# Simulation in the Life Sciences

## *A Look Ahead*

Mechanics = study of forces acting on bodies, including our own…

# 3DEXPERIENCE for Digital Healthcare


**Digital Inputs & Data Accumulation**

**Virtual Trials and Clinical Procedures**

**Translation to Real World Healthcare**

# Simulation in the Life Sciences


**MEDICAL DEVICES**

Well established usage of simulation, but a lot more can be done

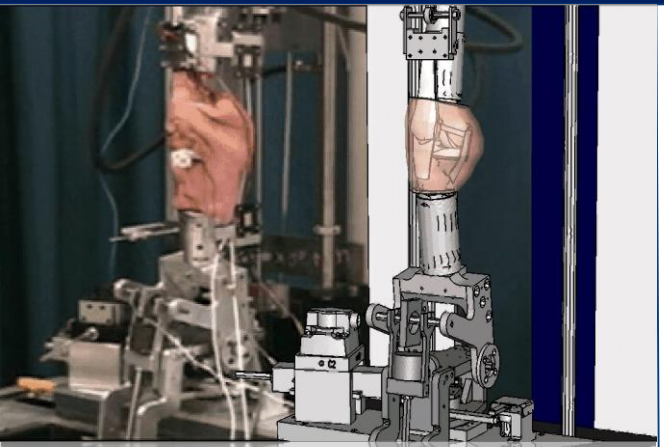
**PHARMA & BIOTECH**

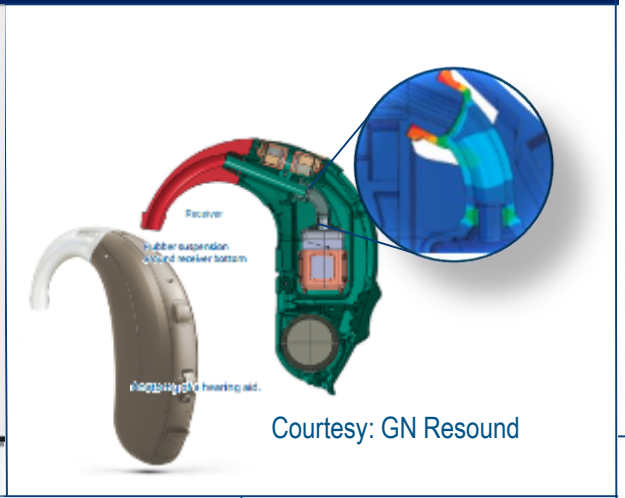
Simulation is widely used, mostly in biochemistry

**PATIENT CARE**

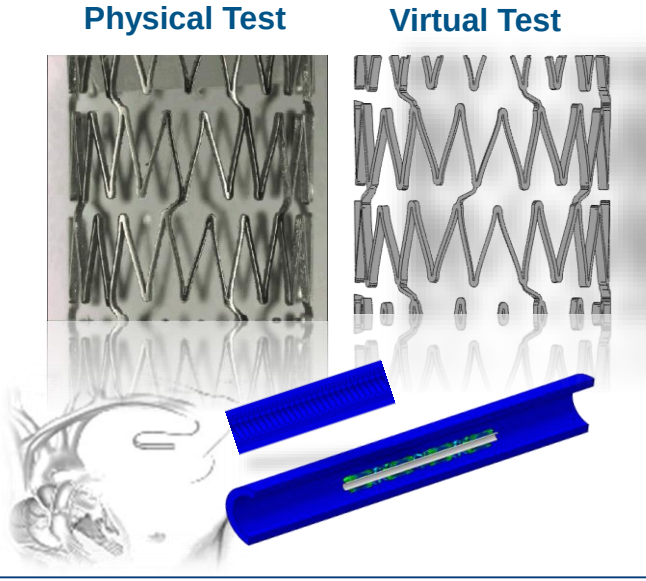
Potential impact is vast, but simulation usage is still in its infancy

