theory (cm/s)	COMSOL (cm/s)	% Difference	Theory (Pa)	COMSOL (Pa)	% Difference
Artery	30.0	30.1	0.333	1.080	1.084	0.370
Arteriole	0.780	0.782	0.256	1.080	1.082	0.185
Capillary	0.096	0.096	0.000	1.080	1.080	0.000

For each result presented in Table I, COMSOL Multiphysics mesh refinement was set to 'Normal'. (The students are taught the necessity of a mesh refinement, but due to computing facilities limitations not all computational studies involved a mesh refinement component.) As can be seen above in Table 1, the average velocities and wall shear stresses predicted by COMSOL Multiphysics® were in excellent agreement with theory.

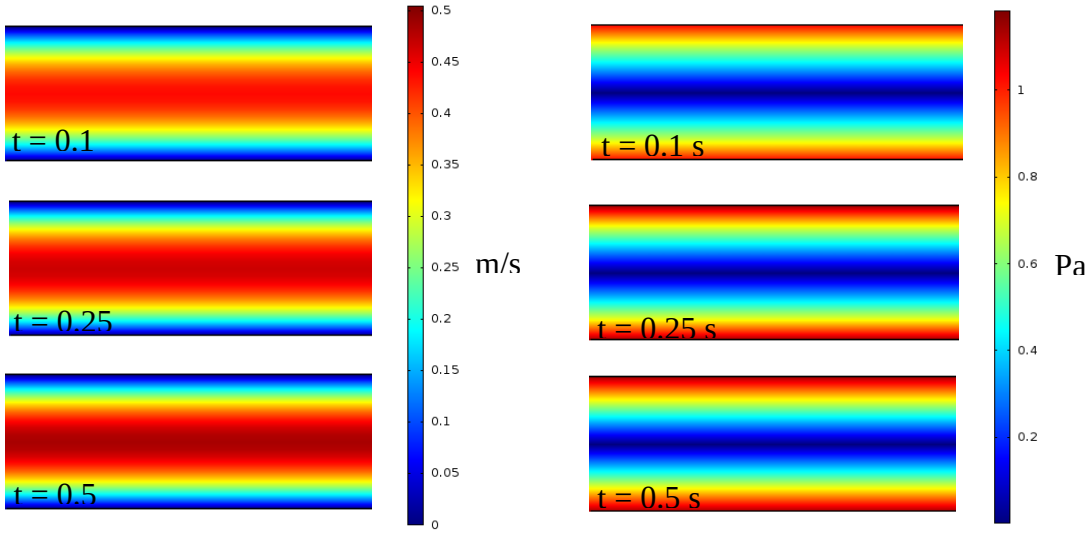
Laboratory Example 2

Following this laboratory, students are introduced to pulsatile flow, the goal being to incrementally approach a more realistic model for blood flow in vasculature. To simulate pulsatile flow, students use a simple sinusoidal representation for pressure drop across the section of vessel, i.e.,

$$\Delta P(t) \approx \Delta P(1 + \varepsilon \sin(\omega t)) \quad . \quad (4)$$

Here, ΔP is the pressure drop given in Eqn. (2) above, ε is a fraction between (0, 1], and $\omega = 2\pi\nu$, where ν is the heart rate in beads per second. The magnitude of ε is estimated from a physiology text and depends on the vessel location in the vascular tree[2]. Human Physiology students learn how to incorporate this time dependent pressure drop into COMSOL Multiphysics

and characterize the maximum and minimum wall shear stresses in the vessel. It should be noted that pulsatile flow only applies to arteries and arterioles. Illustrative snapshots during the cardiac cycle are shown below in Figure 1 a & b.



(a) (b)

Figures 1 a & b. COMSOL Multiphysics Fluid velocity and shear stress as a function of time for pulsatile flow, see Eqn. (4), between parallel plates. The pressure drop and the gap between the plates are consistent with a medium-sized artery. As illustrated in Figure 1 a & b above, students are able to quantitatively analyze and visualize pulsatile flow between parallel plates at specified times during the cardiac cycle. The slight changes in wall shear stress in Figure 1 (b) can be quantitatively evaluated using COMSOL Mulitphysics post processing tools.

