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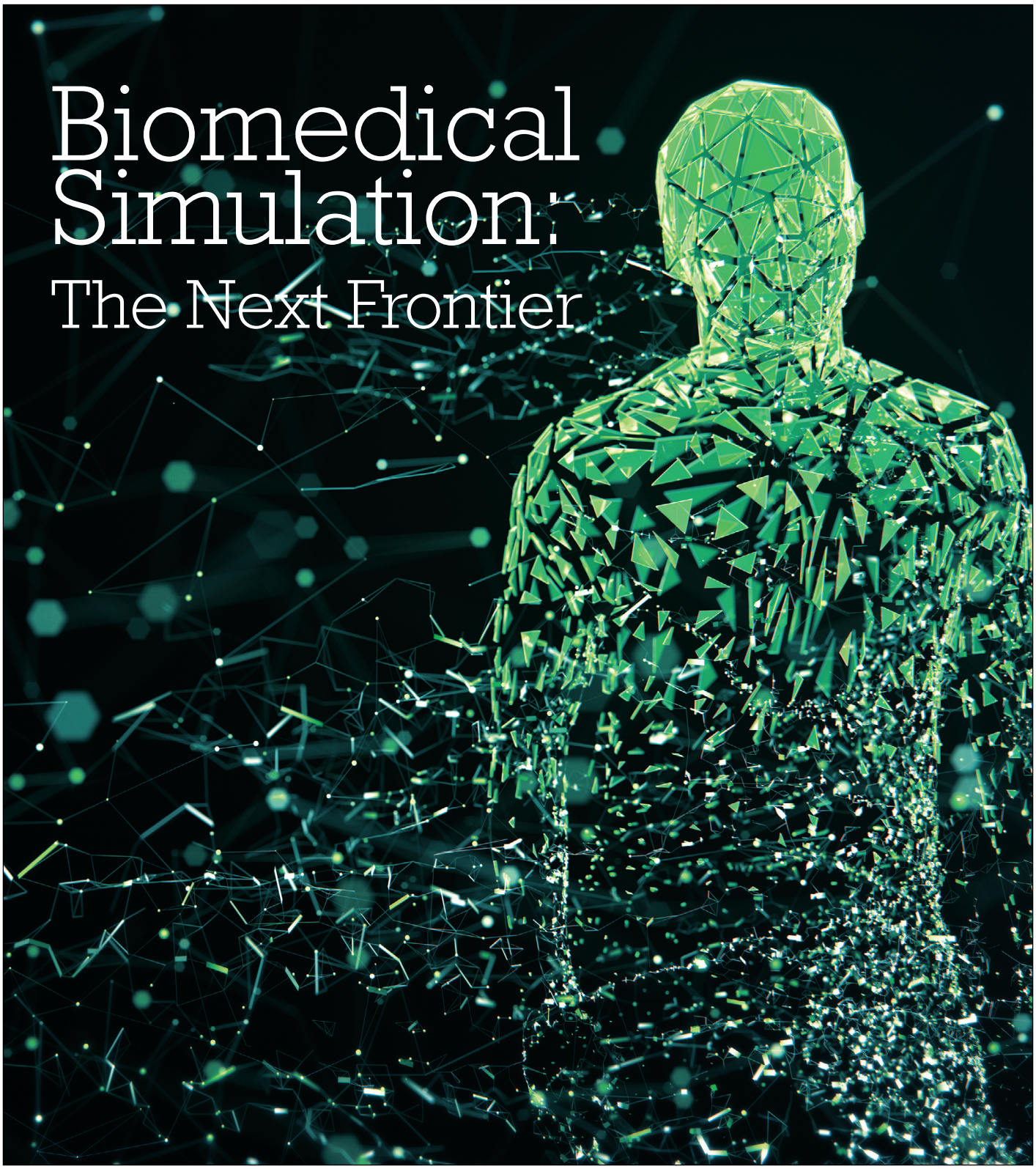

Biomedical Simulation: The Next Frontier

FDA Will Believe it When They See It - Virtually

Steve Levine, Dassault Systèmes

Replacing even a fraction of real patients in clinical trials with virtual patients will be an innovation that will be welcomed by all. In their latest step towards embracing digital technologies, the FDA wants to build a playbook for an in silico clinical trial, which could be a game changer for medical device makers, drug companies, and clinicians.