# Virtual Testing of Medical Devices

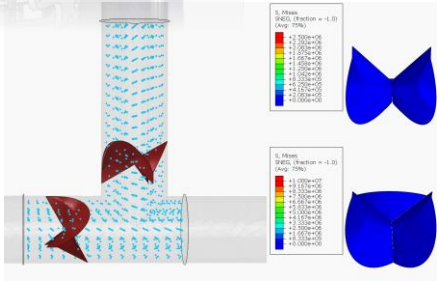


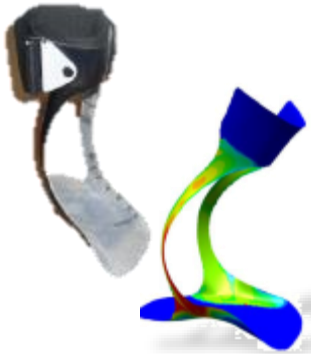


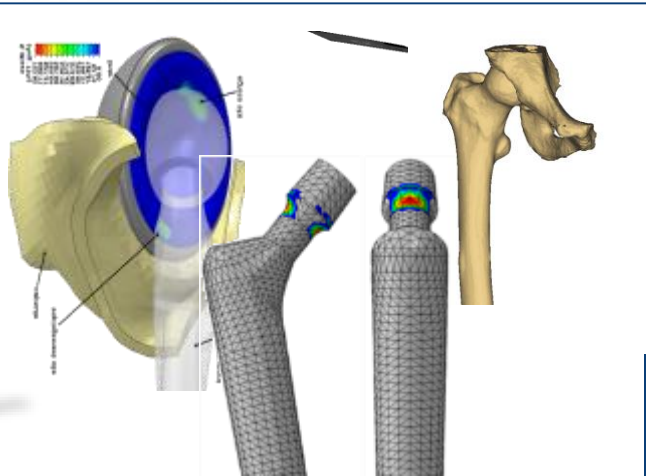

Courtesy: GN Resound



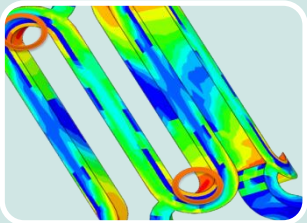

Courtesy: UNILIFE

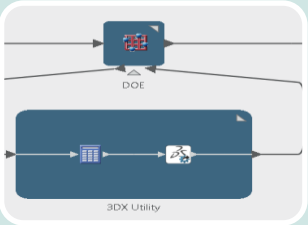


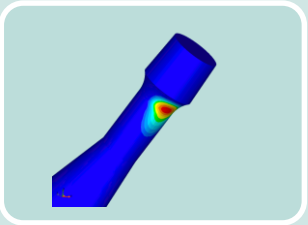




# SIMULIA Solutions for Medical Devices





**Multiphysics**
- Structures
- Fluids
- Electromagnetics
- Multibody Dynamics
- Systems Modeling

**Durability and Fatigue Life**

**Process Automation, Design Studies, and Parametric Optimization**

**Non-parametric Optimization**

**Virtual Human Modeling**

Simulation data management

