# IN VIVO, IN VITRO, IN SILICO!

*Simulation courtesy Foundation of Cardiac Surgery Development.*

## Four best practices help ensure a smooth technology shift to computer modeling and simulation for medical device and pharmaceutical organizations.

**By Thierry Marchal**, Director Healthcare Industry Marketing, ANSYS

Following early engineering simulation adopters such as the aeronautic, automotive and nuclear industries, biomedical and pharmaceutical companies have started to widely embrace computer modeling and simulation (CM&S) to accelerate their product development processes and reduce the huge cost of bringing a new drug to market. (That cost could be up to $2 billion U.S.) Yet, some healthcare practitioners and organizations remain hesitant to adopt this unfamiliar approach and technology.

Medical history shows that those who embraced true technological revolutions early emerged as new market leaders. Others, including some who were previously dominators, simply disappeared. The medical world experienced this shift a few centuries ago by following the example of Leonardo da Vinci, adopting an in vivo approach to understand how the human body works. In other words, researchers conducted tests and experiments on living organisms as well as cadavers. This led to tremendous innovation, such as the development of modern surgery, which saved many lives. Later in the 19th century, innovators developed in vitro testing, which was much faster than in vivo experiment but did not replace it completely. In these instances, researchers conducted tests and experiments in test tubes and on petri dishes. This led to a new wave of innovations, including the emergence of a large pharmaceutical industry.

Today, to maintain the exponential growth of innovation, the medical and pharmaceutical worlds are entering an era in which a growing number of experiments will be done on the computer — known as in silico — to complete and accelerate in vivo and in vitro approaches. This has the potential to revolutionize science and medicine. Some companies still wonder, however, how to navigate through this intimidating transition to a new style or stage of testing.

**Medical and pharmaceutical worlds are entering an era in which a growing number of experiments will be done on the computer.**

**THE ROLE OF NUMERICAL SIMULATION IN MEDICAL DEVICE NPD: PAST, PRESENT AND FUTURE**
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As more technology advocates interact with market leaders and innovators, four best practices emerge.

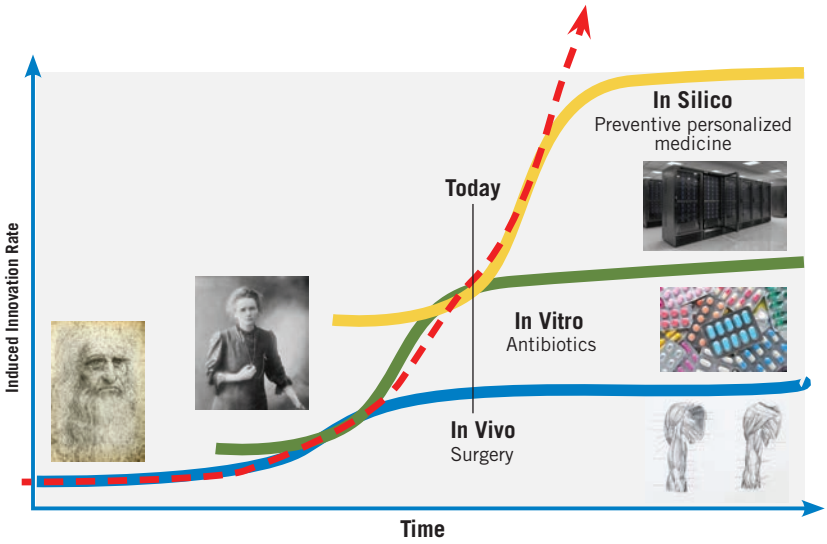
## VIRTUAL HUMAN LABORATORY

Many medical products, and, of course, all drugs, directly interact with the body. Testing them in their working environment is a necessary but also challenging task. It can be difficult or impossible to find volunteers to test the performance of a given treatment without endangering them. Thanks to advances in medical imaging, computational power, and numerical algorithms and models, medical and pharmaceutical companies now can reproduce human environments. If necessary, researchers can extend them with great geometrical and operating condition accuracy, potentially modeling the entire human body through a systems approach.