Laboratory Example 3

This analysis is then extended to three-dimensions, pressure-driven flow in a cylinder to represent a blood vessel. In this case, the average velocity and resulting pressure drop can be found readily from the Hagen-Poiseuille equation, viz,

$$Q = \frac{\pi R^4}{8\mu L(P_1 - P_2)} \quad , \qquad (5)$$

where R is the radius of the vessel (h above for parallel plates) and Q is the volumetric flow rate. All other parameters are the same as described above. The average velocity is found by simply dividing Eqn. (5) by the cross-sectional area, πR^2,

$$\langle v_z \rangle = \frac{R^2}{8\mu L(P_1 - P_2)} \quad , \qquad (6)$$

and the desired pressure drop is $(P_1 - P_2) = \frac{8\mu L \langle v_z \rangle}{R^2}$. For steady-state, pressure-driven flow in a cylinder, the wall shear stress in the r-direction owing to flow in the z-direction, τ_{rz}, is given by

$$\tau_{rz} = \frac{P_1 - P_2}{2L} R \quad . \qquad (7)$$

All other parameters in Eqn. (7) are described above.

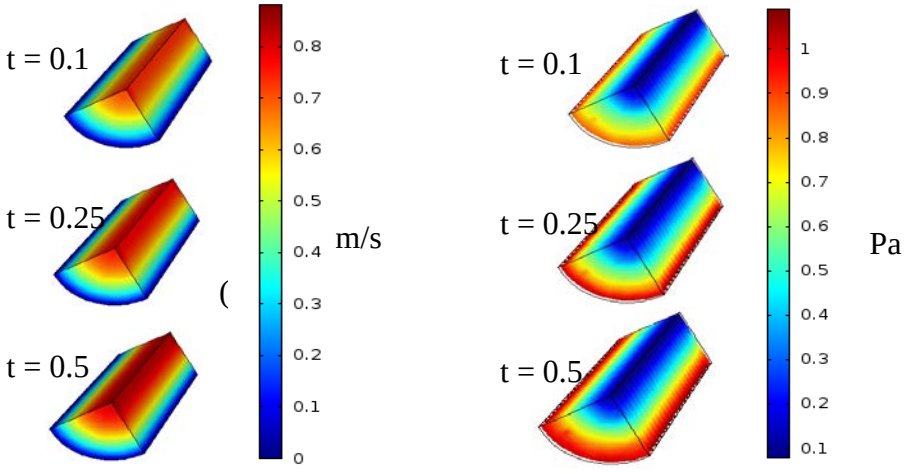
Given below in Table 2 is a comparison between COMSOL Multiphysics and theory.

Table 2. Comparison of COMSOL Multiphysics with theory for steady-state, pressure-driven flow in a cylinder

3D Representation	Average Velocity			Wall Shear Stress $y = h$		
	Theory (cm/s)	COMSOL (cm/s)	% Difference	Theory (Pa)	COMSOL (Pa)	% Difference
Artery	30.0	30.0	0.077	1.440	1.447	0.465
Arteriole	0.780	0.780	0.000	1.440	1.445	0.338
Capillary	0.096	0.096	0.069	1.440	1.451	0.745

Again for the results in Table 2, the COMSOL Multiphysics mesh refinement was set to 'Normal'. Due to limitations in computational facilities, a rigorous mesh refinement was not employed. As shown above, even with a nominally fine mesh, there is excellent agreement between COMSOL and theory for all vessels considered. As with the two-dimensional case, students applied the time-dependent pressure drop as described above in Eq. (4), enabling the students to quantify and visualize the pulsatile effects on the fluid velocity and the wall shear stress, Figure 2 a & b below.

As shown, COMSOL Multiphysics allows symmetry boundary conditions for domains that lend themselves to such simulations, a perfectly symmetric cylinder, for example. In Figure 3 below, the time dependent wall shear stress is shown. Also as is evident in Figures 2 a & b, the students can readily visualize the fluid mechanics throughout the system. One can easily envision incorporating more realistic effects such as stenoses, vessel tapering and distensible walls. Furthermore, one can import actual vessel geometries from CT scans into a program like MIMICs, then import the resulting CAD model into COMSOL Multiphysics (or a program like COMSOL Multiphysics) for a much more realistic model.



Figures 2 a & b. Time dependent fluid velocity, (a), and shear stress, (b), in a cylindrical representation of an artery. The times were selected in accord with the sinusoidal cardiac cycle described in Eq. 4.