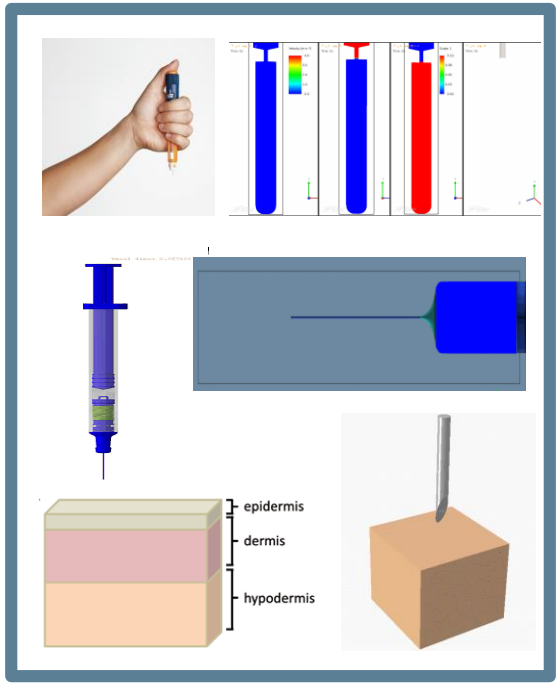
**3DEXPERIENCE Platform**

Collaboration

# Product-Life Interaction Simulation

***Biomechanics of Implants***


***Electromagnetic Safety***




***Drug Delivery***

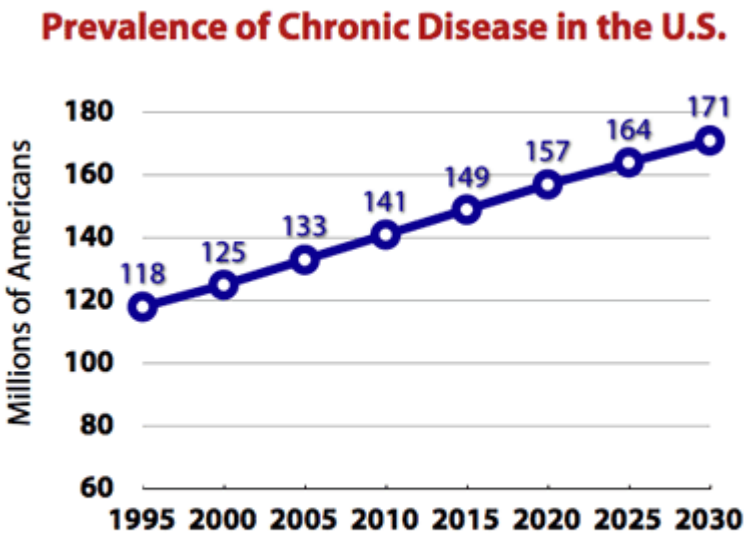
# Can we Simulate a Patient?

- Can we create virtual patients to design and test new medical devices?

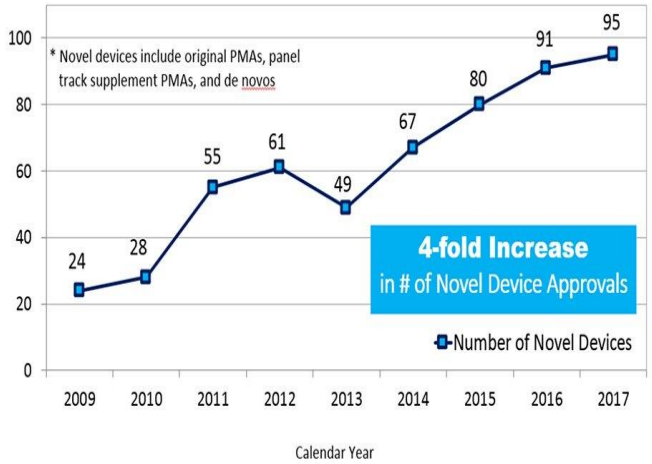

- Can we create virtual patients to test and target new drugs?


- Can we create virtual patients to guide clinical procedures?

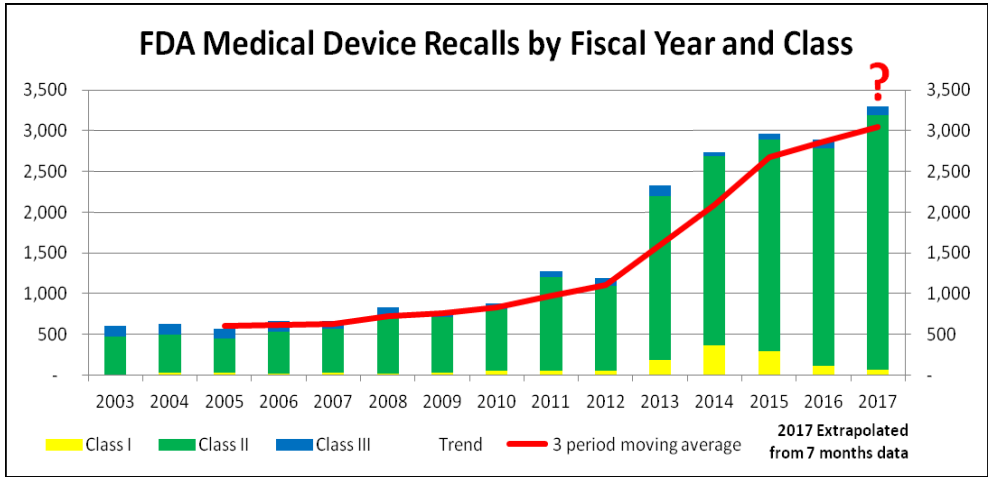
# Do we Need Virtual Patients to Test new Medical Devices?

