The emerging regulatory landscape for *in silico* methods in medical devices

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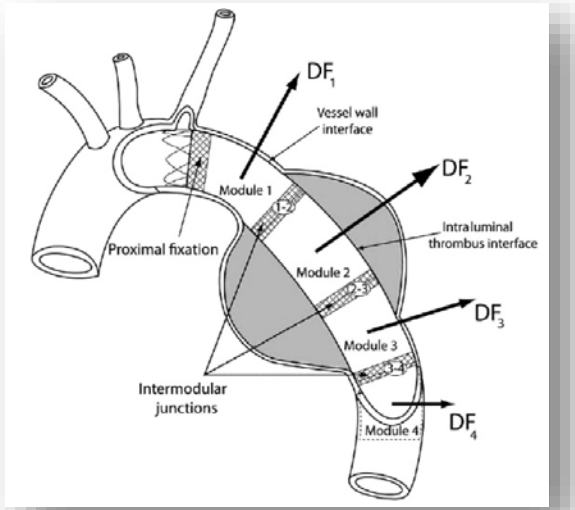
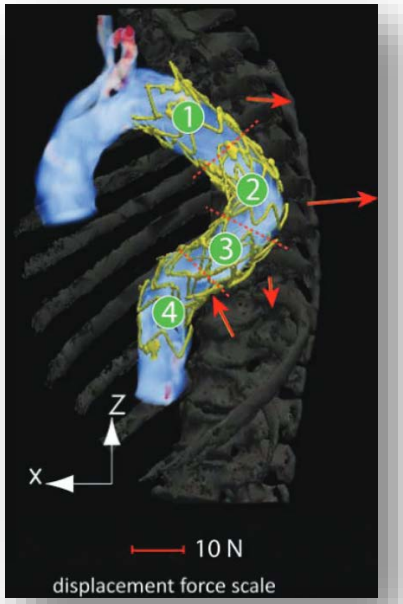
VPH2018 Conference
6 September 2018

VPH Institute
Building the Virtual Physiological Human

Let's start with an example to discuss *Context of Use*





◆ISES ENDOVASCULAR RESEARCH COMPETITION, FIRST PLACE◆

Computational Analysis of Stresses Acting on Intermodular Junctions in Thoracic Aortic Endografts

Anamika Prasad, PhD[1]; Lillian K. To, MSc[2]; Madhu L. Gorrepati, MD[3]; Christopher K. Zarins, MD[3]; and C. Alberto Figueroa, PhD[1]

Departments of [1]Bioengineering, [2]Biology, and [3]Surgery, Stanford University, Stanford, California, USA.

This reference serves as a visual example to illustrate *context of use*.

Four different *contexts of use* for the same simulation platform.

1. Simulation is used to evaluate the performance of the stent graft for a medical device marketing application

   E.g., compute spring stresses and strains

2. Simulation is used to conduct an *in silico* clinical trial to augment endpoint to assess freedom from fracture

   Harness the virtual patient model approach

3. Simulation platform is used to evaluate different endovascular grafts for patient-specific surgical planning

   Software as a medical device

4. Simulation platform is available as a tool for companies for design V&V and evaluation

   Medical device development tool

Opportunities for Tool Developers

FDA Development Tool Programs: scientifically validated tools that aid development and regulatory evaluation

Drug Development Tools (DDT)

The ***context of use*** defines the boundaries within which evidence & justification supports tool use. It should include four key components:

1. Product area (e.g., total hip replacement)
2. Stage of development (e.g., design verification)
3. Specific Role of tool (e.g., predict load limit)
4. Regulatory Evaluation (e.g., performance data for 510(k))

Clinical Outcome Assessments

Biomarker Tests

Nonclinical Assessment Models

Medical Device Development Tools (MDDT)

MDDT: https://www.fda.gov/MedicalDevices/ucm374427.htm

DDT: https://www.fda.gov/downloads/drugs/guidances/ucm230597.pdf

U.S. Food and Drug Administration

2018-2020 STRATEGIC PRIORITIES

Center for Devices and Radiological Health

January 2018

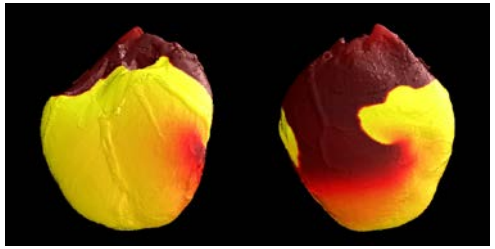
2018-2020 CDRH Strategic Priorities

- Employee Engagement, Opportunity, and Success
- Simplicity
- Collaborative Communities