Diffusion and Convection

Diffusive processes and coupled convective and diffusive processes are at the heart of Biotransport Phenomena. However, diffusive processes are often very slow, difficult to visualize and therefore not feasibly accomplished in a classroom setting. So, how does one help the student study and visualize such processes? In this section, two laboratories are discussed to help illustrate how this can be accomplished using a suitable FEA package such as COMSOL Multiphysics. In the first laboratory students model a drug-eluting stent, and the second laboratory exercise covers tissue oxygenation, more specifically, the Krogh tissue cylinder[3].

Laboratory Example 4

In the drug-eluting stent laboratory, students learn how to perform axisymmetric simulations using COMSOL Multiphysics. In this mode, COMSOL Multiphysics employs axisymmetric governing equations, which mathematically account for the three-dimensional nature of a two-dimensional CAD drawing. To perform the laboratory, equi-spaced stent struts are situated along the vessel wall in a two-dimensional geometry. Students then leverage the axisymmetric functionality of COMSOL Multiphysics to produce a three-dimensional solution from the two-dimensional, axisymmetric geometry. The CAD representation and the COMSOL Multiphysics results are shown below in Figure 3.

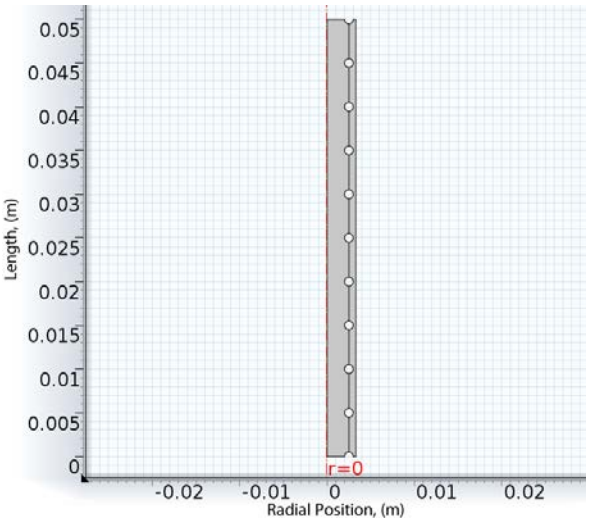
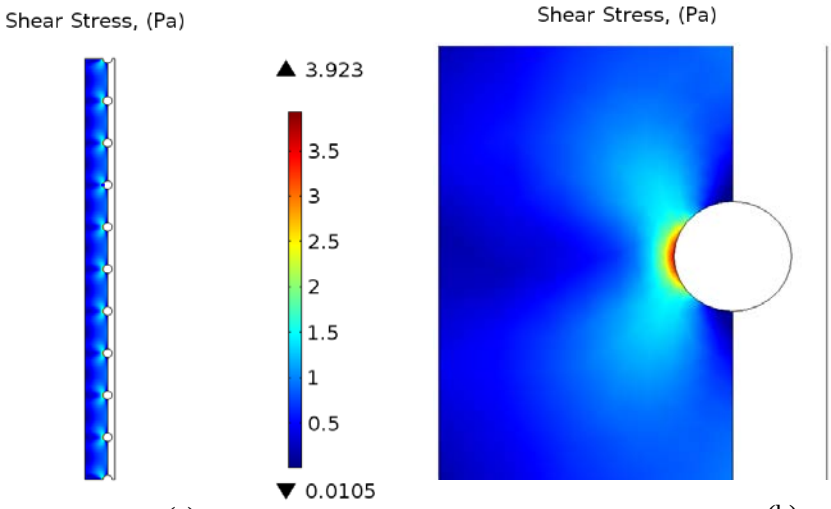


Figure 3. Two dimensional axisymmetric model of an artery with a stent. The circular stent pieces, equi-spaced on the right hand side, are embedded halfway into the tissue denoted by the thinner rectangular region on the far right. The larger rectangle represents the artery. The red dashed line is the axis of symmetry.

