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U.S. Department of Health and Human Services
U.S. Food and Drug Administration

2015 Science Writers Symposium

Using Modeling and Simulation for Medical Device Innovation: Virtual Patients for Regulatory Decision Making

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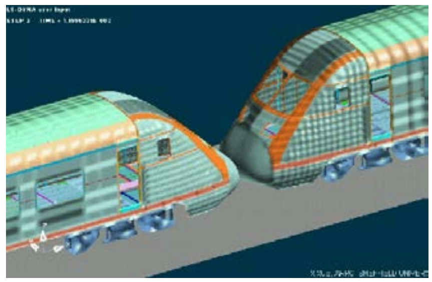
U.S. Department of Health and Human Services
U.S. Food and Drug Administration

Modeling and Simulation (M&S) in Engineering



Credit: Xiangdong Xue – Sheffield University

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While engineering was once an empirical, build-and-test discipline it has been greatly transformed by modeling and simulation.
This image shows a simulated head-on collision of two trains.

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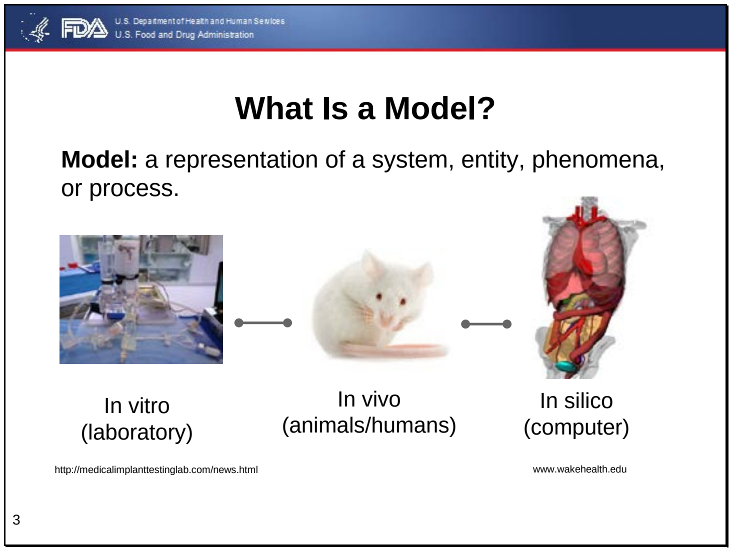

A model is representation of a system, entity, phenomena, or process, which could be a laboratory bench test, animal model (e.g., mouse) or computational model (e.g., of a human organ system).

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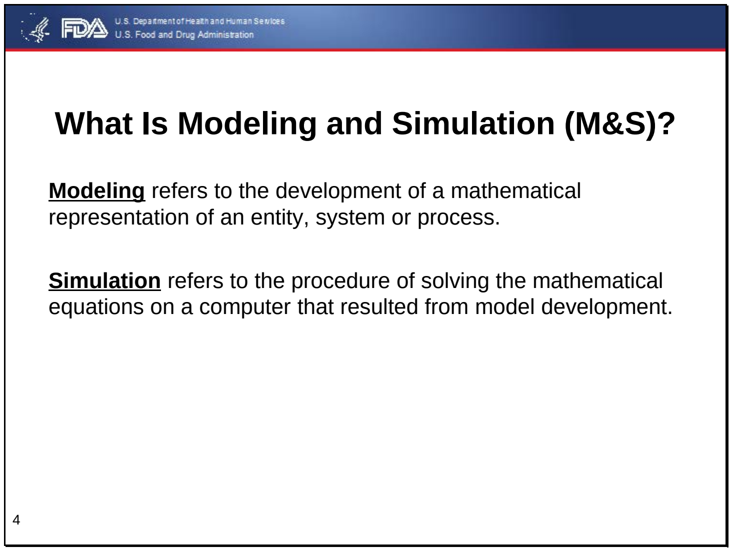

For CDRH, we refer to modeling as the development of a mathematical representation of an entity, system or process and simulation refers to the procedure of solving the mathematical equations on a computer that resulted from model development.