Let's say you drop your smart phone and it does not break. Can you conclude that it is strong enough to withstand being dropped? Or only that it survived that drop, from that height, landing at that angle, on that surface at that temperature, etc. What if you were taller, or the floor was tile vs wood or it landed on a corner, or the front face? What if you dropped it again? How much would it change if you rounded the corners or wrapped the glass around the edges? How would that change the antenna performance? We know that if we had to rely on physical testing to sort through all of that uncertainty, mobile technology would progress at a fraction of the pace it now does. How do we know that? By simply looking at the comparatively slow pace of advancements in medical technology, which remain reliant on physical testing (i.e. clinical trials) as the standard test before a product comes to market.

The US Food and Drug Administration (FDA) hopes to change that. That commitment is stated clearly in the US FDA, Center for Diagnostic and Radiological Health (CDRH) 2018-2020 Strategic Priorities [1], "We must be pragmatic and balance an appropriate level of uncertainty as one of several factors in our decision making rather than as a determinative factor upon which we draw conclusions so that the desire for certainty is balanced against patient access and unmet clinical needs." They recognize that best practices in modern engineering rely heavily on computational modeling to reveal fundamental performance and reliability information not obtainable in any other way. This insight is essential in avoiding unforeseen complications in real-world practice.

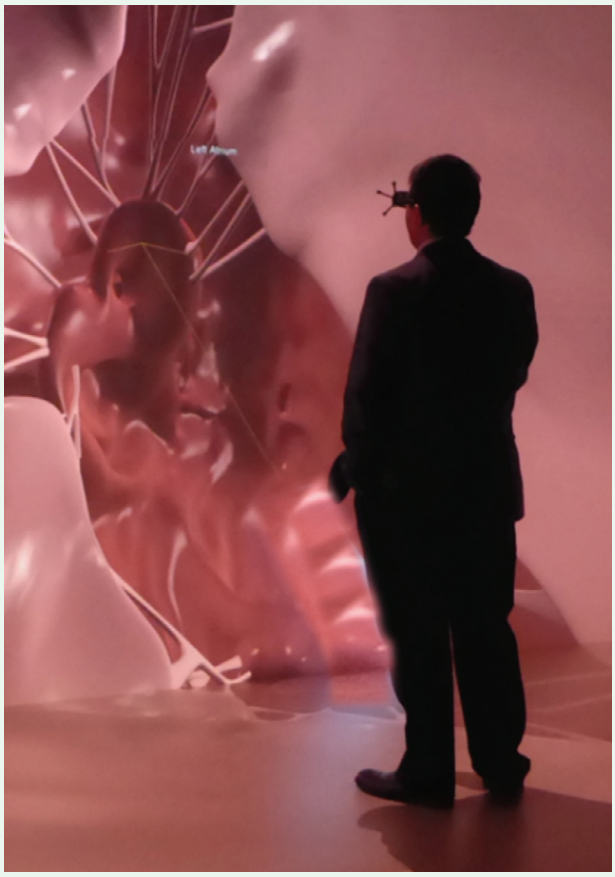

Figure 1: Bakul Patel of the FDA investigating the Living Heart represented in a virtual reality cave

The limitation in applying this for medical treatments is that we don't build humans. We didn't design them; we have no blueprint, bill-of-materials or engineering specification to work from to ensure we can digitally replicate the real world use cases during design and testing to avoid physical testing in clinical trials. Even in the most advanced engineering industries such as automotive and aerospace, most humans are represented by very sophisticated models of very unsophisticated humans, e.g. crash dummies. Good enough for them but not for medical applications, so to achieve their vision, the FDA began to investigate what it would take to build virtual patients.

The Virtual Patient Journey Enters its Second Decade

The development of regulatory grade virtual patients began back in 2009 at an FDA Workshop on Computer Methods for Cardiovascular Devices in Rockville, MD. From that, the ASME Validation & Verification 40 (V&V 40) committee was born with a goal to create a definitive guidance document for the use of modeling and simulation as digital evidence directly supporting regulatory approval. The guidance was finally published in 2018, an important step motivating the industry to invest in simulation and run the experiments necessary to develop and validate their models. However, the unique challenges of simulating the patient population was not the focus until a task force within the Medical Device Innovations Consortium (MDIC) in 2015 took on the challenge of building a virtual patient framework.