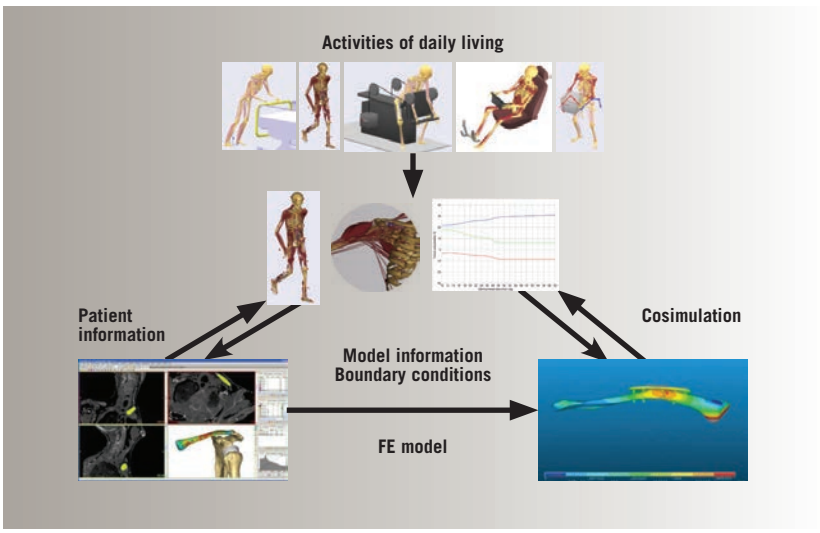
Best-in-class companies develop a detailed model of both the device and the part of the body interacting with it. They predict the complex thermal, structural, fluid and/or electromagnetic behavior of the natural components — such as soft tissues, bones and blood — by using advanced models previously validated through experiments. Proper boundary conditions mimicking different patient activities and pathologies are considered through a combination of 3-D modeling and systems-level simulation to perform full-body simulation. Understanding in detail how the device might work is crucial in the early concept development stage of the product development process. It reveals possible failures and opens the door to optimization.

Developing such advanced models of the human body is usually done step by step — with each adoption level providing valuable insight.

As a first step, a company using engineering simulation adds the components of the human body that directly interact with the device, a first-level adoption of the virtual human interaction laboratory best practice. Researchers can then add more to mimic the complexity of the human body — by