> Modeling and simulation enables us to perform investigations where experimentation does not exist, or is costly or unethical.

>> It can give us higher confidence in medical products, especially if they're thoroughly evaluated on the computer because we can perform (in theory) an infinite number of simulations.

>> It can reduce our reliance on animal models and human data, and reduce costs and speed innovation. These benefits will enable M&S to revolutionize medicine the way it has other fields.

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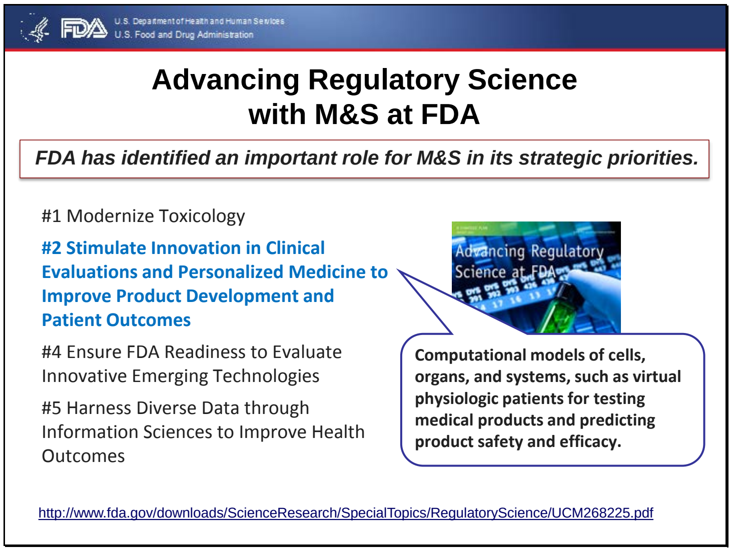

In 2012, FDA published a report on Advancing Regulatory Science and note that M&S can play an important role in 4 of its 8 strategic priorities. One in particular: *Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes*, would involve the development of Computational models of cells, organs, and systems, such as virtual physiologic patients, to better predict product safety and efficacy and performance of medical products.

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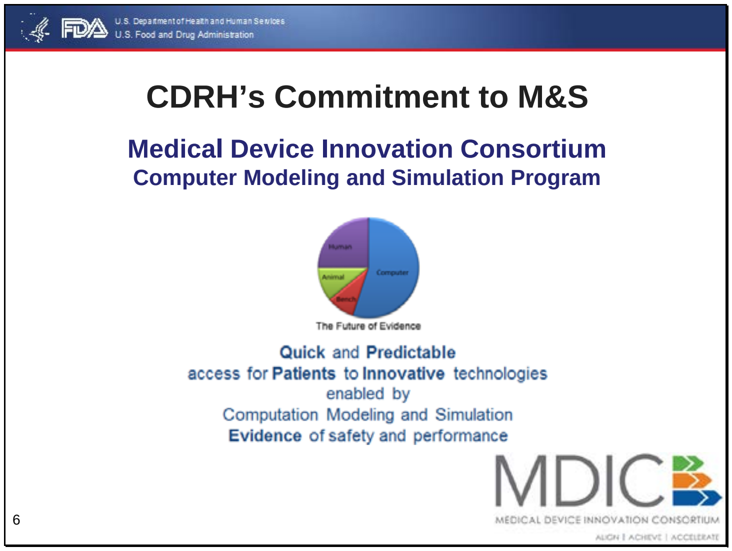

CDRH maintains its commitment to M&S; one important initiative is the public private partnership that CDRH helped to establish in 2012, the Medical Device Innovation Consortium (MDIC). One of the four program areas is computer modeling and simulation. The vision is “quick and predictable access of innovative technologies to patients enabled by M&S.”