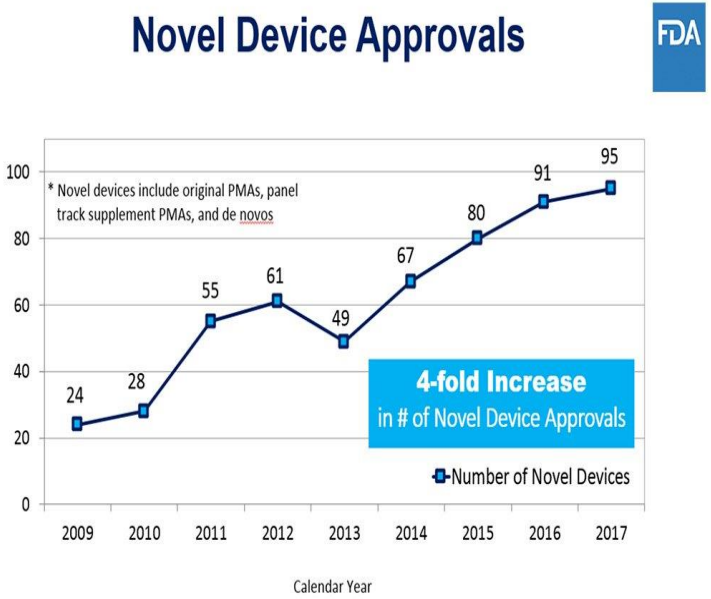



Source: Wu, Shin-Yi *et al.* 2000. Projection of Chronic Illness Prevalence and Cost Inflation. RAND Corporation.



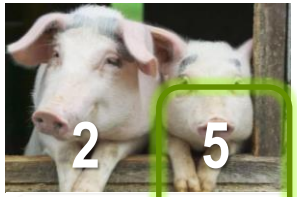
# Do we Need Virtual Patients to Test new Medical Devices?




**Device failures are on the rise, yet FDA is under pressure to lower the time/cost barriers to approval**

# Potential of Simulation - FDA Assessment of Sources of Evidence



| 11 Factors | 2 Animal | 5 Computer | 1 Bench | 4 Computer | 5 Clinical Trial | 6 Computer |
|---|---|---|---|---|---|---|
| Predict clinical outcomes relevant to patients | | | | ✓ | ✓ | |
| Predict *in vivo* performance of the device | | | | | ✓ | |
| Predict *in vivo* safety of the device | ✓ | | | | ✓ | |
| Predict performance beyond IFU | | ✓ | | | | ✓ |
| Represent disease state | | | | ✓ | ✓ | |
| Adaptable for patient specificity | | ✓ | | ✓ | | ✓ |
| Predict performance with few assumptions | ✓ | | | | ✓ | |
| Maintain experimental control | | ✓ | | | | ✓ |
| Ability to vary parameters | | ✓ | | ✓ | $$$ | ✓ |
| Cost | | ✓ | ✓ | | $$$ | ✓ |
| Time | | | | | $$$ | ✓ |

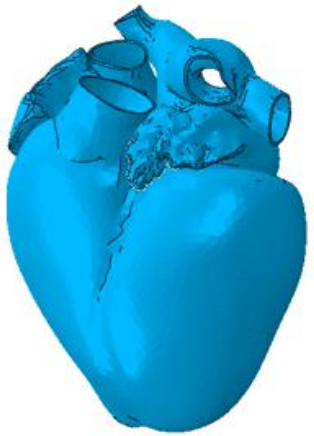
U.S. FOOD & DRUG ADMINISTRATION

Presented by the ORS Industry Engagement Committee

| Model's ability to represent aspects of device performance | Good | Fair | Poor |
|---|---|---|---|