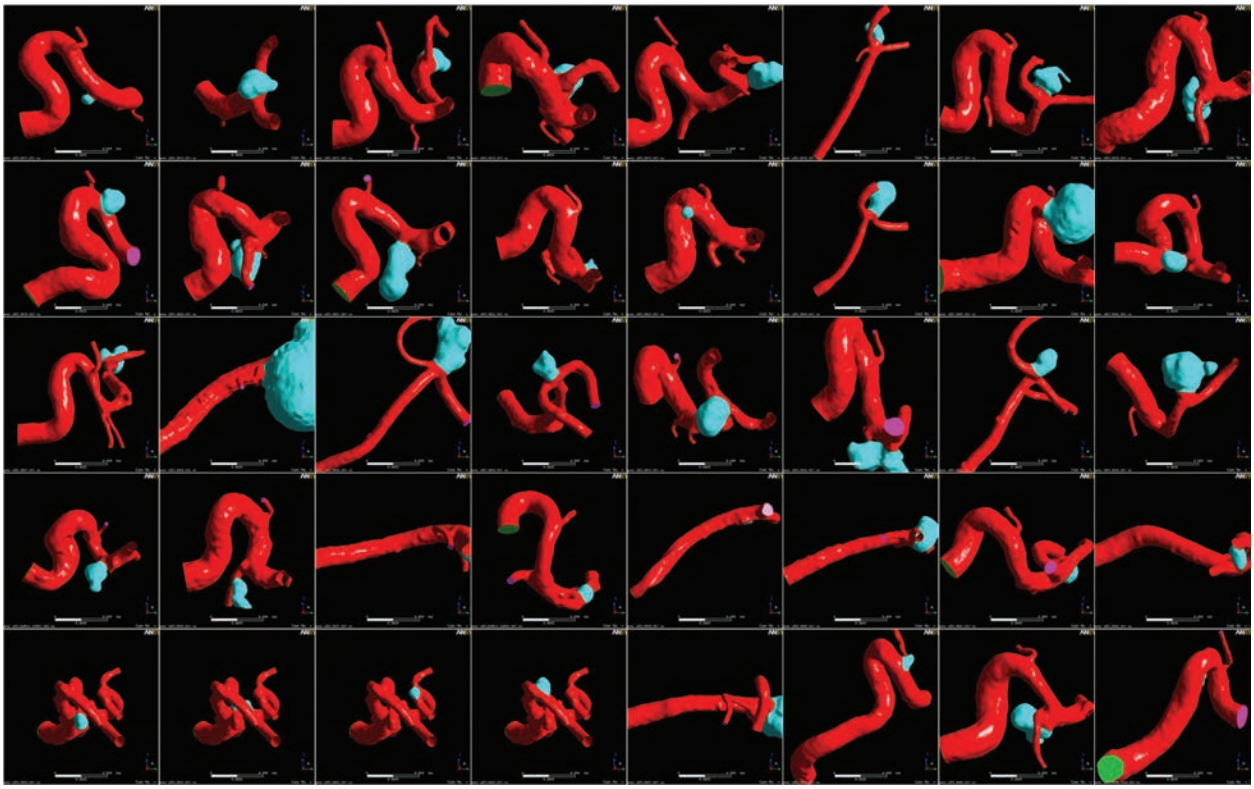



▲ The in silico approach will complement in vivo and in vitro testing to boost the innovation rate.




▲ Testing new devices in the working environment of the human body during various activities minimizes the risk of post-release failure. *Courtesy Hochschule Regensburg University of Applied Science.*

**The in silico approach has the potential to revolutionize science and medicine.**



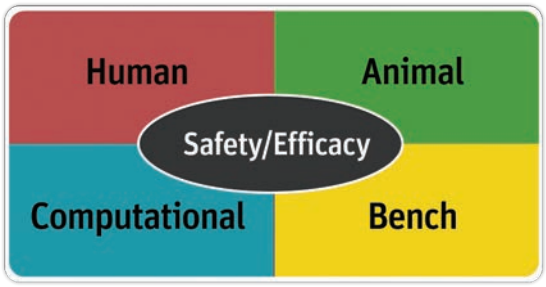
▲ Testing new cerebral aneurysm treatment on more than 300 patient-specific aneurysms was the goal of the @neurIST project. *Courtesy the @neurIST project.*

considering more-advanced nonlinear models or by adding more physics — to understand body–device interaction with greater fidelity. They also should progressively expand the number of body parts until they encompass the full body, possibly by using a reduced-order model approach. Through this progressive approach, innovative companies continually improve their virtual testing processes.

For example, the VIRTUheart™ project featured on page 25 helps doctors determine the best form of treatment. It uses simulation to improve the diagnosis of the severity of coronary artery disease in a given patient. Starkey Hearing Technologies employs simulation to ensure that hearing aids and their controllers perform reliably by taking into account both the device and the wearer. (See page 18.)

## IN SILICO TESTING

The medical community faces a unique challenge from human variability; it is not enough to prove that a new device works well for a single person. Device manufacturers need to state with confidence that medical equipment will work as expected for the entire target population. Typically, new devices are tested on hundreds or thousands of patients in clinical trials to confirm that the prototype does not endanger the patient and that it provides the expected results despite the physiological and pathological variability of the target population.




▲ Regulatory authorities today recognize the importance of the computational approach to complement human, animal and bench testing.

The similarity and repeatability of these clinical tests is an obvious opportunity to use computer models and simulation. By doing the same simulation on large databases of patient-specific geometries and material properties, researchers can develop in silico clinical trials based on just a few key parameters and arrive at conclusions that are valuable to clinicians. Furthermore, as testing proceeds on virtual patients, there is no risk of harm or threat to safety. It is possible, therefore, to push the test to the extreme and determine the actual operating window for a given solution.

Developing such in silico clinical trials is a time-consuming task, as it requires accumulating large databases of patient-specific geometries, material properties and operating conditions. Modeling the interactions of the device

▲ As the number of implantable and wearable devices increases, medical product developers must guarantee safe interaction with the body and minimize the risk of interference.

