Adding Quantitative Systems Pharmacology to the Pharmaceutical Sciences Curriculum

The University of Oklahoma College of Pharmacy is teaching PhD students in pharmaceutical sciences how to create multiscale models in order to analyze drug disposition within the human body.

by **BRIDGET PAULUS**

Optimizing drug dosages, evaluating side effects, improving clinical trials, and reducing costs and time to market — these are just a few of the benefits of model-informed drug development. Due to these advantages, the United States Food and Drug Administration (FDA) is encouraging pharmaceutical companies to include simulation in their product development cycles. There is just one problem: Companies often have a hard time finding candidates with strong experience in simulation, as mathematical modeling is minimal in most pharmaceutical sciences programs.

To address this issue, the Institute of Quantitative Systems Pharmacology and the College of Pharmacy at the University of Oklahoma Health Sciences Center partnered in 2014 to develop an innovative curriculum. Within this program, Research Assistant Professor Roberto A. Abbiati designed a PhD-level course on simulation for pharmaceutical sciences students at the University of Oklahoma College of Pharmacy. The class gives an overview of numerical analysis and the modeling workflow in the COMSOL Multiphysics® software. Students learn how to apply modeling to pharmacokinetics, the branch of pharmacology that studies the effect of the human body on the administered drugs. Specifically, Abbiati applies modeling to streamline the quantification of drug concentration levels in the human body and the intended target sites over time — an important concern when developing potentially life-saving treatments.

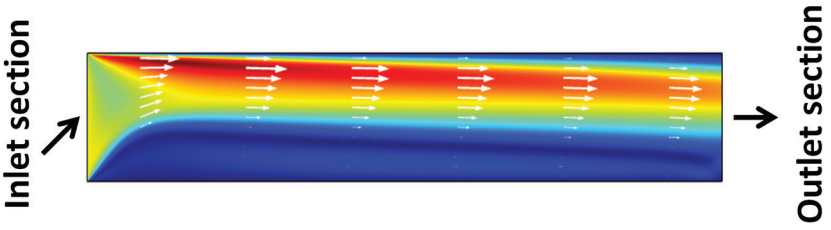


FIGURE 1. Velocity map for laminar fluid flow in a channel.

⇨ TEACHING MODELING TO THE NEXT GENERATION OF PHARMACEUTICAL SCIENTISTS

Pharmaceutical sciences students learn about a wide variety of subjects, but simulation is not typically one of them. According to Abbiati, this is a problem: "Besides being a desired skill by companies, modeling and simulation help design better experiments," he says.

Abbiati's courses are designed to teach PhD students in pharmaceutical sciences how to take advantage of simulation software in their work. The course starts students off with the MATLAB® software, which serves as a bridge to other kinds of mathematical modeling software. As the course continues, Abbiati and his students delve into numerical analysis and the finite element method.

Eventually, students learn how to build models in COMSOL Multiphysics. Abbiati takes them through each step of the modeling workflow. Students learn how to build geometries (starting in 2D, like the laminar flow example in Figure 1); set up the physics; determine the best mesh for a model (Figure 2); and postprocess the results (Figure 3).

Throughout the course, the class learns how to create both compartmental and multiscale models. The former is the standard for pharmacokinetic applications and is an easier concept to understand. Abbiati says that a standard compartmental model "assumes the human body is like a box, with one flux in and one flux out." Using ordinary differential equations, compartmental modeling is a simple way to determine the drug concentration in the human body over time. There is a major limitation with this type of model, though. Abbiati says, "It cannot determine where the drug is localized within specific tissues, which is a critical limitation in several applications including cancer treatment."

> "I'm using COMSOL® to understand why and how the physical structure of the tumor is a barrier for the delivery of the drug."
>
> — ROBERTO A. ABBIATI, ASSISTANT PROFESSOR, UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

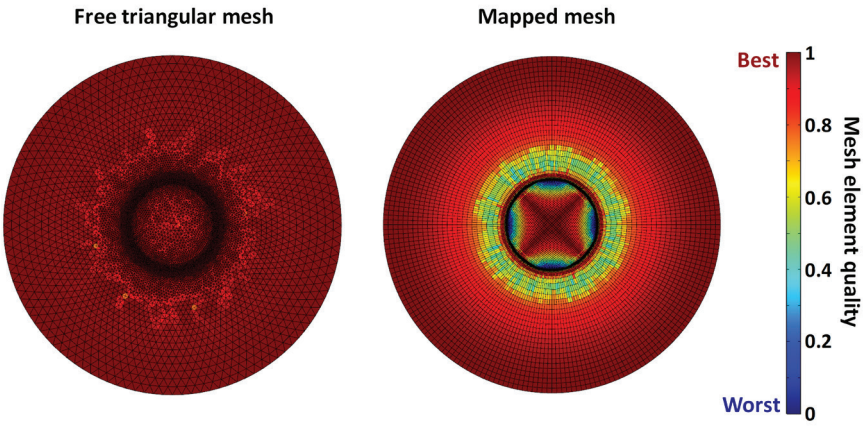


FIGURE 2. Mesh comparison used to introduce students to various mesh options.