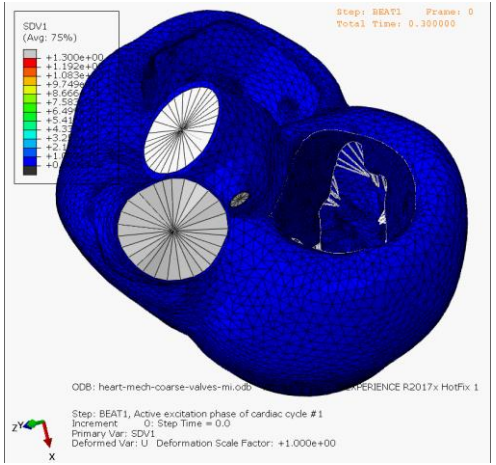
# Can we build a physically realistic simulation of a human heart?

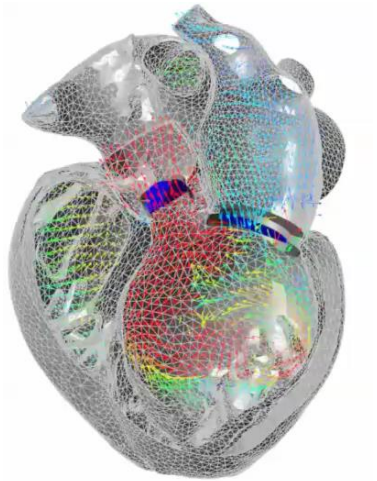
# Cardiac Behavior is Multiphysics



***Electrodynamics*** *to model propagation of cardiac action potential that controls muscle contraction*

$$\dot{\phi} + div\big(q(\phi)\big) = f^{\phi}(\phi, r)$$



***Structural mechanics*** *to model cardiac tissue behavior and beating of the heart*

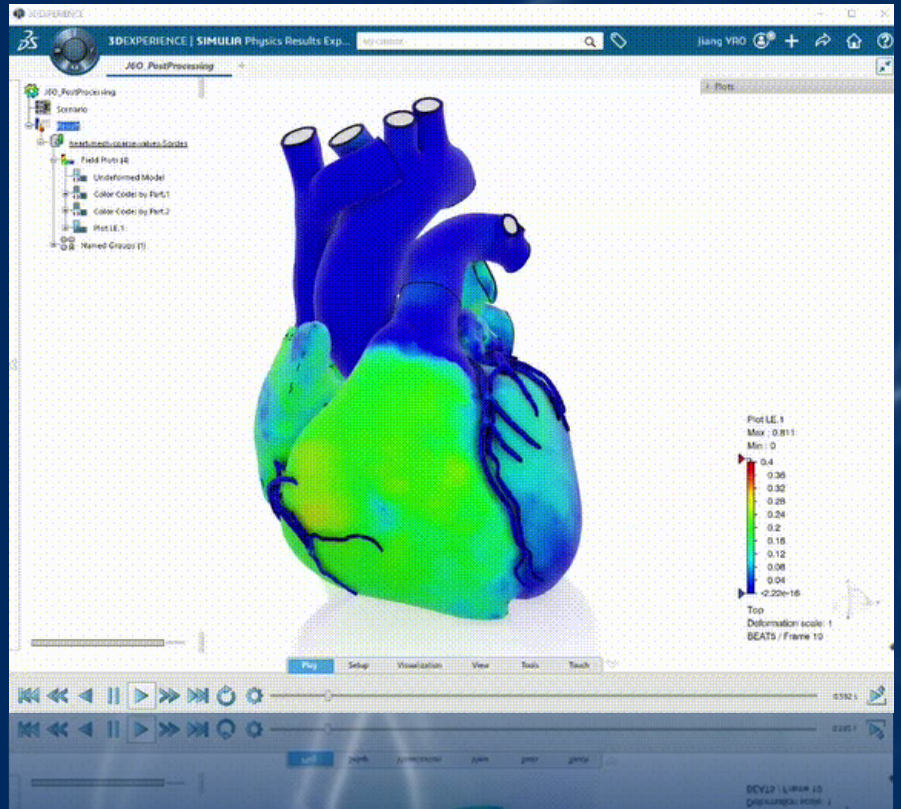
$$\sigma_{af}(t, E_{ff}) = \frac{T_{max}}{2} \frac{Ca_0^2}{Ca_0^2 + ECa_{50}^2(E_{ff})} \left(1 - cos\left(\omega(t, E_{ff})\right)\right)$$

