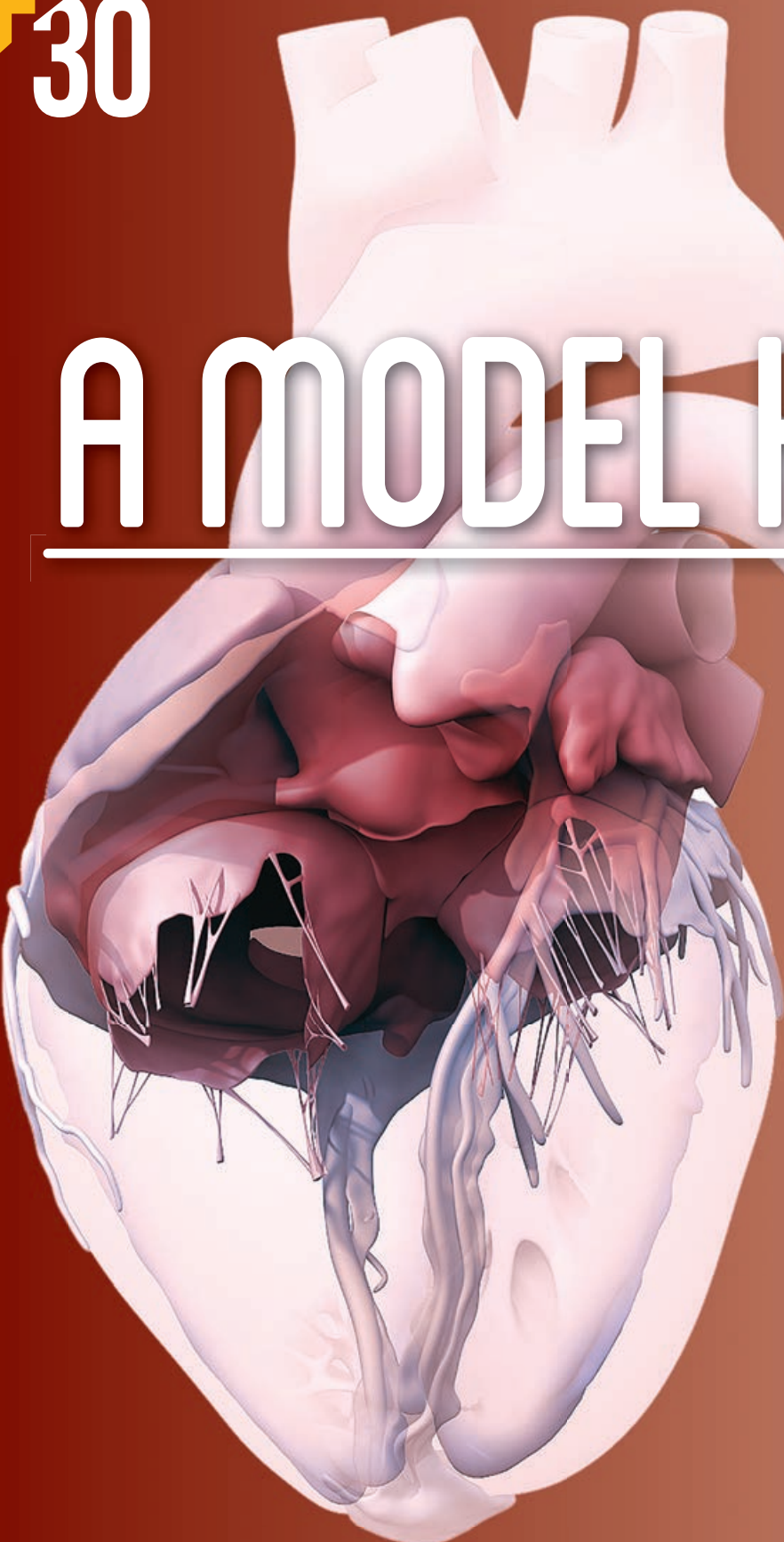




A MODEL HEART

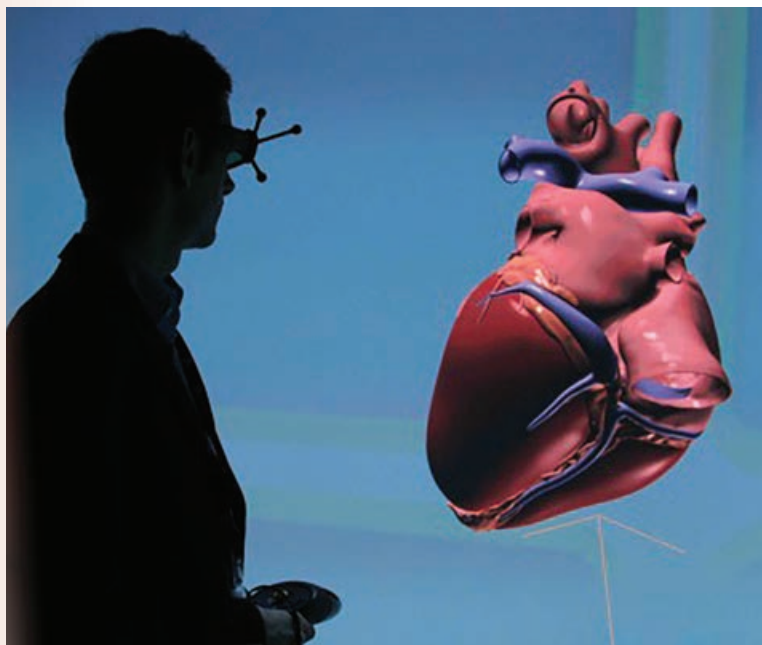
DIGITAL SIMULATION TAKES ON ITS TOUGHEST CHALLENGE

BY ALAN S. BROWN

Steven Levine remembers when the light bulb lit up in his mind.

His daughter had been born with the left and right chambers of her heart reversed. She received her first pacemaker at age two and her fourth at 20. While in medical school, she talked with her cardiologist about future treatments.

"It was clear that he didn't have much data to go on," Levine recalled. "He would have liked her to go into an MRI machine, but there is a risk because she has three broken pacemaker leads still in her body. So they had a negotiation about risk versus the value of the data."



Dassault's Living Heart model is a larger-than-life 3-D representation that enables surgeons, researchers, and engineers to look at the human heart in different ways.

"Then my daughter asked him what he would do with the data. And he said, 'I don't know, but maybe I'll be able to figure something out.'"

After she told Levine, he thought, "This is what I do for a living. If he could get the data, why couldn't I come up with a structural analysis of it?"

To do that would require a realistic simulation model of the heart. It would not only help answer questions about his daughter's treatment, but revolutionize cardiovascular care.

A model might help cardiologists predict how a heart condition would progress. It would provide new ways to design and approve cardiovascular devices, which rarely undergo large-scale human testing before commercialization.

Surgeons could use the model to test new procedures or plan the best intervention for patients. Researchers could use it to develop better ways to image constantly beating hearts.

As chief strategy officer of Simulia, an engineering modeling and simulation software firm, Levine was ideally placed to create that model.

Simulia is part of Dassault Systèmes, which makes a broad range of industrial design and simulation software. Dassault was looking for a highly visible challenge to showcase its multiphysics Simulia software, which let users combine such previously separate tools as finite element analysis and computational fluid dynamics in a single model.

The heart posed that challenge, and more. Its behavior is driven by a complex combination of mechanical, electrical, and fluid properties that called for multiphysics solutions spanning different size scales.

The heart also showed behaviors unlike the purely mechanical components Dassault has modeled in the past. For example, its walls change their stiffness almost instantaneously, depending on whether they are generating or responding to force.

Levine kicked off Dassault's Living Heart Project in early

2013. By May 2014, he had released a beta version of a surprisingly realistic model. Previous simulations, mostly academic, had resembled idealized spheres or heart segments. Dassault's model was a complete heart, with four chambers, valves, papillary muscles, blood vessels, and even some surrounding chest muscles. Future releases will include blood flow dynamics.