**The in silico revolution will boost medical and pharmaceutical innovation and provide solutions so we can all live longer and better at an affordable cost.**

with a single patient's body, however, is a first step toward an in silico testing approach. When medical device manufacturers collaborate with clinical partners and simulation software providers such as ANSYS, it is possible to progressively add more patient-specific geometries (and material properties) to the database. This progressive adoption and amplification of in silico clinical testing provides increasing confidence that new treatments will sail smoothly through the actual clinical testing.

This issue of *ANSYS Advantage* presents an article from Integrated Scientific Services AG on page 11. The company is developing Optimeyes — a clinical tool for ophthalmologists that runs ANSYS Mechanical in the background to produce patient-specific cataract surgical strategies.

**PREDICTING MRI COMPLIANCE OF IMPLANTED DEVICES**
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## SIMULATION-DRIVEN FDA APPROVAL

Recently, regulatory authorities such as the U.S. Food and Drug Administration (FDA) have recognized the value of computer modeling and simulation within their approval processes when simulation is properly applied. Authorities encourage the adoption of simulation to complement other approaches such as bench, animal and human testing. Although computer modeling is still a tiny fraction of the testing, the Medical Device Innovation Consortium (MDIC) said the approach could represent more than 50 percent of clinical trials in the future. (Read more about MDIC on page 22.)

Building on the willingness of various regulatory authorities to accept burgeoning technology, engineering simulation can be an essential part of this approval process. Some medical device companies, including a few featured in this issue of *ANSYS Advantage*, have reported modifications of previously approved devices (and electromagnetic interaction with the body) approved through the exclusive use of simulation results. But, as some regulatory authorities might be less familiar with this technology or require results in a specific format, any organization modifying or developing medical devices should communicate early and often with regulatory authorities to determine expectations for validation and reporting.

Through these interactions, the recommended in silico approval strategy will be as clear for the company as for the authorities and increase the number of cases in which simulation can play an important role to reduce process time and minimize costs.

**A NEW SYSTEM FOR SURGERY**
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## VIRTUALLY CERTIFIED BODY-AREA NETWORK

As wearable and implantable devices connected to the Internet or each other multiply (as the Internet of Things becomes pervasive), individuals are fast becoming a complex network known as a body-area network (BAN). Even with an increasing number of devices directly interacting with the body on a regular basis, the human tolerance to absorb electromagnetic energy remains the same. So, product developers must

ensure that the accumulated energy of implanted or worn devices will not exceed acceptable electromagnetic-field thresholds. It is equally important that these devices, especially those that have the potential to save lives, will not interfere with each other.

It is extremely difficult to test all configurations, and it is also challenging to obtain FCC approval for each new device. Clinical testing is time- and cost-prohibitive, if it were even possible. Market leaders such as Medtronic use engineering simulation to model both the device and the body to demonstrate that the specific absorption rate (SAR) is within safe levels for the wearer. (See page 14.) In silico testing has made it possible to virtually implant and/or wear different devices — and to model interactions between them or between the devices and the body — and even consider different body types (male, female, child, slim, average, overweight, etc.).

Although this approach is not expected to fully replace clinical trials in the foreseeable future — with a few exceptions — it already allows designers to identify potential failures in the very early stages of the product development process.

## DO NOT FEAR THE IN SILICO REVOLUTION

This in silico revolution will boost medical and pharmaceutical innovation and provide solutions so we can all live longer and better at an affordable cost. It already is delivering huge business opportunities to organizations that adopt best practices such as the virtual human laboratory, in silico testing, simulation-driven FDA approval, and safe and reliable BAN. But this technology shift can be intimidating because of the uncertainty inherent in any new approach and the possible investment required.

As many of the articles in this issue of *ANSYS Advantage* reveal, it is important to start adopting these best practices as quickly as possible. Companies can gain significant value even with a minimal commitment to in silico testing. First, it is essential to identify which best practices could deliver the most immediate impact on your business. Next, adopt progressive, multilevel best practices that are most advantageous to you. Although organizations will not gain the full benefits of widespread deployment immediately, this approach will yield important results for a small investment.

ANSYS has extensive experience and a network of resources in this area and is willing to guide you in this important journey toward in silico medical product development.

**Significant value can be gained even with a minimal commitment to in silico testing.**