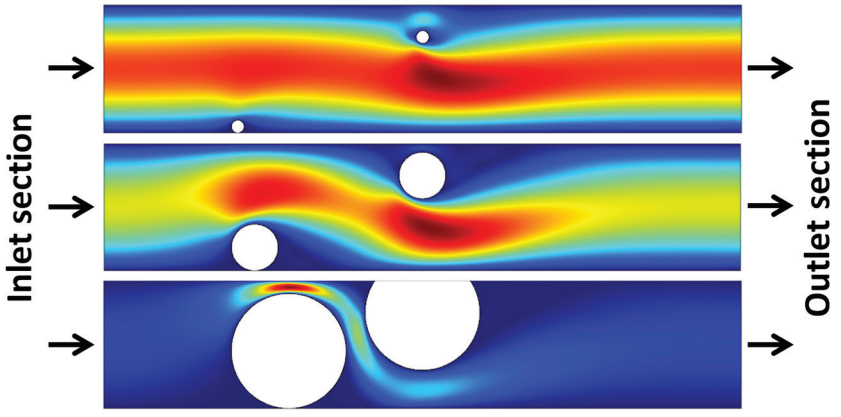


FIGURE 3. Velocity pattern for laminar fluid flow in a channel with obstacles of different sizes, an example from Abbiati's course.

Enter multiscale modeling. While it requires a more detailed understanding of physiological and biological processes compared to compartmental modeling, multiscale modeling is able to provide valuable insight into how deep a drug can penetrate a certain tissue or organ. This type of simulation involves accounting for size scales ranging from the entire human body, individual organs, single cells, down to the molecular level. Although it sounds like a complex subject, Abbiati demonstrates a step-by-step approach that is easier for the students to learn.

⇨ GAINING INSIGHT INTO TUMOR TREATMENT

Dr. Abbiati highlighted the benefits of multiscale modeling for pharmacokinetics by sharing some of his own research performed with his team at the Institute of Quantitative Systems Pharmacology. He is currently studying how drugs interact with solid tumors.

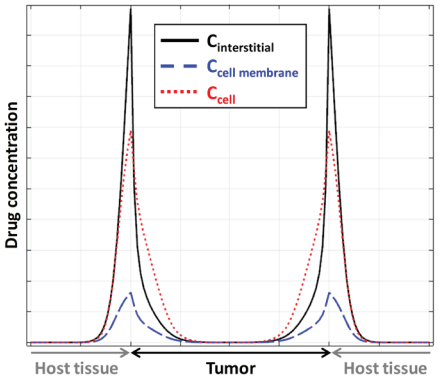


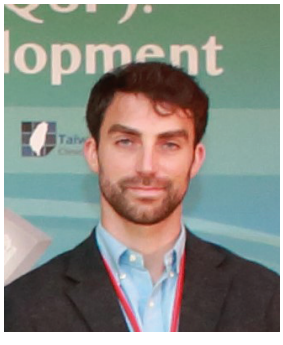
FIGURE 4. The drug concentration profile in a tumor.

These drugs, which typically travel via the bloodstream, can have a hard time getting into tumors. The issue is that these types of masses have "physical barriers that limit drug delivery," explained Abbiati. Tumor sites often have high pressure, which makes it difficult for the drug to penetrate them, for instance.

"I'm using COMSOL® to understand why and how the physical structure of the tumor is a barrier for the delivery of the drug," says Abbiati. To gain such insight, he uses multiphysics simulation to model blood flow in microvascular vessels, drug transport within the tumor interstitial space, and drug interaction with tumor cells. Abbiati modeled how the fluid moves according to the pressure gradient within a tumor mass, assuming that the fluid carries the drug with it. He then used the Transport of Diluted Species interface to describe the drug concentration.

Abbiati said that he was able to use this model "to determine how deep the drug penetrates the tumor, depending on changes in its physical structure over time" (Figure 4). The advantage of using multiphysics analysis was that he could "describe where the drug is located at any given time and any given location of the tumor." From his research, it is clear that multiscale modeling is a useful tool for pharmacokinetics, enabling researchers to better understand how drug concentrations are affected by the human body.

By teaching simulation in his PhD-level pharmaceutical sciences courses, Abbiati is giving students a valuable skill for drug research that could greatly improve future drug development processes. Aside from that, because these students will graduate with a simulation background, they are more attractive to pharmaceutical companies when they are ready to enter the workforce. ❖



Roberto A. Abbiati, Assistant Professor, University of Oklahoma Health Sciences Center