"This is an extremely advanced model," said Jose Navia, a cardiac surgeon at Cleveland Clinic in Ohio, who designed a heart valve implant using the Living Heart.

The project came together so quickly because it adapted an open-source approach. Levine reached out to more than 100 people in 30 organizations, including medical device makers, researchers, physicians, and regulators.

In doing so, he tapped into a quiet revolution in understanding and modeling the cardiovascular system. Over the past two years, Levine has been combining this diverse research into a single collaborative engineering platform.

The Living Heart Project is now reaching critical mass, Levine said. Yet one thing is abundantly clear: This is an effort that is being shaped and led by engineers.

Many never imagined doing anything remotely like it.

FINITE ELEMENTS

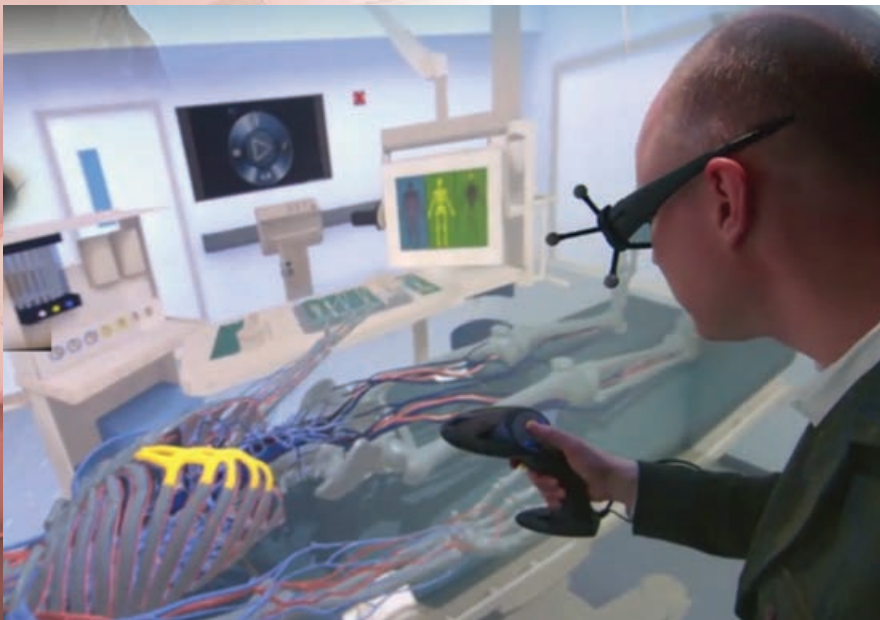
Ellen Kuhl, an assistant professor of mechanical engineering at Stanford University, was one of them.

Kuhl had trained in finite element analysis in Germany, working on "bridges and dams" types of engineering problems. After she came to Stanford in 2007, one of her graduate students asked to build an FEA model of his mother's heart, which had an irregular heartbeat. A second student wanted to design a new heart valve with a local surgeon.

This drew Kuhl into the orbit of physicians from Stanford's medical campus.

"The cardiac surgeons weren't happy," she said. "They

By placing the heart in a body, Dassault's model enables engineers to envision how medical devices might interact with muscles and bones, as well as with the heart.



define themselves as plumbers. They fix leaky valves the way plumbers do, by trial and error, but they get only one shot to do it right.”

They wondered if they could use something like video game technology to simulate surgical outcomes before they opened a patient. Intrigued, Kuhl began attending surgeries.

The surgeons would test new designs by replicating a condition in large animals, implanting the device to see if it worked, and conducting post-mortems to see if the implant damaged any surrounding tissue.

Kuhl would arrive at 6 a.m. and help put the animals on heart-lung machines before surgery.

“I could reach into the animal, hold its heart in my hand, and feel the beating. It’s very soft when filling, and then, in one millisecond it becomes stiff as a rock as it starts pumping,” she recalled.

Her experiences showed the need for a viable heart model.

“These surgeries are incredibly difficult to do in animals,” Kuhl said. “They are time-consuming and expensive, and raise ethical questions. We could save so much time and be so much more precise and accurate if we could test these designs on a computer first.”

