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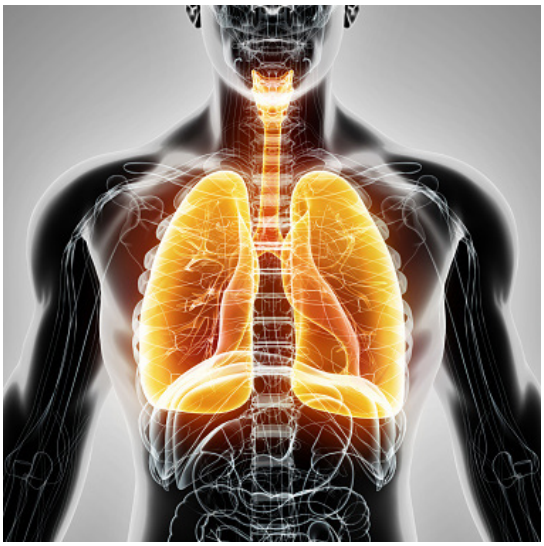

The Expanding Role of Simulation in the Medical Device Industry

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Introduction

Computational modeling and simulation (CM&S) is used across industries to design and test products. Among medical device companies, however, its use has been relatively limited, and the industry has lagged others in taking advantage of the technology. But that could be changing.

The use of CM&S in the medical device field presents some significant challenges—and a significant change from traditional methods.

"The medical device industry has traditionally used a build-and-test approach to product development," says Marc Horner, healthcare industry technical lead at ANSYS, an engineering simulation company. "Build it and test it out on the bench, do animal trials and human trials, and then apply for regulatory approval once you are confident in the performance and safety of the device."

In short, the assessment of safety, reliability, and effectiveness has relied on empirical knowledge gained through physical tests—an approach long deemed critical in a medical field where health and lives are at stake.

The use of CM&S in the medical device field presents some significant challenges—and a significant change from traditional methods.

While CM&S is typically used in the early design and development of devices, it has been less common in downstream activities, especially in the rigorous testing required to meeting regulatory requirements. But the industry is increasingly concerned about the costs of development and testing.

At the same time, CM&S tools have been evolving and opening up more and more possibilities for medical device companies. The U.S. Food and Drug Administration (FDA), which regulates medical devices, is actively embracing CM&S and exploring ways to use it to support safety and innovations in medical devices. As a result, companies are exploring the broader use of the technology. As that happens, CM&S promises to revolutionize the medical

device industry.

Expanding the development toolkit

Traditionally, the development of medical devices has involved physical testing in labs (bench tests, or *in vitro* testing) and in humans or animals (*in vivo* testing). These tests provide valuable insights, but they can also be slow, costly, and limited. Testing on humans, for example, runs into practical constraints, such as the difficulty of measuring the performance of a device when it is in a person, the inability to quickly test variations of a device, and ethical considerations about the best way to conduct such tests.

CM&S provides another avenue for looking at devices. Companies can build models of devices and the body's systems, and run simulations of how the device will perform when it is deployed. They can quickly adjust variables to try out different scenarios, making it possible to run through a large number of possibilities in a relatively short time to find the optimal result.

"One of the key advantages simulation offers is the ability to reduce physical prototyping," says Valerio Marra, marketing director at COMSOL, a maker of multiphysics simulation software. "Challenging designs and new ideas can

THE ALLIANCE OF ADVANCED BIOMEDICAL ENGINEERING

ASME unveiled the Alliance of Advanced Biomedical Engineering in the spring of 2017 to promote collaboration and information sharing by bringing together and providing resources to the biomedical engineering community.

Through its website, AABME.org, the Alliance engages members of the multidisciplinary biomedical engineering arena across industry, research, academia, and government.

The site offers engineers, scientists, and physicians a platform where they can keep up to date on topics ranging from cell therapy and thermal medicine to medical devices and 3-D printing, as well as gain access to ASME's collection of bioengineering-related journals, standards, conferences, and products.

Visitors to the site can complete a free registration to join the Alliance. Membership offers a connection to a community of like-minded technical professionals seeking networking opportunities, as well as the ability to sign up for a newsletter with exclusive content on data, analysis, technology, and business insights in biomedical engineering and related markets. Members also receive discounted access to select ASME biomedical events and conferences.

be built and tested without having to be physically constructed. In an industry where safety is of paramount importance, the ability to investigate different scenarios by specifying boundary conditions, material properties, and physiological mechanisms allows for early and harmless correction of design mistakes."