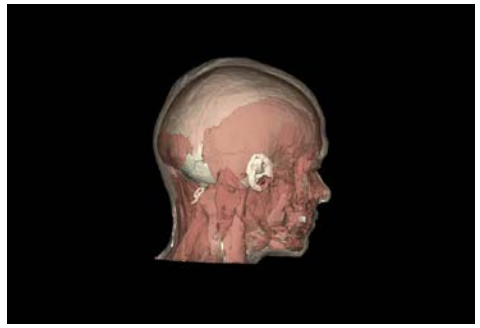
CDRH Regulatory Science Priorities

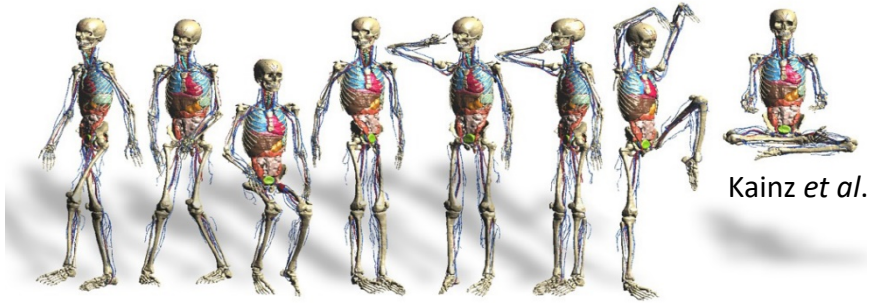
- ***Big Data***
- Biocompatibility
- ***Real-World Evidence***
- Clinical Trial Design
- ***Computational Modeling***
- Infection Control
- Patient Input
- ***Digital Health*** and Cybersecurity
- ***Predicting Clinical Performance "Virtual Patients"***
- Precision Medicine and Biomarkers

Pathmanathan *et al*.



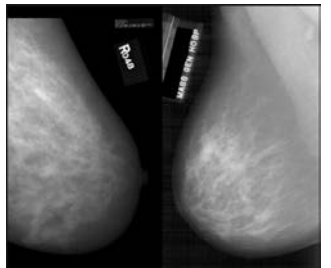
Iacono *et al*.



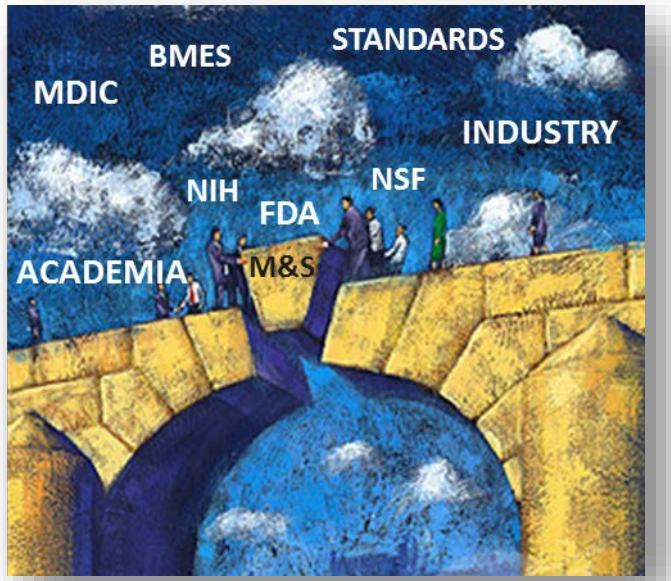


Kainz *et al*.

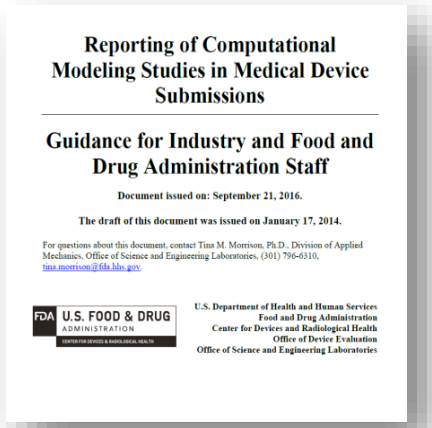
Badano *et al*.



Progress with Simulation over the last 5 years



Regulatory Review of Computational Modeling Community of Practice


Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

The draft of this document was issued on January 17, 2014.

For questions about this document, contact Tina M. Morrison, Ph.D., Division of Applied Mechanics, Office of Science and Engineering Laboratories, (301) 796-6310, tina.morrison@fda.hhs.gov.

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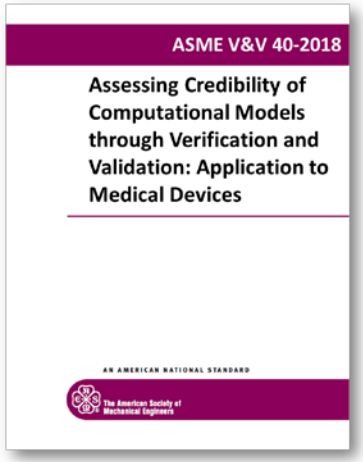
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Science and Engineering Laboratories