The result was a set of tools to statistically approximate a population based on a more limited set of physical tests, where the balance between real and virtual tests were directly dependent on the agreement between them. This meant that if a device company had virtual patient simulations, they now had a way to use them.

The challenge remained to create reliable computational models of patients, and the FDA did not sit back and wait. FDA funded internal projects and collaborations have led to computational models of the head and breast, closed loop systems for control devices and families of models for electromagnetic radiation safety. In what likely their most ambitious effort, they joined the Living Heart Project in 2014, to support development of regulatory grade multipurpose, multiphysics models of the human cardiovascular system. The unique approach of the project was to build a global community of experts across research, industry and clinical practice, aligned on common heart models so all results could be shared, reused and independently validated. The project's crowdsourcing model, led by Dassault Systèmes ensures that the progress made by the community will not only be made available to all members, but also on a commercially supported platform for industry to immediately use to develop new products. The project, now entering its sixth year, has been successful in delivering commercial grade models, now in use in dozens of labs across the world to recreate a range of diseases, test devices and mimic real patients. A unique body of literature is now available and the project includes 130 organizations who continue to build it further (www.3ds.com/heart).

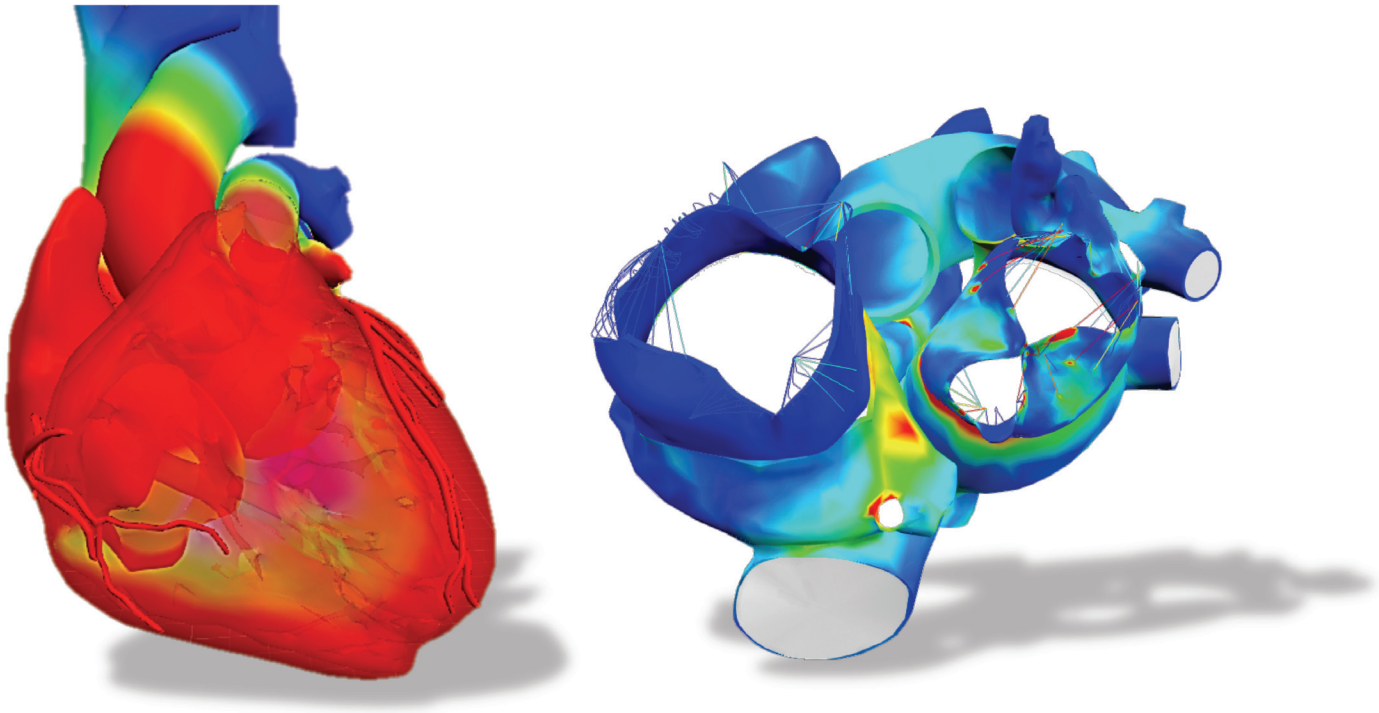

Figure 2: The Living Heart Model showing electrical depolarization field on the left, strain fields resulting from clipping of the mitral valve is on the right