CM&S can be a powerful tool in the design and testing of devices. But that does not mean that these "*in silico*" tests are expected to totally replace the traditional *in vivo* and *in vitro* tests. Rather, they can complement them, allowing researchers to shift more of the overall testing workload to CM&S and hopefully reduce reliance on bench, animal, and human testing.

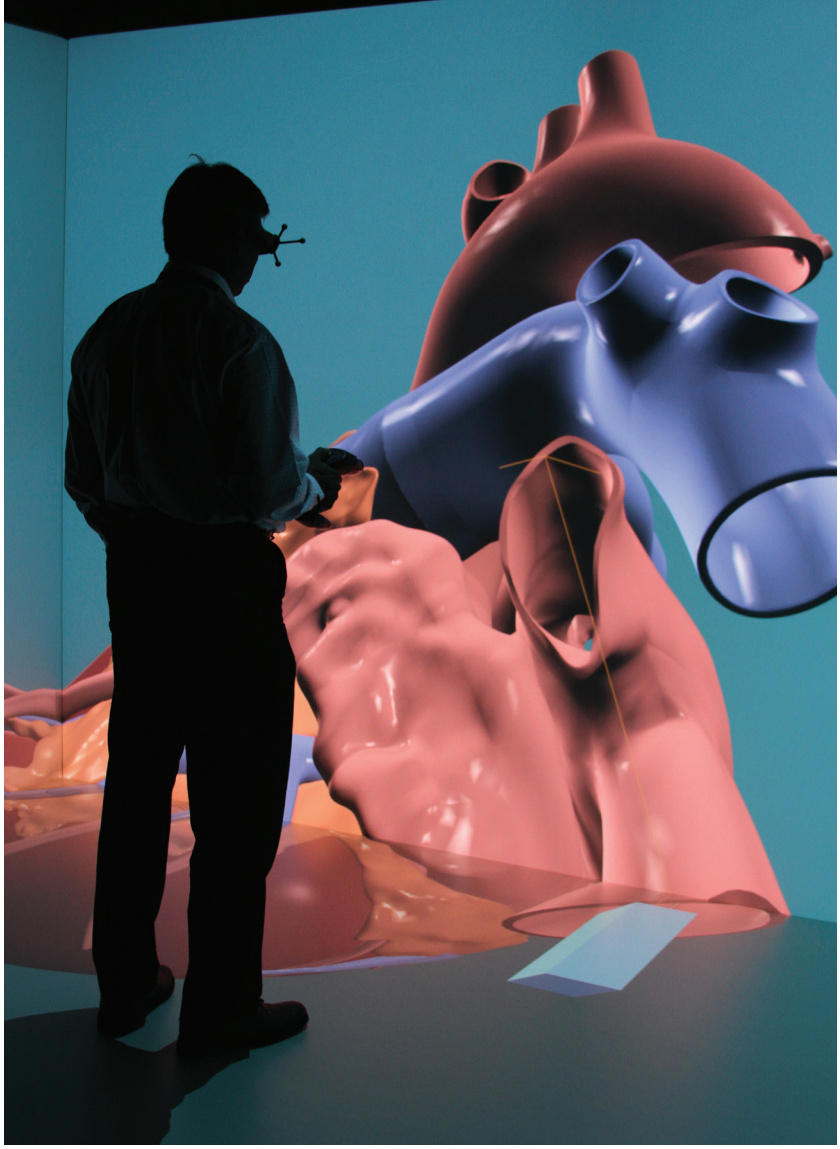
Proponents see a range of potential benefits from the increased use of CM&S in the medical device arena. It promises to take time and cost out of developing and testing processes. It could also boost confidence in devices, because it expands the number and range of tests that can be run on them.

Perhaps most important, it makes it possible to conduct tests that would not be feasible in the physical world because of practical limits on testing in humans or because of the difficulties presented in testing sophisticated equipment.

For example, a new computed tomography (CT) machine from GE Healthcare takes images that "freeze" the motion of the heart. To do so, the equipment rotates in an arc around the patient at high speed.

"You get between 20 and 40 Gs of force on the equipment," says Chris Unger, chief systems engineer at GE Healthcare. "But if the structure shifts by more than a few microns between the calibration state and the actual operational state, you get an artifact. Even if you built a physical model and tried to test it, how could you measure a few microns on something rotating at 50 or 60 miles per hour? So you just have to design in modeling space with this kind of thing. There is no option."

With these types of benefits in mind, many see CM&S as a key to accelerating innovation in medical devices, and getting better product to patients more quickly.