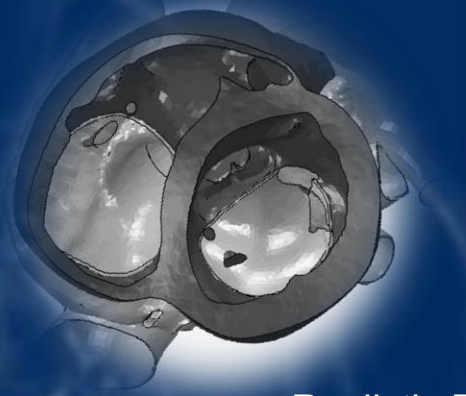
***Fluid mechanics*** *to model hemodynamics and determine cardiovascular performance*

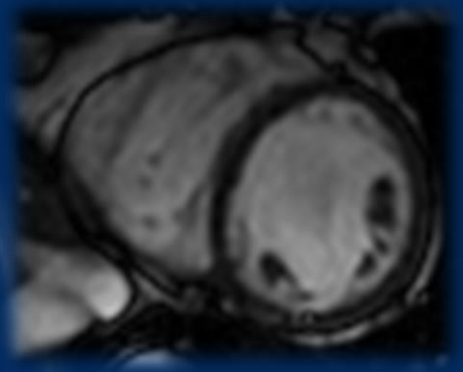
$$\frac{\partial \boldsymbol{u}}{\partial t} + \boldsymbol{u} \cdot \nabla \boldsymbol{u} = -\frac{\nabla P}{\rho} + v \nabla^2 \boldsymbol{u}$$