Regulatory Guidance



Consensus Standards

Regulatory Science Publications*

2019 Conference

The Role of *Digital Evidence* to Support Personalized Patient Healthcare

*Morrison et al, FMED 2018, 10.3389/fmed.2018.00241

2019 BMES/FDA

FRONTIERS IN MEDICAL DEVICES CONFERENCE

The Role of Digital Evidence to Support Personalized Patient Healthcare

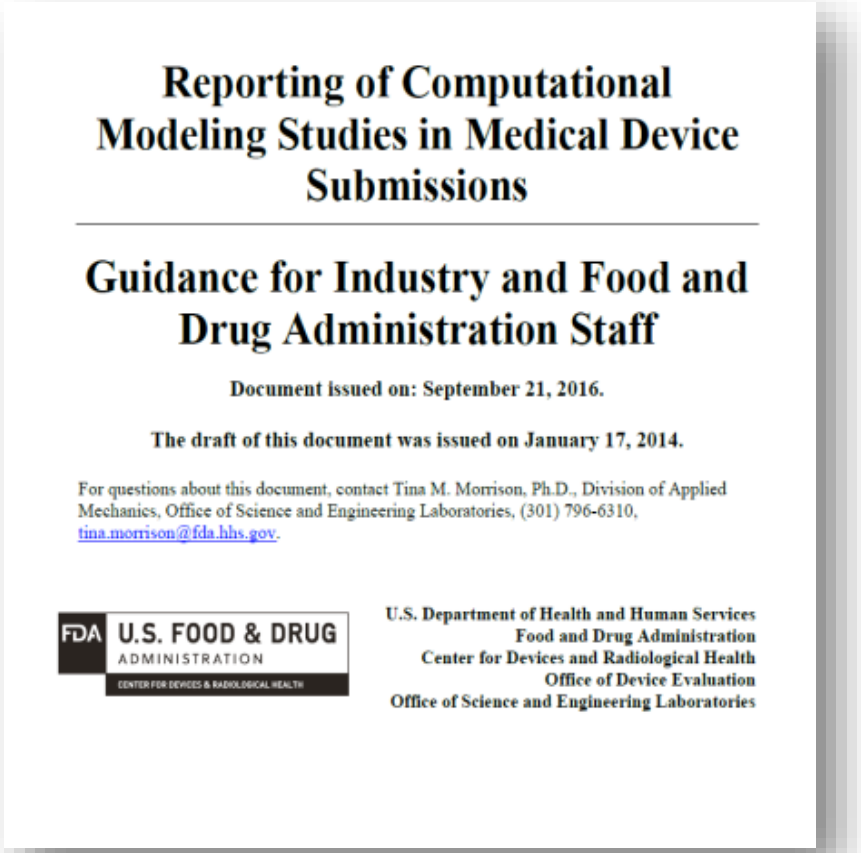
Meeting with FDA, Industry & Academia

MARCH 19-21, 2019 | GREATER WASHINGTON DC AREA

The College Park Marriott Hotel and Conference Center at the University of Maryland

I. FDA Final Guidance

Reporting on Computational Modeling Studies in Medical Device Submissions – September 21, 2016



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U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Science and Engineering Laboratories

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- Introduction
- Scope
- Outline of Computational Modeling Report
  - 15 components
- Glossary
- Five subject matter appendices
  - Fluid Dynamics and Mass Transport
  - Solid Mechanics
  - Electromagnetics and Optics
  - Ultrasound
  - Heat Transfer

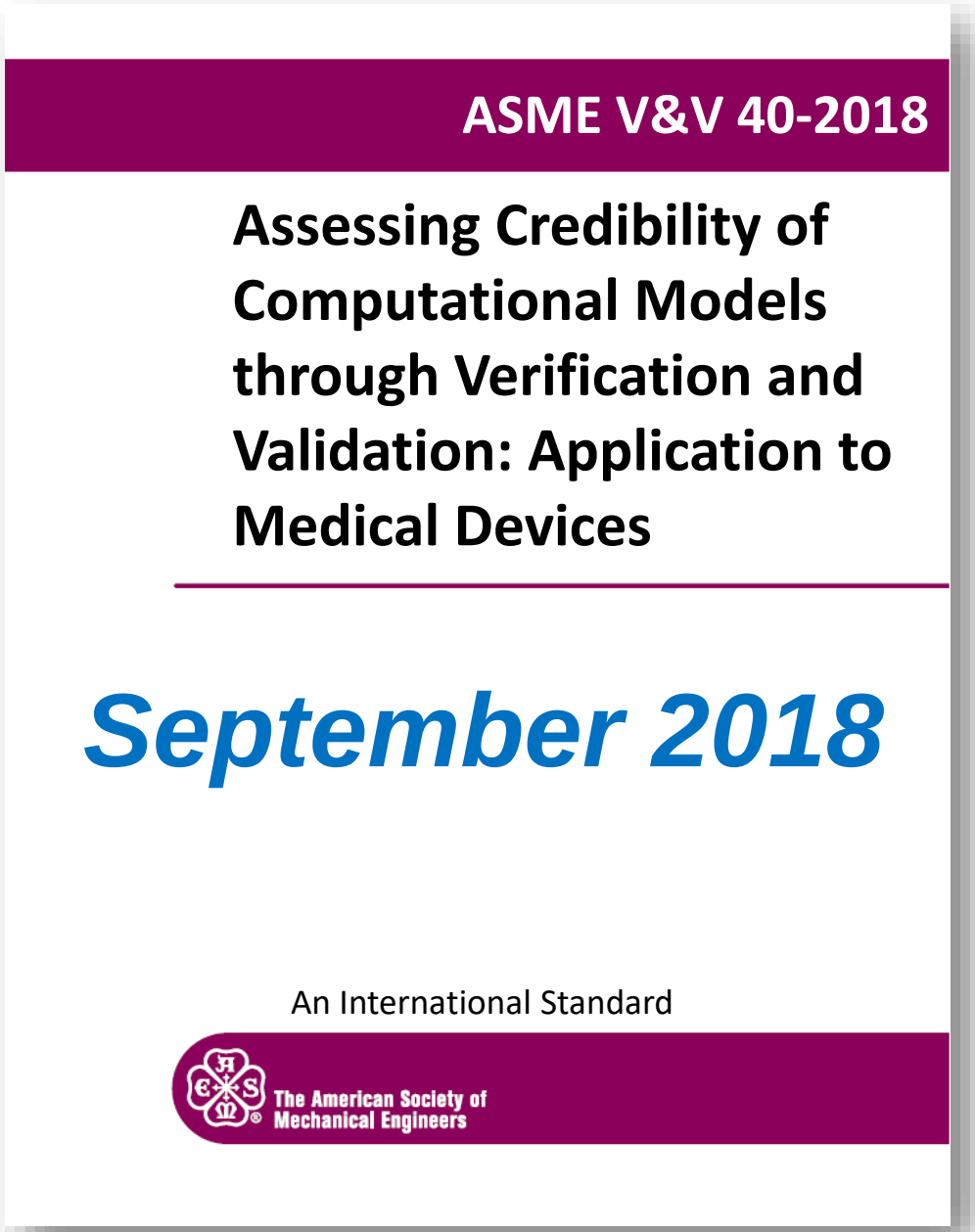
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381813.pdf