CM&S at work in the medical device field

CM&S has the potential to be applied at points throughout the product life-cycle, from discovery and ideation to regulatory decision making, product launch, and post-market monitoring. Today, it is often used in the development of orthopedic devices, especially in the early stages, where the ability to quickly test a number of options makes its impact especially significant.

"You can use these tools to help avoid sending poor designs downstream in the development cycle. This is important because the cost of a design change increases significantly during the later stages of development," says ANSYS's Marc Horner. That is especially important with medical devices, where follow-on processes can include animal tests and clinical trials that can be expensive and time consuming to repeat.

CM&S can also be of value later, once a medical device is in use. It can be used to predict potential problems in devices in the field, for example, or to understand problems that arise in devices that are in use in order to guide

remedial action and ongoing improvement to the device.

CM&S can also be used to assess certain qualities of devices that are already on the market. For example, ANSYS has utilized CM&S to understand the safety of medical devices during magnetic resonance imaging (MRI) procedures. An MRI, Horner says, "emits an RF field, and if you have a metal implant, like a hip or knee implant, that acts like an antenna that focuses the MRI field in and around the region of the implant. The result is some level of tissue heating." Simulation is used to determine whether the heat generated around an implant will be severe enough to damage the surrounding tissue. An electromagnetic simulation tool is used to determine how the MRI field will interact with an implant, then a finite element analysis simulation tool uses the results of the electromagnetic simulation to perform a thermal analysis.

Horner also points to the use of modeling in clinical applications. ANSYS helps create tools that simulate the positioning and deployment of various types of stents.

"You can use these tools to help avoid sending poor designs downstream in the development cycle."

"Clinical simulation helps doctors by performing virtual surgeries, such as stent deployment in the heart or the brain," Horner says.

There are various types of CM&S currently being used to design, enable, or support medical devices. These include models of:

- **ANATOMY, SUCH AS MUSCULOSKELETAL STRUCTURES.** "People can perform statistical shape modeling to understand population distributions of different anatomical characteristics, which can be important for understanding its impact on the design and sizing for devices," says Tina Morrison, Deputy Director of the FDA's Division of Applied Mechanics and chair of the FDA Modeling and Simulation Working Group.

- **PHYSIOLOGY OF VARIOUS ORGAN SYSTEMS.** For example, says Morrison, "modeling the electrophysiology of the heart for simulating arrhythmias is a growing area of research. You need to be able to simulate those arrhythmias in order to simulate the therapies that can treat those arrhythmias."

- **THE DEVICE ITSELF,** which can then be "virtually placed" in simulated/anatomy models for testing. Similarly, device parts can be modeled and tailored to individual patients and drive the 3-D printing of custom parts. "With patient-specific implants, you can bring together a simulation of the anatomy and the device, so you can design the device to fit that anatomy before it's printed," Morrison says.

Today, simulation technology is even starting to be embedded into medical devices. Here, says Morrison, there can be a closed-loop control system inside the device that senses the physiological state of the patient, decides what the therapy to the patient should be, and then delivers that therapy. She points to an "artificial pancreas" that has the ability to measure a patient's glucose levels and then, based on factors such as time of day, predict the individual's glucose levels in the near future and deliver the correct dose to the patient.

"So there's simulation and algorithms actually embedded in the medical device," Morrison says. "There are not many of these autonomous medical devices on the market yet, but this field is evolving rapidly."

Yet other applications of CM&S are on the horizon. Simulations of the toxicology of various molecules, for example, could be run to test materials used in medical devices.

"When a new polymer for devices is developed, there is a lot of work that needs to be done to assess its bio-compatibility as it comes in contact with patients. Are patients going to have a reaction to this device? Those types of tests are extremely expensive, and animal studies can have inconsistent outcomes," Morrison says. "So there is a group at our agency working towards using simulation to assess the chemical toxicity of different molecules."

SIMULATION IN BIOMEDICAL RESEARCH

According to a November 2017 U.S. Food and Drug Administration presentation, biomedical research efforts taking advantage of modeling and simulation technology to better understand the challenges and help inform the device design process include:

- **Applicability analysis for trustworthiness of models**
- **Ultrasound-enhanced drug delivery**
- **Dynamics of cardiac fibrillation**
- **Biomarkers for allergic risks**
- **Credibility of computational models of the heart**
- **Electromagnetic exposure maps**
- **Benchmarks for computational fluid dynamics**
- **Multimodal imaging-based models of the head and neck**
- **Virtual clinical trials for regulatory evaluation**

More sophisticated tools and models

In recent years, CM&S tools have been evolving, with a shift toward multiphysics platforms that bring together mechanical, fluids, electrical, heat transfer, and other models to support more comprehensive simulations that can look at larger or more complex systems.