There are seven priority areas of active research:
1. Simulation of the heart and vasculature
2. Orthopedics
3. Blood damage, hemolysis and thrombosis
4. Neurostimulation
5. Magnetic resonance-induced heating
6. Libraries for publicly sharing models, inputs, and validation data
7. Combining simulations and experiments to inform clinical trials

The last area of research is of particular importance because it sets the stage for many of the other areas to have an active role in augmenting the evaluation of medical devices and thus meeting FDA’s strategic goals.

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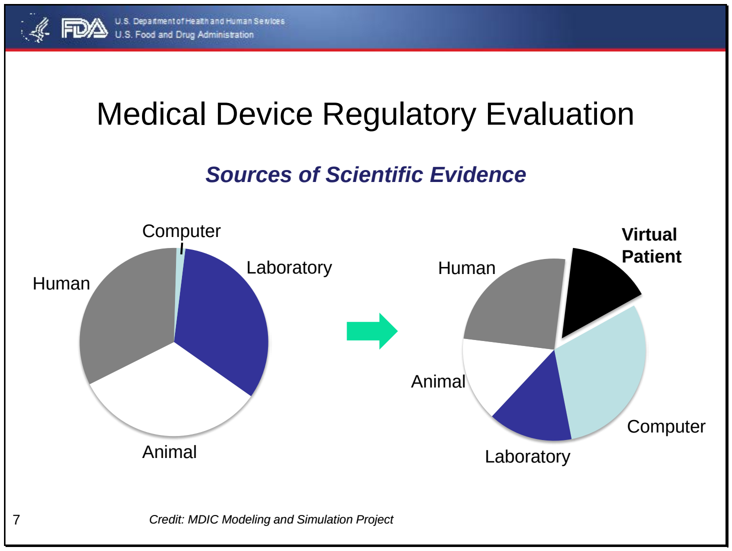

The current paradigm of medical device evaluation involves the review of scientific evidence from four models: animal data, laboratory data (or bench tests), human data (clinical trials) and data from computational modeling (albeit little). We want the future to include more computational modeling; but we don't necessarily need "more" data, just less reliance on animal and human data with the greater influence of data from virtual patients.

The first pie chart shows the current level of evidence as relying mostly on data from human, laboratory and animal models. The second shows the future of evidence of data from animal, computer, bench, and human testing (e.g., clinical trials), where the biggest piece of the pie is computer simulation, including a virtual patient.

A Few Examples

- Virtual Family Models
- Virtual Patient Model
  - Clinical Trials Augmented by Simulation and Bench Testing
- Virtual Head Model
- Virtual Heart Models
  - Electrocardiogram Signals
  - Arrhythmias: Cell to Whole Heart

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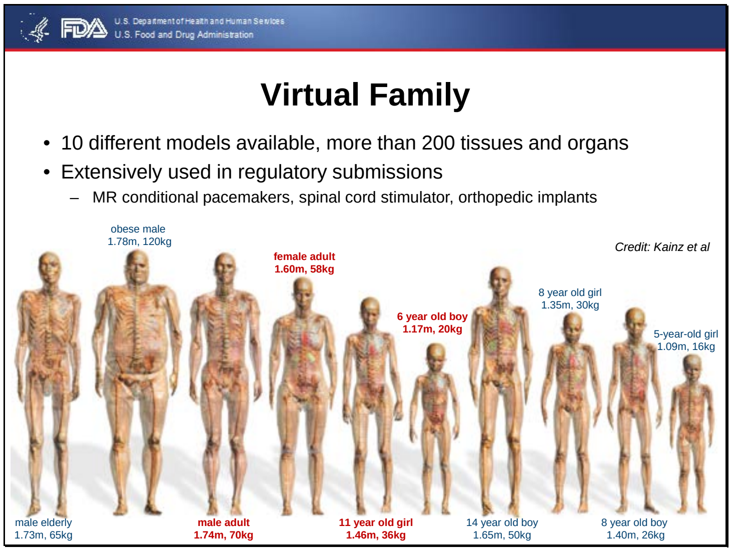

The virtual family, which started as a family of four when it was released in 2008, has grown into the virtual population. It is used routinely in medical device submissions (130 to date) to investigate the amount of energy absorption in patients who undergo magnetic resonance imaging.