Her team started by incorporating existing data on the heart’s electrical behavior into a finite element model. It chopped the complex geometry of the heart into thousands of tiny tetrahe-

drons. By solving for the electrical response of each small tetrahedron, or cell, and modeling how that change affected neighboring cells, her model could reproduce the sprint of pulses across the heart.

After validating the model against students’ EKGs, her team added the mechanics. They used data from researchers who measured the contractions of heart muscle tissue in Petri dishes. By linking FEA cells together into muscle tissue, she could replicate the crisscrossed strands of muscle that reproduce the heart’s characteristic twisting pump motion.

The FEA model let her produce a broad range of behaviors.

“By changing the properties of the tetrahedrons, we can make different regions of the heart contract faster, slower, stronger, or weaker, and reproduce different diseases and conditions,” Kuhl said.

She could also project how a diseased heart would evolve over many years.

Kuhl’s model was very sophisticated but far from perfect. It lacked many features and simplified others. Her modest Living Matter Lab had no way to incorporate all the latest cardiovascular research. So when Levine approached her in 2013, she was happy to join the Living Heart Project. Her model became its FEA core.

As Dassault reached out to other researchers, it upgraded the model. Cleveland Clinic’s Navia, who holds joint appointments in surgery and



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bioengineering, was the first to apply it to design.

Navia worked on an annuloplasty ring, which squeezes together the flaps of a heart valve to keep it from leaking.

Navia used the model to simulate the ring in different types of diseased hearts and measure precisely the stresses the ring puts on the valve and surrounding muscles.

“The model was fantastic, and proved the concept,” he said. “We could run simulations under different conditions, including ones we could not recreate in living animals, and change the design to improve performance.”

THE LIVING HEART GROWS

Many medical device makers already used Dassault products, and Levine had foreseen a role for the Living Heart in design. As the project began to incorporate the work of other experts into the model, the focus broadened to include surgery and imaging.

For example, Julius Guccione, a bioengineer and professor of surgery in residence at University of California, San Francisco, Medical Center, has been developing heart models since the late 1990s. He was part of a team that pioneered polymer injection, a technique that reduces stress on

heart walls by 35 percent.

“When we tried to publish, the reviewers thought the results were too good to be true, and wanted to see our raw MRI images,” he said.

His experience shows how models can help innovative surgeons. In the mid-2000s, researchers thought they could treat damaged heart muscle by injecting stem cells, which would grow into muscle cells and strengthen the heart wall. Tests showed noticeable improvements.

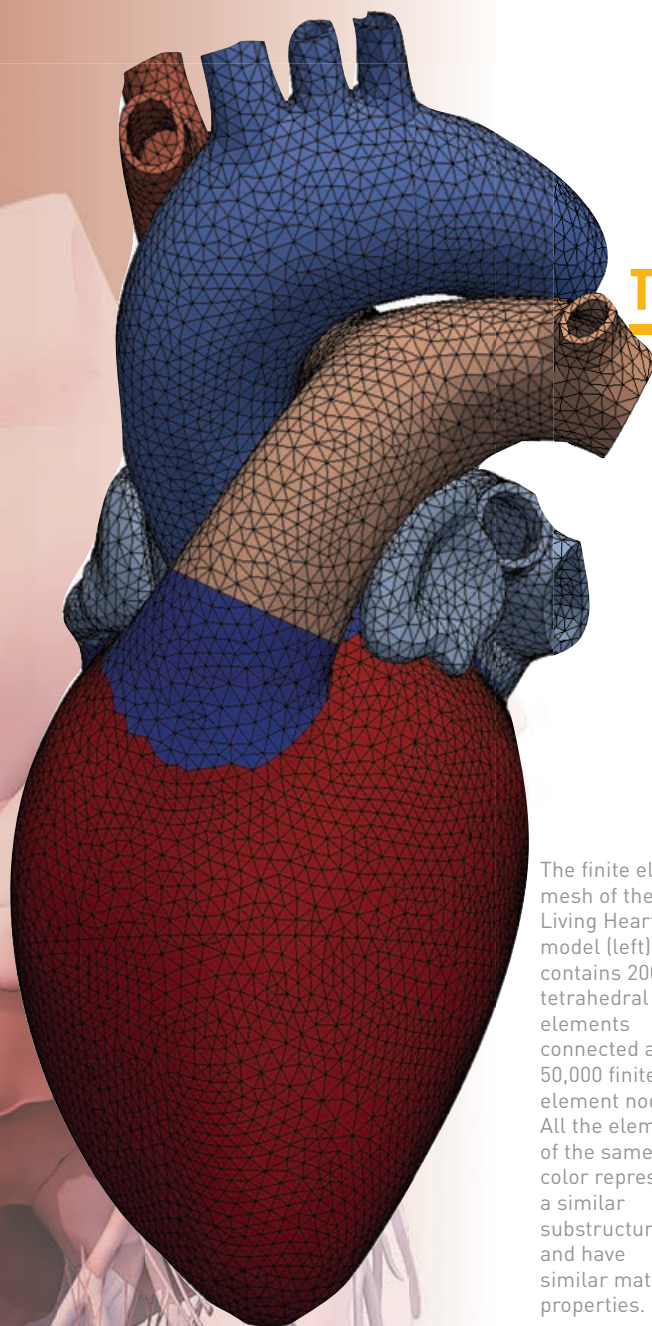
UCSF surgeon Mark Ratcliff and Kevin Healy, a bioengineer and materials scientist at the University of California, Berkeley, thought differently. They argued that injecting any material into the heart would increase the wall’s thickness and improve its load-bearing ability.