"Multiphysics models are used across industries, but they are especially valuable in the biomedical field because of the complexity of the body and the devices that go into it," says Nagi Elabbasi, a principal engineer at Veryst Engineering, an engineering services company that does modeling for medical device companies and other types of clients.

"Multiphysics models ... are especially valuable in the biomedical field because of the complexity of the body and the devices that go into it."

For example, he says, "a heart valve is a solid mechanics and fluid flow problem—you can't separate those. You need to analyze them together. Or, if you are looking at tissue ablation [the intentional destruction of diseased tissue], you need to bring together electrical and thermal fields, and possibly solid mechanics and fluid flows. Many medical devices involve several different types of physics working together."

Medical devices that need a lot of power usually rely on external batteries, with wires running into the body. One possible alternative—using inductive power transfer, with one coil in the body and one outside—could work much like some smartphone charging platforms. But the technology's use in medical devices presents special challenges. "The tuning of a resonant coupled system has to be very precise," says J. Freddy Hansen, staff research physicist at Abbott, a healthcare company, who has used multiphysics modeling tools to explore this approach for implanted heart pumps.

A number of factors can affect the magnetic field, such as nearby metallic objects and heat generated by the medical device itself. At the same time, both coils are moving around.

"As people go through their daily activities, they are shifting all the time," Hansen says. "You have to compensate for this up to maybe a 1,000 times per second." In this type of case, the use of multiphysics modeling tools is critical.

Using these kinds of capabilities, a number of organizations have been developing models of the human heart. The Living Heart Project, for example, is a consortium of researchers, medical device developers, regulators, and physicians that is working to use heart models and simulation to develop effective cardiovascular devices and treatments. A virtual heart developed by a project member—Dassault Systèmes—is a multiphysics model of a healthy

human heart and surrounding vessels that includes electrical, structural, and fluid-flow physics. Researchers can modify or redefine various model attributes—such as geometry, load, and material properties—and apply models of medical devices to the heart to assess their performance and their effect on the functioning of the heart in a wide range of conditions.

The FDA's Morrison points to another, more focused model that simulates arrhythmias in the left ventricle of the heart. Developed by a group at Johns Hopkins University, this model "is relatively simple enough and focused to do a really good job of simulating the arrhythmias. It isn't trying to tackle all the complex issues of the heart," she says. "It has made tremendous progress in helping to figure out which patients need pacemakers and which ones don't." The lesson, she says, is that "models don't always have to be complex to be useful. They just need to do enough with the appropriate accuracy to help you address the question you're trying to answer."

EFFECTIVENESS OF BIOMEDICAL MODELS IN REPRESENTING PERFORMANCE METRICS

	ANIMAL TRIALS	BENCH STUDIES	CLINICAL TRIALS	COMPUTER SIMULATIONS
Predict clinical outcomes relevant to patients	Fair	Poor	Good	Fair
Predict in vivo performance of the device	Fair	Fair	Good	Fair
Predict in vivo safety of the device	Good	Fair	Good	Fair
Predict performance beyond IFU	Fair	Good	Poor	Good
Represent disease state	Fair	Poor	Good	Fair
Adaptable for patient specificity	Poor	Fair	Fair	Good
Predict performance with few assumptions	Fair	Poor	Fair	Poor
Maintain experimental control	Fair	Good	Fair	Good
Ability to vary parameters	Poor	Fair	Poor	Good
Cost	Fair	Good	Poor	Good
Time	Fair	Good	Poor	Fair

Four different methods can be used for regulatory evaluation of peripheral intervention and vascular surgery devices. Each box represents an interpretation of how well the method at top can be used for a specific aspect of performance, listed at left. Computer modeling and simulation meets adaptability and cost considerations quite well. *Data courtesy: Food and Drug Administration*

That's not to say more-complex models aren't useful. Researchers have plans to build on increasingly sophisticated CM&S capabilities, and bring together various models to create a "virtual patient." The virtual patient concept has been around for some time, and the term often refers to fairly limited models used in medical education. Now, however, researchers are focusing on more comprehensive digital versions of the body's systems.

For example, the Medical Device Innovation Consortium, a public private-partnership, focuses on using virtual patients to test devices and treatments in order to augment clinical trials with human beings. Where a clinical trial might look at 500 or 1,000 patients with an actual implanted device, the virtual patient could potentially simulate thousands of patients and identify problems early on, before the devices are tested with humans. These simulations could be used in the design of clinical trials. Eventually, this approach could lead to researchers using a combination of real patients and "virtual patients" in clinical trials, which could reduce the number of humans required and help speed up the process significantly.