For example, when a new MRI machine is developed, it is crucial for the company to understand how the electric and magnetic fields will affect a patient receiving the MRI, especially if they have an implant (such as pacemakers, spinal cord stimulator, orthopedic implants). An MRI costs around $1,000/patient, as compared to running one simulation… Companies will run thousands of simulations to evaluate the energy absorption because they have the ability to vary different parameters with respect to the configuration of the medical device implanted in the body, the MRI coil, the patient's position and anatomical characteristics, etc. As for clinical data, we can realistically capture data from say a 300 patients in a trial. But we can run thousands of simulations by making small variations to capture the appropriate and relevant variations, something that is not realistically possible with a clinical trial.

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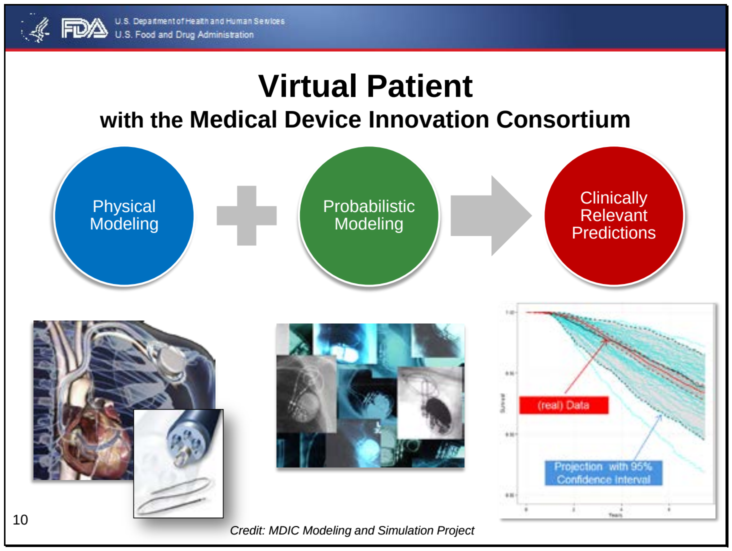

The virtual patient is the concept of taking a physical engineering model, say of a pacemaker lead (the component that attaches to the pacemaker and sends the electrical stimulus to the heart) and applying probabilistic methods to account for patient activity, patient variability in size, variations in manufacturing due to tolerances, et cetera, and performing thousands of simulations to predict the survival rate of the lead (meaning how long it will last without a fracture because a fracture prohibits the necessary electrical signal from getting to the heart). The data from the virtual patient model is then used as “prior knowledge” for designing an adaptive clinical trial where the clinical endpoint for lead fracture is evaluated with a combination of the data from the real patients AND virtual patients, albeit much less. The MDIC is developing the paradigm and Bayesian methods needed to augment a clinical trial with a virtual patient, thereby streamlining the clinical evaluation of medical products and reducing costs. The images show a pacemaker and the lead in the heart, X-ray images of different pacemaker configurations, and the Kaplan-Meier survival curves, both from real data and computational models.