II. ASME V&V 40 Standard

Credibility: the trust, obtained through the collection of evidence, in the predictive capability of a computational model for a context of use

- Focus is on ***HOW MUCH*** V&V is necessary to support using a computational model for a context of use.

http://go.asme.org/VnV40Committee



Initiating a Clinical Trial with Simulation and Digital Evidence

FDA Critical Path Project Underway

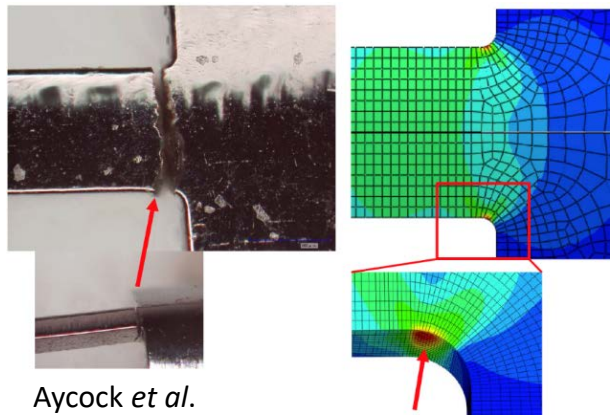
Mock Submission Team:

Industry: four medical device companies and one medical device manufacturer: expert modeler & regulatory affairs from each

FDA: expert modelers, experimentalists and regulatory

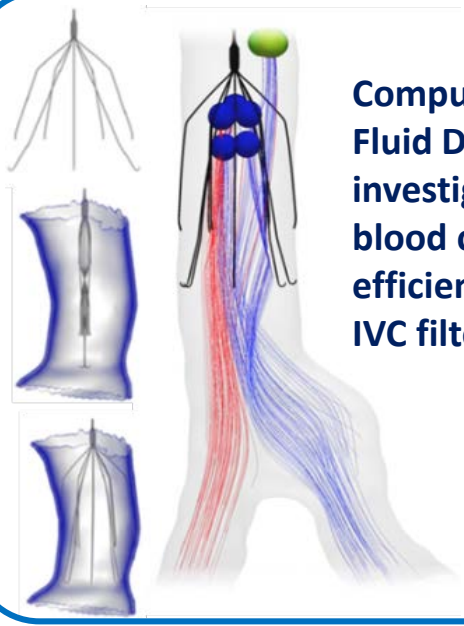
Key Objectives:

1. Generate & demonstrate "regulatory-grade" digital evidence for a mock IDE submission
2. Prepare mock IDE submission using FDA reporting guidance & ASME V&V40 Standard
3. Conduct independent FDA review of mock IDE submission
4. Assess & improve regulatory review process for computational modeling
5. Share content and develop training materials for industry & FDA staff



Aycock *et al.*

Finite Element Analysis to determine the potential for fracture due to fatigue

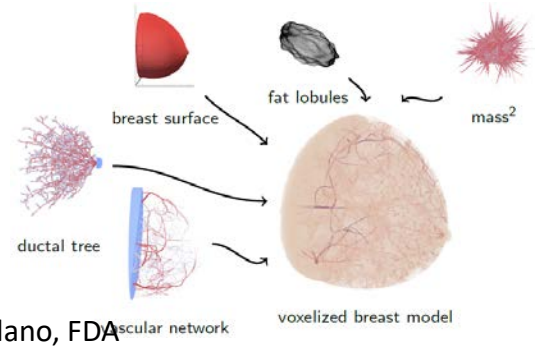


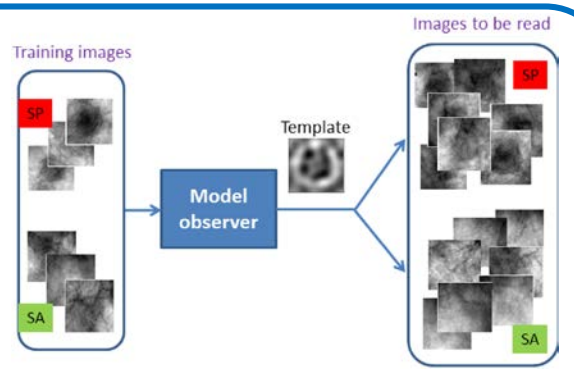
Computational Fluid Dynamics to investigate blood clot trapping efficiency of the IVC filter