In time, the virtual patient could also enable highly personalized approaches to medical devices. Here, the virtual patient would be developed using data about a given individual, creating a "digital twin." This concept is already used in other industries; digital twins of aircraft engines and turbines are used to plan equipment maintenance, for example. In medicine, a digital twin could be used by physicians to predict the safety and effectiveness of a medical device for a specific patient.

Remaining challenges to adoption

While CM&S is finding a range of applications in the medical device field, it is still not used as widely as it could be—and there are still scientific and technical challenges that need to be overcome before that happens.

A key one is lack of readily available information about the human body that can be put into models. For example, the properties of materials used in medical devices are typically well understood, but not so the tissues in the human body.

"If I want to know the electrical conductivity of copper, that's easy to look up or measure," says Veryst Engineering's Elabbasi. "But what about the electrical conductivity of muscle or fat at 400 kilohertz, roughly the frequency that is applied in tissue ablation? That's hard to find, and it varies with temperature."

At the same time, materials in the body can differ from person to person, and they can change as people age or as tissue is affected by disease. There are efforts underway to gather more of this type of data, but doing so will take time.

Another key hurdle is regulatory uncertainty—that is, the question of whether evidence from computer models will be accepted by regulators in the rigorous device-approval process. The FDA has made it clear that it sees tremendous potential in CM&S, which fits with several of the agency's strategic priorities, including using data for improving clinical outcomes, evaluating new technologies, and stimulating innovation in development.

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Typically, Morrison says, "companies have been using simulation to design and test their devices, but they weren't quite sure if they should put that information in their regulatory package." Applications for device approvals have used CM&S-based tests for some time, she says, but often they lacked detail about the models and how they were being used to make them useful.

To help, the FDA published a guidance document in 2016 that discusses how to report on CM&S studies that are used in regulatory submissions. In addition, the FDA has been working with ASME to develop standards for verifying and validating CM&S models—that is, for determining if models are "credible." The result—to be published as a standard in 2018—is a risk-based approach in which companies essentially define the risk of using the model to support the decision, which then drives the level of model credibility that would be needed to support using the model. The decision could be for a regulatory application or for some business decision. Tests involving higher-risk devices will likely be subjected to more rigorous validation and verification. As such efforts help to reduce regulatory uncertainty, CM&S adoption is expected to increase.

At the same time, Morrison says, there is a need for training and outreach. That applies not only to reviewers at the FDA, but to regulatory affairs staff at medical device companies, as well. R&D people at such companies are familiar with the potential of CM&S in design and testing—but the regulatory affairs staff typically is not, making them reluctant to rely very heavily on CM&S test results in FDA submissions. To help bridge that gap, ASME is holding a meeting for R&D professionals—and asked that they bring a regulatory affairs person from their company in order to get into the event with the goal of raising awareness about the successes and challenges with CM&S.

Although there are still obstacles to overcome, they are not insurmountable. CM&S is already proving to be a powerful tool for moving the medical device field forward. Companies are changing their perspective on what is possible with the technology, often working together to find new ways of putting it to work. And the FDA is opening a critical regulatory pathway that is enabling wider adoption of the technology.

With these developments, CM&S promises to become a familiar engineering tool in the field—which will benefit the industry and the patients who rely on effective, innovative medical devices.

ASME TO PUBLISH NEW MODELING STANDARD

Later this year, ASME will publish a new validation and verification standard devoted to the challenges of modeling the biomedical device industry. The publication of V&V 40-2018 is the latest milestone in ASME's longstanding interest in the field.

The FDA hosted the first in an annual series of workshops on computational modeling for medical devices in 2008. The intent of that series was to bring together researchers, medical device manufacturers, and regulatory agencies to present advanced research, review best practices, and address barriers to the use of computational modeling for the design, development, and evaluation of medical devices.

Based on several years of input, it became clear that guidance on V&V for computational models was necessary to support and promote appropriate use of computational modeling in medical device design, development, and evaluation. Due to the growing interest in V&V of computational modeling for medical devices within the ASME Verification and Validation subcommittees, the ASME Verification and Validation Standards Committee proposed the development of a new subcommittee focused on this area with broad representation from device manufacturers, academic groups, consultants, software developers, and government agencies (primarily the FDA). The breadth of knowledge of the subcommittee members spans solid mechanics, fluid dynamics, electromagnetics, kinematic modeling, and other physics-based modeling.

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