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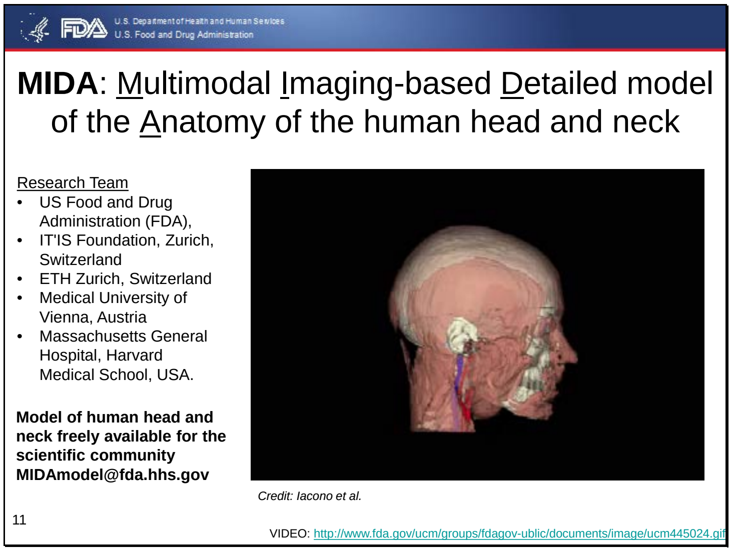

The virtual head, or MIDA, is the result of an FDA-lead international collaboration. The group has created the most detailed high resolution computational model of the human head. It includes more than 200 structures. This effort complements the virtual family because it is a more functional model in that you can not only evaluate the energy absorption in the head under MRI, but they will be able to study the propagation of the electrical current through the individual structures of the head and their effect to the response of the brain. This is important for evaluating the safety and effectiveness of devices used in the head under MRI, such as deep brain stimulators. We are not capable of easily performing these experiments on patients.

Three months ago the model was made available for public download; more than 30 groups from around the globe have been using the model since. This number is expected to grow.

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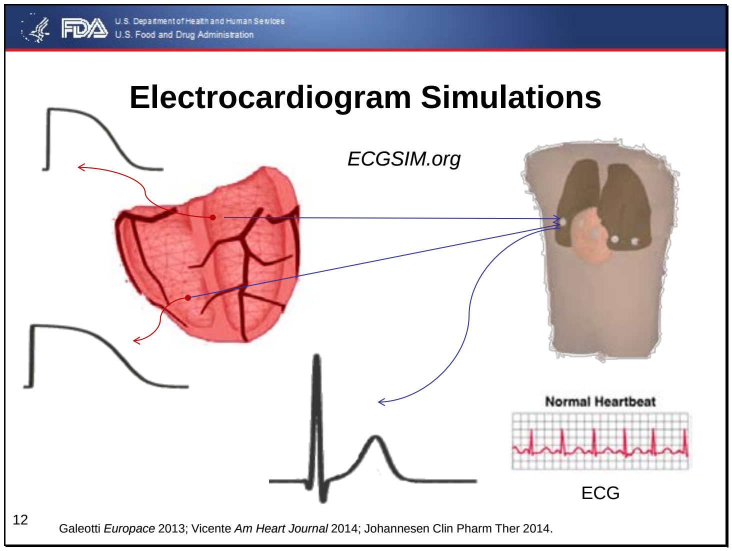

The electrocardiogram (ECG) is a tool to that shows the electrical activity in the heart, and can be used to better understand abnormal heart rhythms, or arrhythmias. However, it's not always possible for clinicians to determine the source of the arrhythmia. One team set out to simulate the ECG and determine criteria that would identify which patients have left ventricular dysfunction (such as an enlarged ventricle or thick walls) and would benefit from cardiac resynchronization therapy (CRT), a special pacemaker to treat left ventricular dysfunction.
Image shows a torso with links to the heart and locations on the surface of the heart where the action potential is modeled. The second image is an ECG of a normal heartbeat.