Craven *et al.*

3 Examples of *in silico* medicine approaches

1

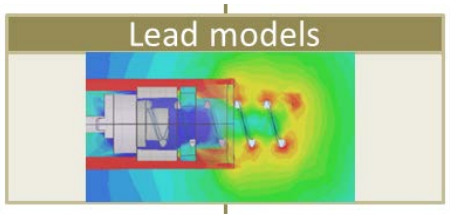


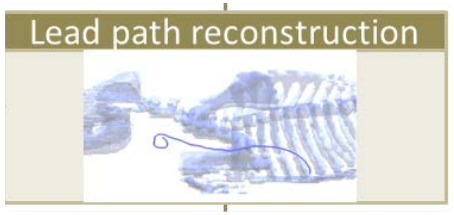


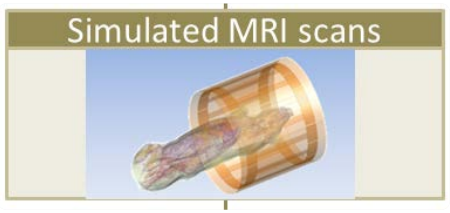
Courtesy Badano, FDA

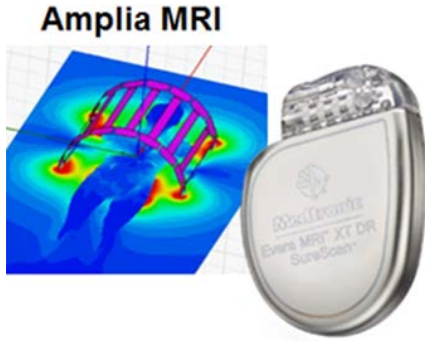
Keywords:
VICTRE

2





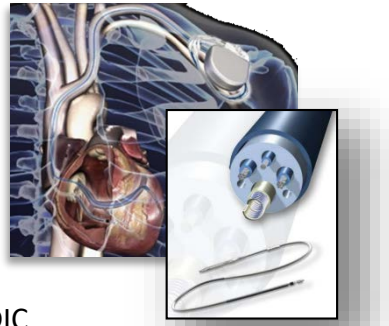


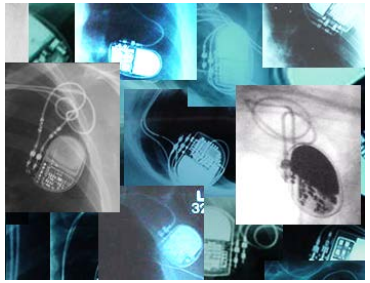


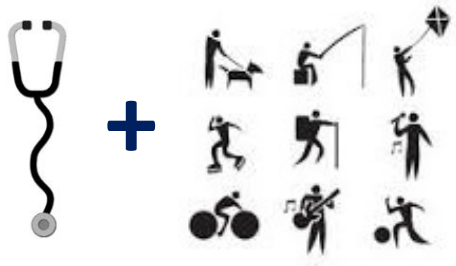
Courtesy Medtronic, Inc.