As described above in Figures 3, the stent members are arranged in a highly idealized configuration, i.e., circular stent members orthogonal to the flow in the vessel. While this is an idealization, stent members orthogonal to the flow do represent the worst-case scenario for stent erosion, that is, stent members orthogonal to the flow experience the greatest shear stresses. The fluid flow is from top to bottom. Students are able to quantify and visualize the distribution of shear stress between stent strut members with COMSOL Multiphysics as shown in Figures 4 a & b. In Figure 4 (b), the shear stress on the circular stent member illustrates where erosion is likely to be the greatest, i.e., at the fluid-side stent member tip. Also, on the endothelium, the shear

stress approaches zero on the up and down stream edges of the endothelium. These low shear stress regions on the endothelium are on the order of the stent member radius. The endothelium is healthiest when experiencing a basal level of shear stress; therefore, understanding the shear stress distribution is critical for endothelial lining health and therefore a critical aspect of stent design. In addition to enabling exploration of changes in endothelial shear stresses, the orthogonal members do give a reasonably good representation for the analysis of drug elution and drug concentration distributions in tissue and in the blood stream, see Figure 5 below.



(a) (b)

Figures 4 a & b. Shear stress on and between stent members. In (a) the shear stress distribution is shown along all stent members, In (b), the shear stress distribution is more easily visualized on a single stent member.

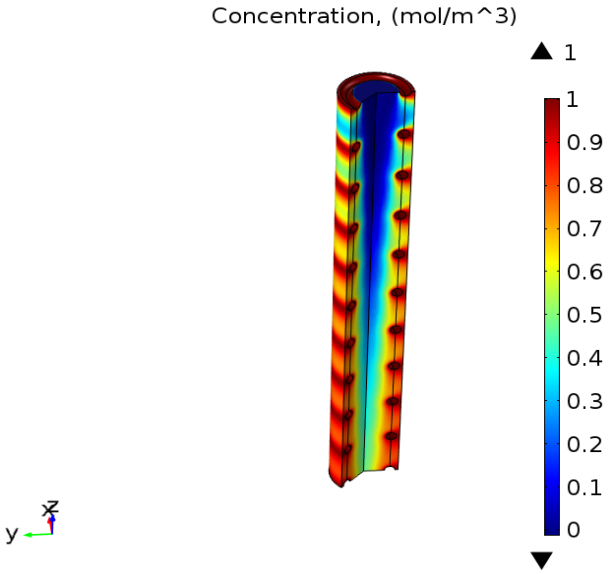


Figure 5. Drug concentration distribution from Axisymmetric COMSOL analysis of a drug- eluting stent. The drug experiences both diffusion and convection due to blood flow.

COMSOL Multiphysics allows visualization of drug diffusion and convection under blood flow conditions. The drug, an anti-inflammatory, elutes and diffuses into the endothelial lining of the

artery to prevent restenosis. A portion of the drug diffuses into the tissue and the remainder is lost in the blood stream. Note the incursion of drug in the downstream region of the vessel. The computational exercise allows students to observe and quantify drug concentrations in both the tissue and in the blood. Once set up and performed, the students gain the ability to incorporate and analyze coupled physical phenomena, i.e., fluid flow and diffusion in COMSOL Multiphysics. With this foundation, students or researchers can leverage a basic model like this to gain insight into shear stress and concentration distributions results associated with more realistic stent designs in a true three-dimensional model. (For the purpose of a teaching laboratory, incorporation of a realistic stent design would be a project in and of itself and beyond the scope of a single laboratory assignment.)

Laboratory Example 5

Another essential physiological process is tissue oxygenation. Again, by developing an axisymmetric model of a capillary with surrounding tissue, students are able to determine optimal tissue radii around capillaries in muscle to sustain cell viability. This is precisely what Krogh did analytically in 1919[3]. A CAD drawing for an axisymmetric representation of a capillary surrounded by tissue is shown below in Figure 6.