# The Living Heart Model on the 3DEXPERIENCE Platform

*Cloud-based Virtual Testing of Cardiovascular Devices*





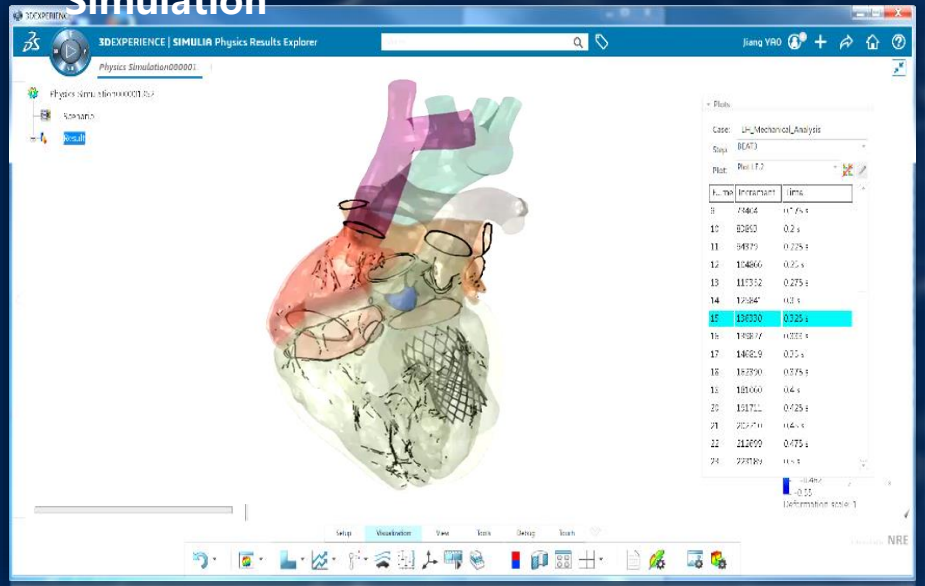
## Realistic Physiology

| Output | Model Result | Published Normal Ranges |
|---|---|---|
| L. Ventricle (LV) Ejection Fraction | 53% | >50% |
| R. Ventricle (RV) Ejection Fraction | 41% | 40-60% |
| Max LV Pressure | 113 mmHg | 100-140 mmHg |
| Min LV Pressure | 3.79 mmHg | 3-12 mmHg |
| Max RV Pressure | 15.9 mmHg | 15-30 mmHg |
| Min RV Pressure | 1.5 mmHg | 2-8 mmHg |
| R. Atrium Pressure Range | 2-6 mmHg | 2-6 mmHg |
| L. Atrium Pressure Range | 5-13 mmHg | 4-12 mmHg |
| LV Apex-Base Shortening | 11.0 mm (see Section 12.3) | 11.2 ± 3.8 mm |
| Apical Twist | 21° (see Section 12.4) | No Result[1] |

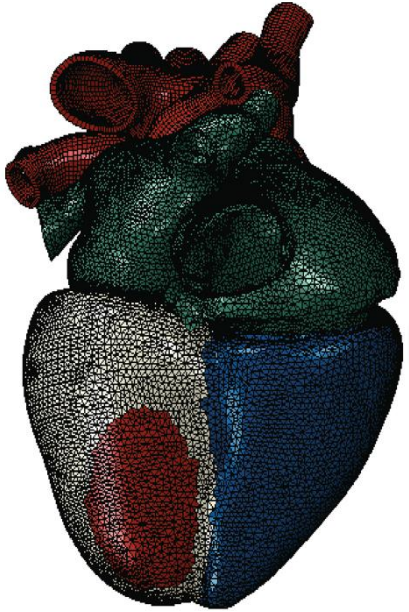
# The Living Heart Model on the 3DEXPERIENCE Platform