The Clinic Trial Renaissance Begins with ENRICHMENT

With 1) V&V 40 Guidance published, 2) the virtual patient framework in place and 3) the Living Heart Model now available, the stage is set for the next plateau. Could the Living Heart accurately represent a patient population used within the virtual patient framework to test a real medical device and build an entire in silico clinical trial? Would the V&V 40 guidelines be sufficient for the FDA to understand how to interpret the data to speed device approval? These were the type of questions posed by the CDRH director, Dr. Jeff Shuren when he signed a commitment for another five-year collaboration between the FDA and the Living Heart Project. Only this time, as he announced at the MDIC public forum, the FDA would not just observe, but rather take on the challenge of developing an in silico clinical trial digital playbook.

What does this mean? The collaboration will run a first-of-a-kind trial (called ENRICHMENT), that will have two key objectives:

- Demonstrate that digital evidence from 3D simulated virtual patients can be used to significantly reduce the time, cost, and risk with human clinical trial data collection,
- Demonstrate that submissions via a collaborative digital platform can improve the robustness, response time, and transparency of the medical device review process by enabling regulators with rapid access to all of the relevant information and people required to make an informed regulatory decision.

In the ENRICHMENT trial, a novel medical device will be designed, manufactured, physically and virtually tested. Multiphysics computational models of the device in functioning human hearts representing a virtual patient

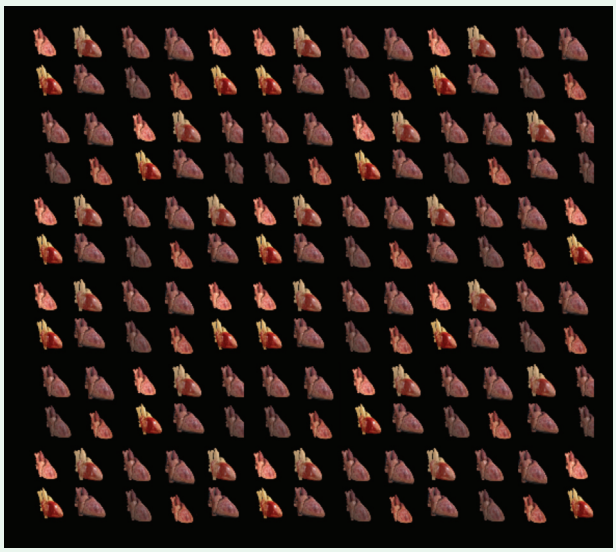

Figure 3: Heart models can be adapted to represent any size, shape or disease condition as part of a virtual library of patents. The statistical virtual patient framework can use this information to extrapolate to the entire population of intended real patients. Machine learning algorithms can process the information to identify valuable insights such as risk factors, side effects, and lifetime prediction

population will provide the digital evidence to support a regulatory submission. Assessment of the model credibility will be in accordance with the ASME V&V 40 standard. Digital evidence from simulations will be combined with physical evidence from bench tests and real subjects in a mock submission for an Investigational Device Exemption based. A blinded FDA team will review these materials and document their evaluation. The public will receive the results in the form of an in-silico trial playbook describing best practices learned.