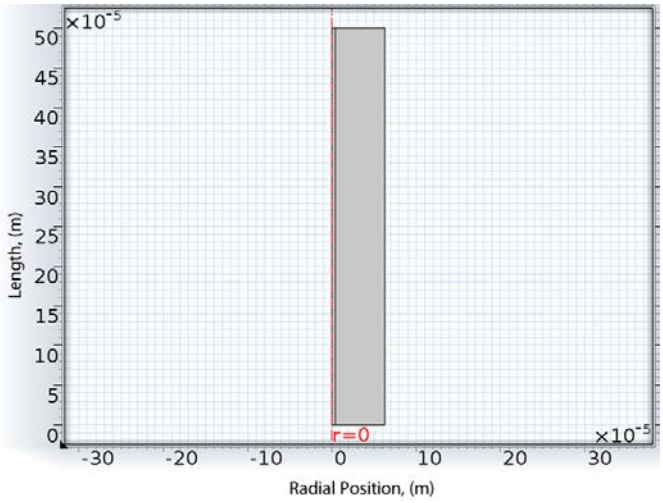
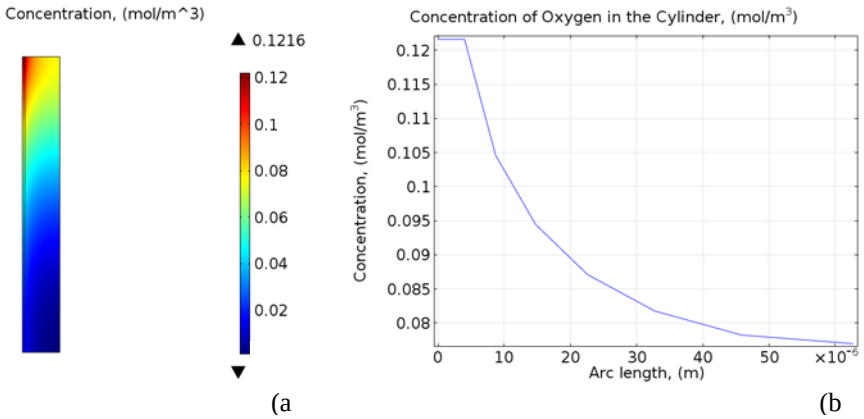


Figure 6. The Krogh tissue cylinder. An axisymmetric CAD representation of tissue surrounding a capillary. The large rectangle represents the tissue and the thinner rectangle adjacent to the axis of symmetry, at r = 0, represents the blood vessel.

In Figure 6 above is a two-dimensional CAD representation of a Krogh tissue cylinder. The tissue consumes oxygen at a specified metabolic rate. As the oxygenated blood enters and passes through the vessel, oxygen diffuses radially through the capillary wall into the tissue where it is consumed. If the tissue cylinder radius is too large, then the concentration of oxygen in the tissue on the venous side of the capillary (efferent end) is reduced below concentrations needed to sustain cell life, resulting in hypoxia and tissue necrosis; however, during developmental physiology, the capillaries are arranged such that there is an optimal spacing between capillaries to sustain cell life; therefore, there is an optimal Krogh tissue cylinder radius. Students are given an oxygen inlet concentration, a consumption rate of oxygen in the tissue, blood flow rate, and diffusivities of oxygen in both the blood and in the surrounding tissue. Using these data,

students are able to utilize COMSOL to visualize the metabolic consumption throughout the tissue given various tissue radii, as shown in Figures 7 a & b.



Figures 7 a & b. Concentration profiles in a Krogh Tissue cylinder. In (a) shows a surface plot demonstrating the concentration throughout the cylinder. In (b) is the concentration profile from the capillary, far left, radially to the edge of the tissue cylinder, at the top of the cylinder.

The students can then use tools in COMSOL to analyze the concentration in different parts of the Krogh tissue cylinder, furthering their understanding of how oxygen levels behave due to the coupled diffusive and convective effects. In the laboratory exercise, students determine the optimal tissue radius surrounding a capillary. Then they are asked to explore the effects of a sudden 20% increase in blood flow rate. Does the tissue become hypoxic? Through this laboratory, students further investigate Krogh's work. Furthermore, students explore various scenarios, that is, changes in flow rates, to quantify and visualize oxygen concentrations in the blood and tissue.

Conclusions

COMSOL Multiphysics has proven to be an excellent resource for computational laboratories, complementing and augmenting the teaching of BioTransport Phenomena at Cal Poly San Luis Obispo. As illustrated in this article, COMSOL Multiphysics exhibits excellent agreement with theory for both average fluid velocity and wall shear stress. Through the use of computational methods, students are able to study diffusive processes within the allotted time of the laboratory class. Furthermore, students are able to explore mathematically intensive Bioengineering problems with relative ease through an easy to use, commercially available FEA package. Most importantly, students are able to visualize physiological transport processes via COMSOL Multiphysics with which they previously experienced difficulty or were not able to observe. Finally, COMSOL Multiphysics is becoming an industry relevant FEA capability, and through this course, students gain valuable experience applying this FEA capability to relevant Biomedical Engineering problems.

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