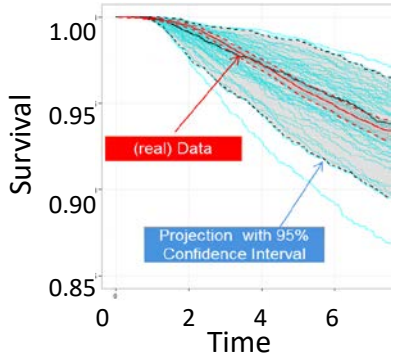
Keywords:
NEJM
FDA viewpoint

3





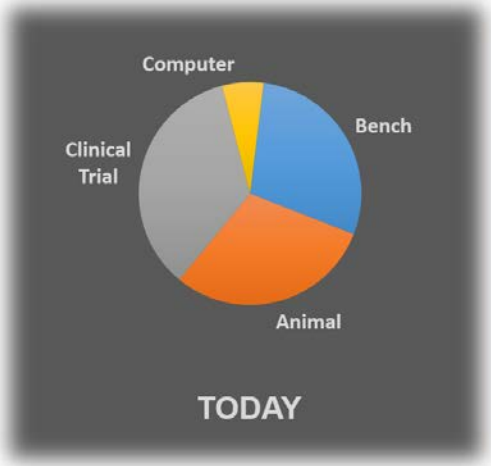


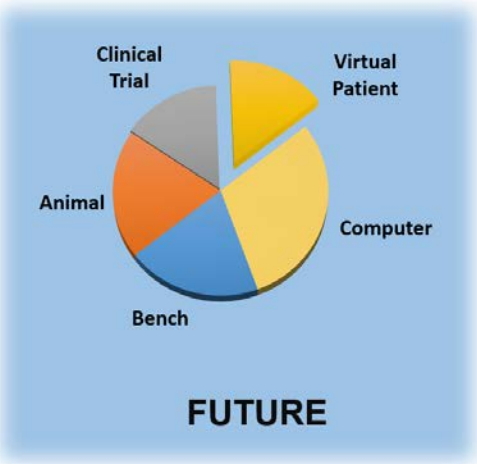


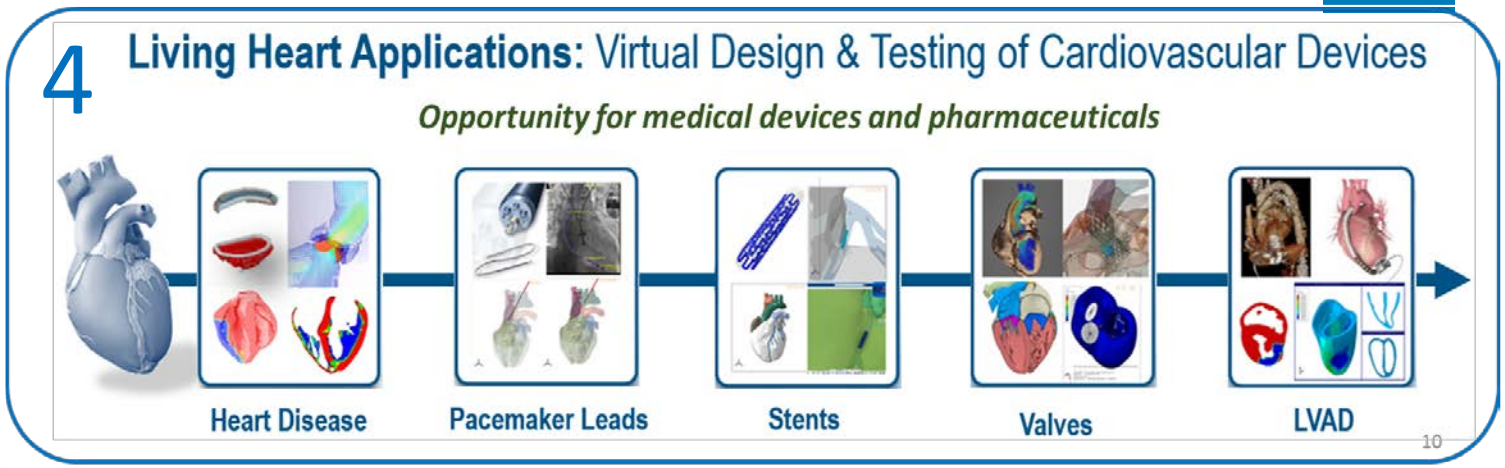
Courtesy MDIC

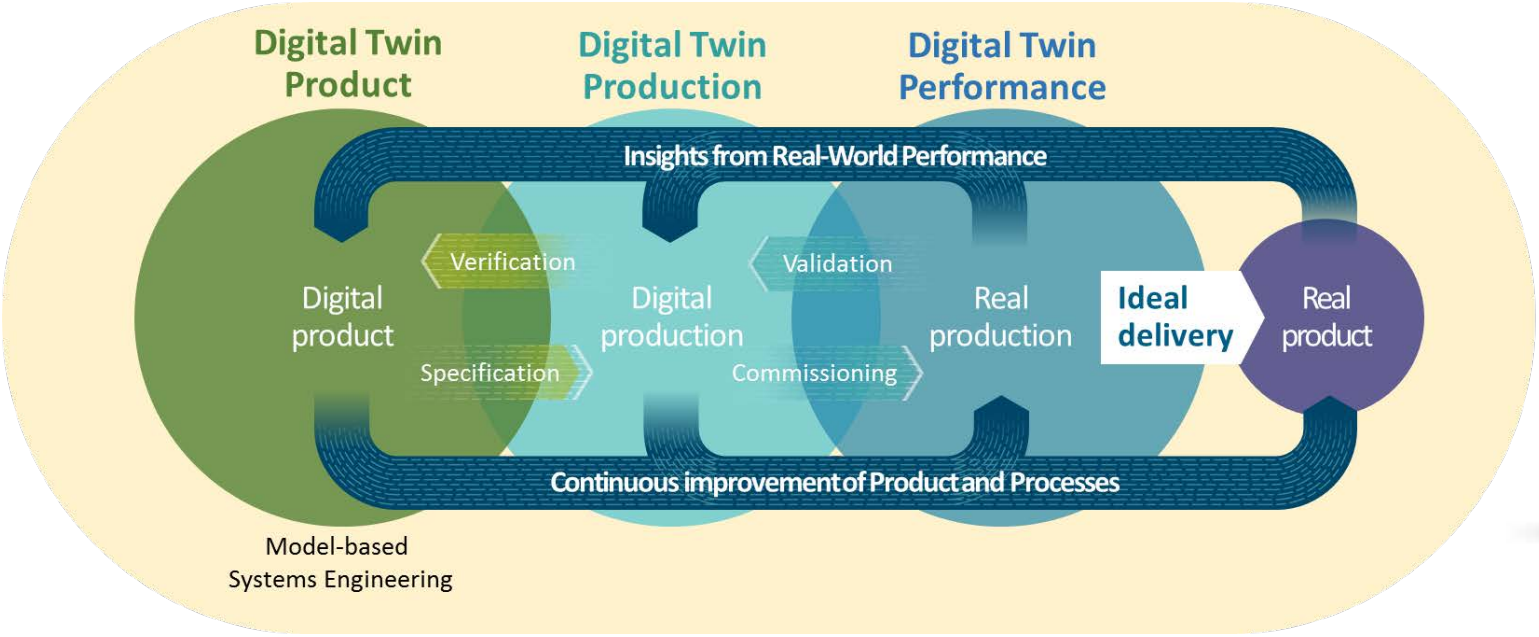
Keywords:
MDIC &
virtual patient

Looking to the next 5 years









DIGITAL HEALTH Pre-Certification

Digital Evidence as External Evidence

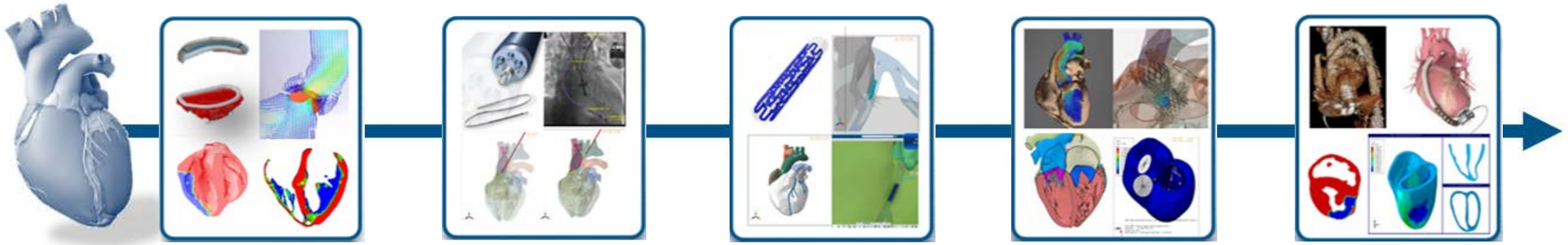
Implementing the Virtual Patient Model with Evidence from Simulations