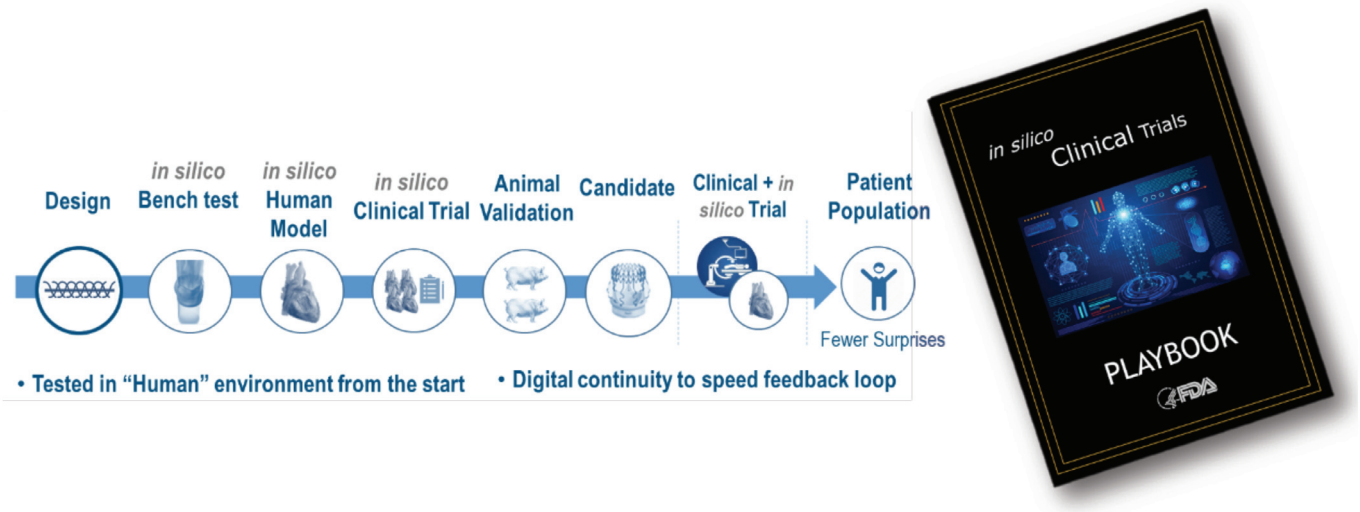

Figure 4: The ENRICHEMENT trial will capture the details of this new kind of trial into a playbook for medical device companies to follow

Figure 5: Members of the Living Heart Project meet annually to share progress and evaluate advances. In July 2019 the project meeting included a series of planning workshops focussed on driving the direction of the ENRICHMENT trial

Even in Science, It Takes a Village

The Living Heart Project community continues to advance the quality and breadth of human heart models, provide critical reviews, and deliver insightful performance data. Through the ENRICHMENT trial, the last decade of advancements in regulatory simulation will come together to deliver a clinical trial that could open the doors to a new world of innovation efficiency. Imagine you could run a clinic trial in the first week of a device design? Imagine you could test it immediately on patients representing every size, shape, age, gender, ethnic and genomic community. Patient populations based on robust, validated human models will not only address reliability of device treatment, but also reveal detail on how it works, when it will fail, why it will fail and what likely side effects will appear in time. The future for these patients is very bright. They will volunteer time and time again to test new devices and get better at it each time.

With virtual clinical trials, the FDA could be your partner in safety to ensure risks are identified early, allowing R&D and ultimately clinical validation to focus on those risks at a fraction of the effort to recreate the entire patient population and risk factors.

Further, imagine speeding clinical adoption by transforming the virtual patients into training materials to demonstrate how and when to use the new device and ultimately to match the right device to each patient by matching to a matching the virtual patient first.

The world of medical innovation is changing, there is a renaissance happening in clinical trials and we have an unlikely hero to thank. ■

References

[1] U.S. Food and Drug Administration, "2018-2020 Strategic Priorities- Center for Devices and Radiological Health," 1st January 2018. [Online]. Available: https://www.fda.gov/media/110478/download. [Accessed 24 September 2019].

Steve Levine is Sr. Director of Life Science and the Executive Director of the Living Heart Project at Dassault Systèmes. Steve is responsible for leading the DS strategy for digital healthcare, including the 3DEXPERIENCE Twin, which uses advanced AI and VR to create functioning 3D human models. He is also responsible for incubating a startup community within the 3DEXPERIENCE Labs at DS and creating a marketplace of digital healthcare services.

Dr. Levine holds a Ph.D. in Materials Science from Rutgers University and was elected as a Fellow in the American Institute for Medical and Biological Engineering (AIMBE). He also has nearly 30 years of experience driving innovation in technology, beginning his career in health tech at the San Diego based startup Biosym that went public as Accelrys in 2004 and acquired by Dassault Systèmes in 2014.

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