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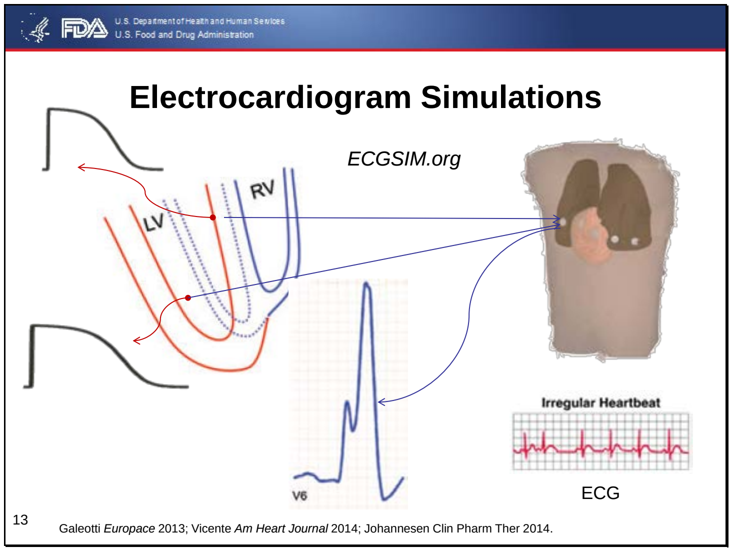

The ECG simulations are created from heart and torso models derived from MRI or CT imaging, and are combined with the electrical activity of the heart, generated by action potentials at different locations on the heart. The researchers were able to make the geometric changes to the heart and see how it affected the ECG, thereby creating criteria for determining, based solely on an ECG from the hospital, which patients would benefit from CRT.

Moreover, they can study sex-specific ECG biomarkers to improve prediction of which patients benefit from pacemakers for heart failure, because women typically do better with CRT.

The image shows a torso with links to the dilated large heart and locations on the surface of the heart where the action potential is modified. The second image is an ECG of a irregular heartbeat.

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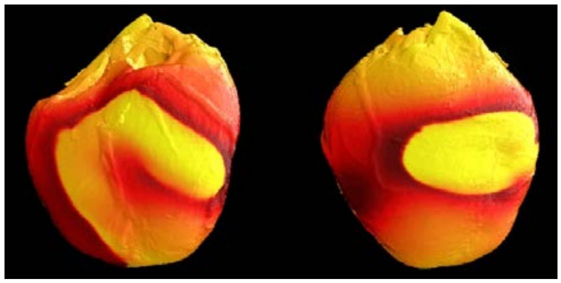
Electrical Arrhythmias



YouTube video and more information: http://tinyurl.com/VFsim

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Credit: Gray & Pathmanathan

A duo of researchers at CDRH are developing complex models of the hearts, developed from the cardiac cell, including the details of what happens starting at the ion channels, to simulate electrical activity across the whole heart. One researcher is making great contributions to the field by linking cardiac cell models to whole organ models. The other is working alongside him to help determine what is needed to establish the credibility (the belief in the prediction of the computational model). This includes leverage methods of verification and validation. Verification asks, are you solving the mathematical equations correctly? Validation asks, are you solving the right equations?
In this pursuit, he and I are collaborating to develop a framework to assess model credibility and how much verification and validation is needed to support using a computational model for regulatory decision making. When we are able to demonstrate the validity and direct applicability of these tools, we can foster confidence and broader acceptance. (Image shows arrhythmias across the surface of the heart.)

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Then we'll be able to have less reliance on human models. New medical products are being developed by companies across the globe, and in order for FDA to achieve its mission of bringing innovative therapies to patients first in the world, we need to find a balance of the number of patients necessary to evaluate the experimental therapies, and rely on other scientific data sources, such as computational models.

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CDRH Scientists and Collaborators

- Virtual Heart: Electrocardiograms
  FDA: Loriano Galeotti, Jose Vicente, Lars Johannesen, David G. Strauss
  Collaborators: Peter van Dam
- Virtual Heart: Arrhythmias
  FDA: Richard Gray, Pras Pathmanathan
- Virtual Head
  FDA: Maria Iacono, Leonardo Angelone
  Collaborators: IT'IS Foundation, ETH Zurich, Medical University of Vienna, Massachusetts General Hospital, Harvard School of Medicine
- Virtual Patient
  Medical Device Innovation Consortium
- Virtual Family
  FDA: Wolfgang Kainz
  Collaborators: IT'IS Foundation