They asked Guccione to model the left ventricle, and use the model to find the right material. They needed an injectable liquid that polymerized quickly. It had to be stiff enough to provide support, but supple enough to flex during pumping.

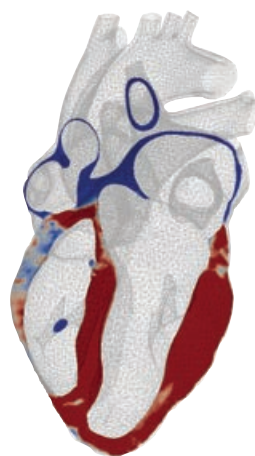
Guccione identified a resin, and also showed that seven injections was the best tradeoff between support and flexibility.

The researchers then reproduced failing left ventricles

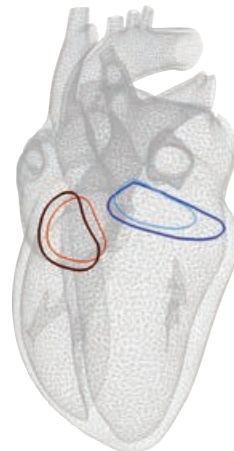
THE FINITE ELEMENT MESH MODEL



The finite element mesh of the first Living Heart model (left) contains 200,000 tetrahedral elements connected at 50,000 finite element nodes. All the elements of the same color represent a similar substructure and have similar material properties.



In the model above, the red regions show that wall thickness increased by up to 50 percent as the heart responded to increased pumping pressure. Cardiologists may soon use similar models to predict how the disease will progress in different patients and, ultimately, design individualized treatment plans.



The left side of the heart in this model has grown too large, and the base of its valve has expanded to the dark blue circumference from the light blue size. Cardiac surgeons typically implant a ring to make the valve smaller and prevent backflow. The model provides detailed stress and strain data that could help them design the rings.

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SAN DIEGO.**

in dogs. The injections stopped the disease from causing death. The procedure reduced heart wall stress by an average of 35 percent on 11 heart patients in Germany, with no adverse effects.

Guccione’s model provided a deeper understanding of how the procedure worked, and shaved countless weeks off materials development and animal testing.

Others are using models to guide treatment. One is James Perry, a heart surgeon and director of electrophysiology and adult congenital heart programs at Rady Children’s Hospital in San Diego.

Perry reconstructs the hearts of children born with only one working ventricle. This involves several complex operations, starting in childhood. Some of the children who received this procedure have grown up to be healthy adults, “some as functionally normal as me and you,” Perry said.