NEW *c*ollaboration with Dassault Systèmes to develop a digital platform to:

- Use physics-based models with statistical models to demonstrate *virtual patients* from simulation
- Demonstrate the "submission of the future"
  - Develop a platform to incorporate digital, clinical and real-world evidence which supports product-lifecycle-management and continuous improvement
  - Create a new "review experience"

Living Heart Applications: Virtual Design & Testing of Cardiovascular Devices

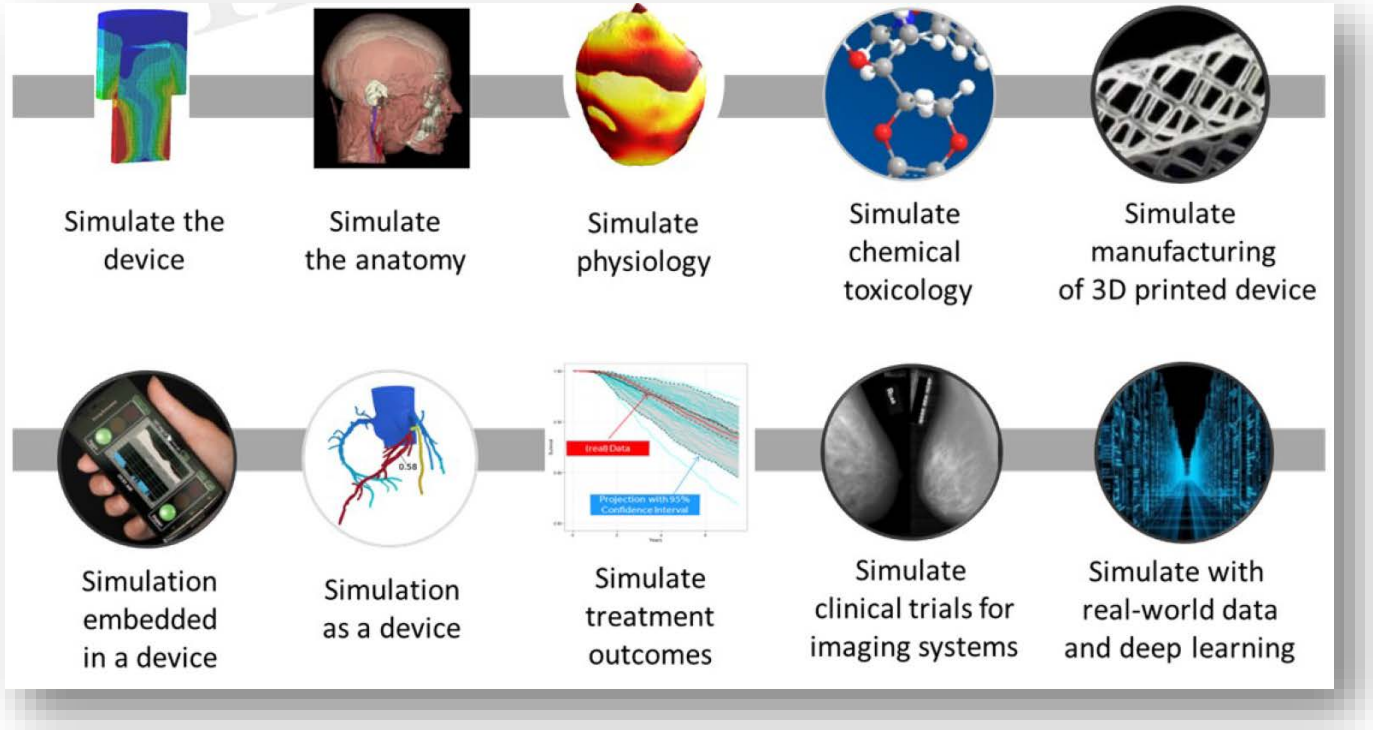
Opportunity for medical devices and pharmaceuticals



Additional Recent Materials

- Slides and link to recording of FDA Grand Rounds – August 9, 2018
  - Success stories with modeling & simulation across FDA
  - Details on in silico clinical trials

    https://doi.org/10.6084/m9.figshare.7028450.v1
- New manuscript on Simulation Opportunities for Medical Devices



Morrison et al., **Advancing Regulatory Science with Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories**, Frontiers in Medicine, *in* press, 2018

doi: 10.3389/fmed.2018.00241

Summary

- **Context of Use** matters and it's important for navigating the complex regulatory landscape
- *In silico* acceptance at FDA has grown in the last 5 years
- There's more to do but we're excited about the upcoming projects and progress
- Stay tuned for a changing medical device ecosystem, one that harnesses sophisticated tools to transform the regulatory landscape.