Yet no two patients are the same, and Perry must decide

how to treat each one. “Early on, do we operate or put in a pacemaker? We do what we think is best for that child with that particular defect and that particular cardiovascular physiology,” he said.

“But there is no way of knowing if that’s right. If we could model that procedure, I would know what would be the better choice looking 40 years down the road.”

With no simulation model to give him answers, Perry began developing a mathematical model that analyzed data from several thousand patients with similar conditions. A surgeon could measure a heart’s output and responses, and the model would calculate the most likely outcomes for different treatments.

The model has already given Perry new insights. Some of his patients, for example, have leaky valves. Most surgeons do not want to do open heart surgery until they must. Perry’s model shows that operating early, before leaks grow larger, produces better long-term results.

The Living Heart might also improve the ability of imaging equipment to identify heart conditions, W. Paul Segars said. An associate professor of biomedical engineering and radiology at Duke University, Segars developed a model that simulates how the body absorbs X-rays, ultrasound, and other radiation generated by medical imaging devices.

By modeling the absorption of skin, bone, and organs, Segars can analyze how well a specific imaging device would be able to locate small tumors or other medical conditions in a wide range of patients and positions. Segars and his collaborators use this information to improve image accuracy.

For a beating heart, it remains a challenge.

“The heart beats once each second, so if you were trying to image plaque around a valve, it would get blurred out. You need a way to process this motion to get a clear image,” Segars said.

By recreating the condition in a model, Segars can see how the imaging equipment responds to the challenge. Sometimes, all it takes to remove the blur from the data is a different measurement protocol or a better algorithm. Other times, it may require an equipment redesign.

Segars created his heart model by scanning MRI data into his software. While it is anatomically correct, he has little control over its parameters. He signed on early with the Living Heart Project so he could work with a more realistic model.

“With the FEA model, we can dig deeper and change the size of some features and the blood flow, or place a blockage in the arteries,” Segars said. “We can simulate all types of patient data.”

Segars was attracted to the Living Heart because it offered broader capabilities than his models. That realism opens new doors. The ability to change a wide range of parameters lets researchers access behaviors they cannot replicate with more narrowly focused tools.

TAKING IT TO MARKET

Levine plans to commercialize the Living Heart slowly, in steps.

“We’re systematically targeting problems that are readily addressable by the sophistication of the model at each of its stages,” he said.

For example, the Living Heart model is already suitable for testing pacemaker leads, since it needs to model only mechanical stress during motion. Projecting the progression of heart disease will require a more sophisticated model that incorporates the behavior of the underlying heart tissue.

Dassault is also partnering with the U.S. Food and Drug Administration to test how its model simulates the insertion, placement, and performance of pacemaker leads and other cardiovascular devices. If FDA verifies the model, device makers will be able to use simulations for regulatory approval.

While the FDA relies mostly on bench models, and animal and human tests, it has begun using some computational models, said Donna Lochner, associate director of regulatory science research programs at the FDA’s Center for Devices and Radiological Health.

For example, the FDA uses CFD models to characterize fluid flow through and around cardiovascular devices. Models also play a “significant role” in evaluating how MRI radiation might cause tissue damage by heating implants.

For simulations to play a larger role in regulatory approval, the industry will need more realistic models and a better understanding of how much it can trust the results of those models, Lochner said.

Dawn Bardot agrees. She is senior program manager for modeling and simulation at the Medical Device Innovation Consortium. The group seeks to advance regulatory science, and includes medical device makers, software developers, and such government agencies as the FDA and National Institutes of Health.

Bardot believes the Living Heart Project is breaking new ground.

“I think we’re on the cusp of something really big right now,” Bardot said. “When they look at my condition, they are not going to choose the same medical device they used to treat my grandmother. They’ll choose a device specifically for me.

“We can’t do that now, because we can’t run clinical trials on one thousand Dawns to see which device works best,” she said. “There’s only one of me.

“And that’s what modeling really offers, a way to simulate one thousand Dawns to find the best way to treat my particular condition,” she said.

Or, for Steven Levine, the best way to analyze his daughter’s heart. **ME**