Questions/Comments:

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U.S. FOOD & DRUG ADMINISTRATION & Devices

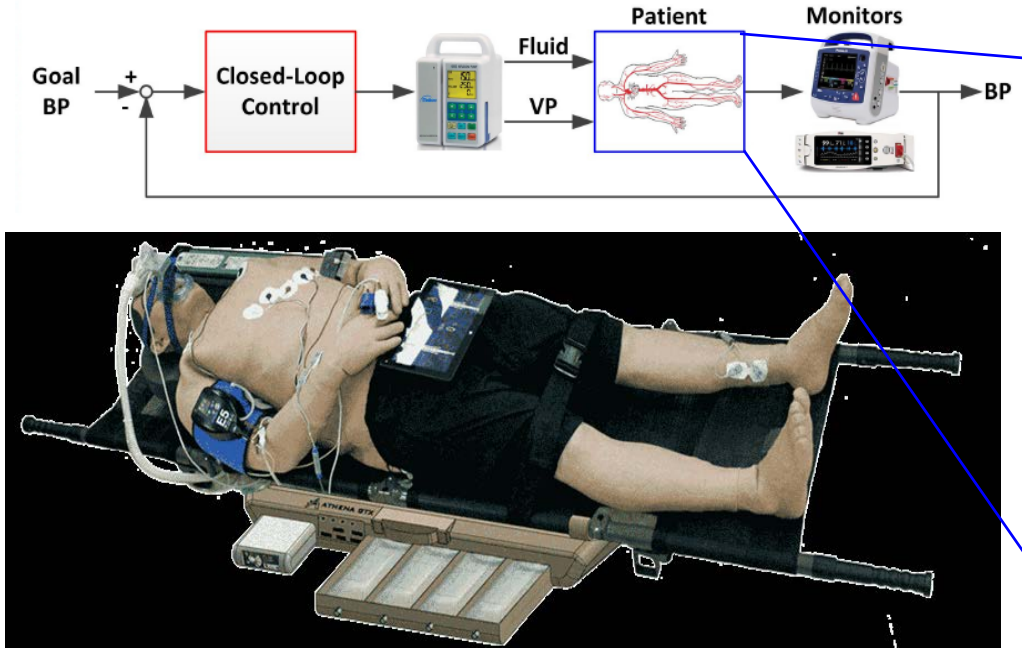
figshare

All content available: **https://figshare.com/authors/Tina_Morrison/556289**

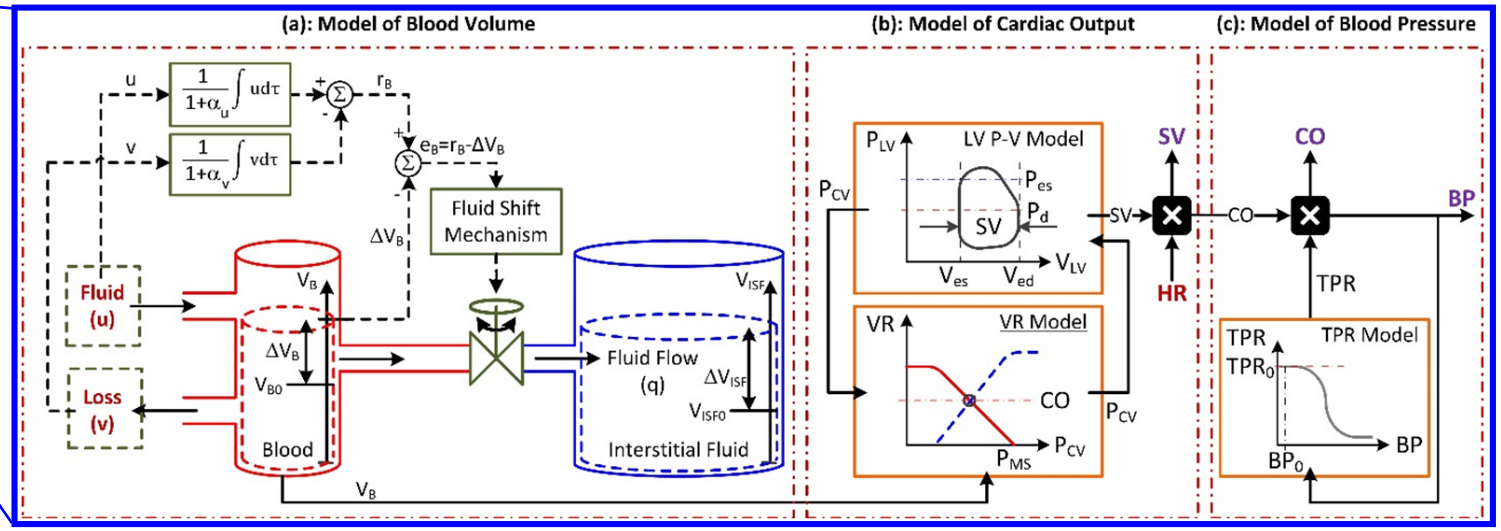
Physiological Closed-loop Control (PCLC) Medical Devices

Develop & Validate Computational Patient Model

- In silico methods for the design and evaluation of PCLC devices, a validated patient model for a specific context of use is needed.
  - Physiological, mechanistic-based model with ASME V&V40 approach
- Harness model-based engineering for *complete* in silico evaluation



doi: 10.1115/1.40338330



BV – blood volume, HR – Heart rate, CO – Cardiac output, LV – Left ventricle, SV – Stroke volume, BP – blood pressure

 Credit: Parvinian et al