*Cloud-based Virtual Testing of Cardiovascular Devices*

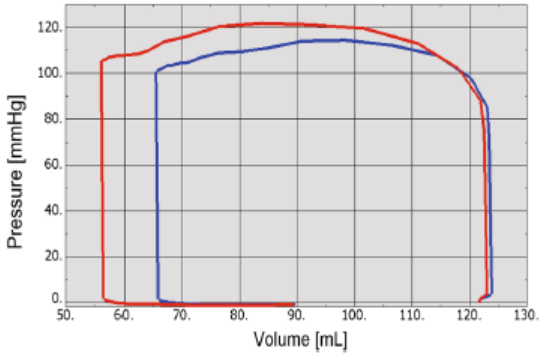
***Real World*** **Device Simulation**



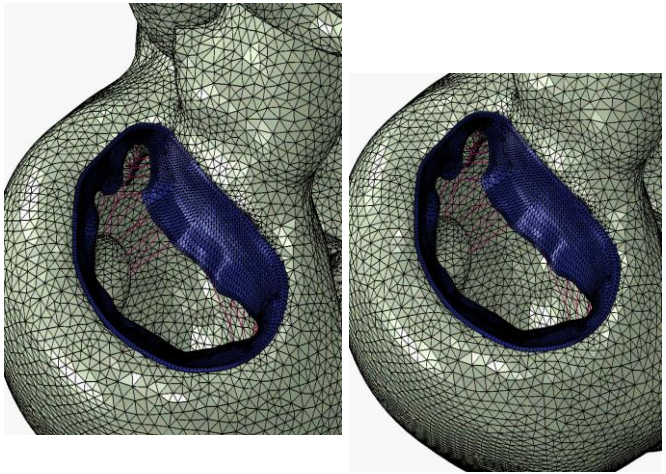

# Virtual Patients for Device Testing



*Living Heart with Myocardial Infarction (MI)*




*MI reduces cardiac output from 55% (healthy) to 45% (diseased)*

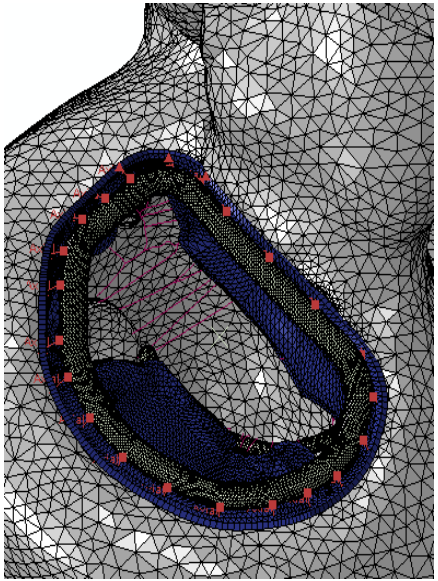


*Healthy Mitral Valve (left) vs MI-affected Mitral Valve (right)*

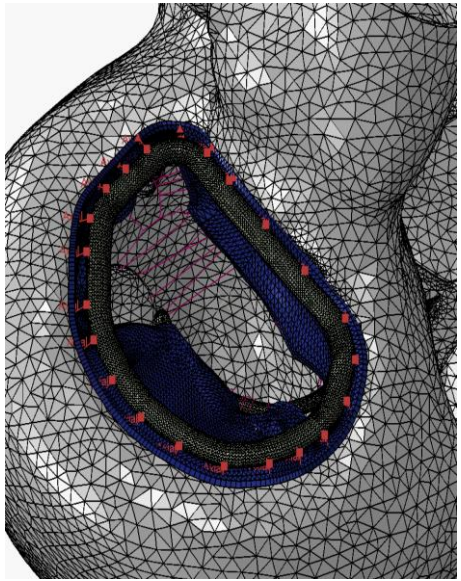
**Living Heart can be used to create Virtual Patient Populations**

# Virtual Patients for Device Testing

*Annuloplasty Ring used to treat Mitral Regurgitation*

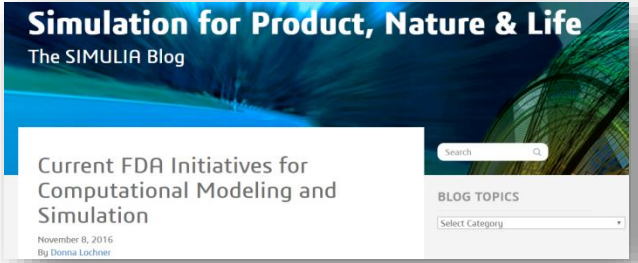


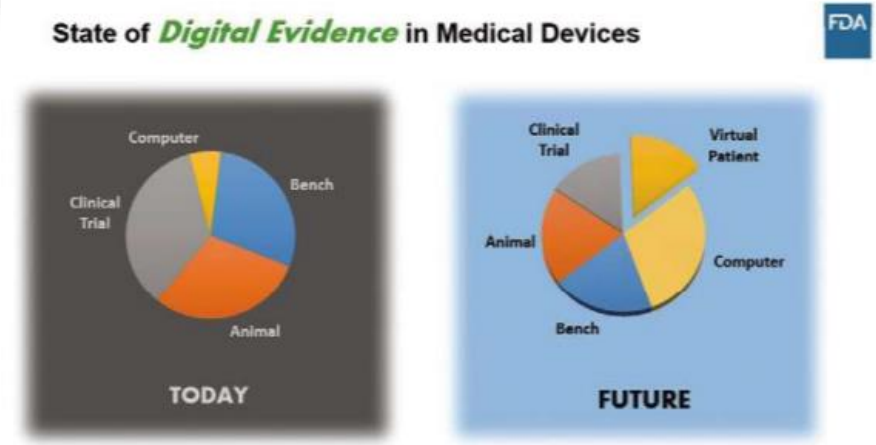
*Annuloplasty Ring sutured to Mitral Valve in Diseased Heart*



*Ring reduces severity of Mitral Regurgitation in Diseased Heart*

# Regulatory Support for Simulation




Source: Dr. Tina Morrison, U.S. Food and Drug Administration - Access 17 Nov 1, 2017

The FDA recently developed the *Medical Device Development Tools* (MDDT) program to allow for new methods for evaluating medical devices to be qualified for use in regulatory submissions to CDRH.

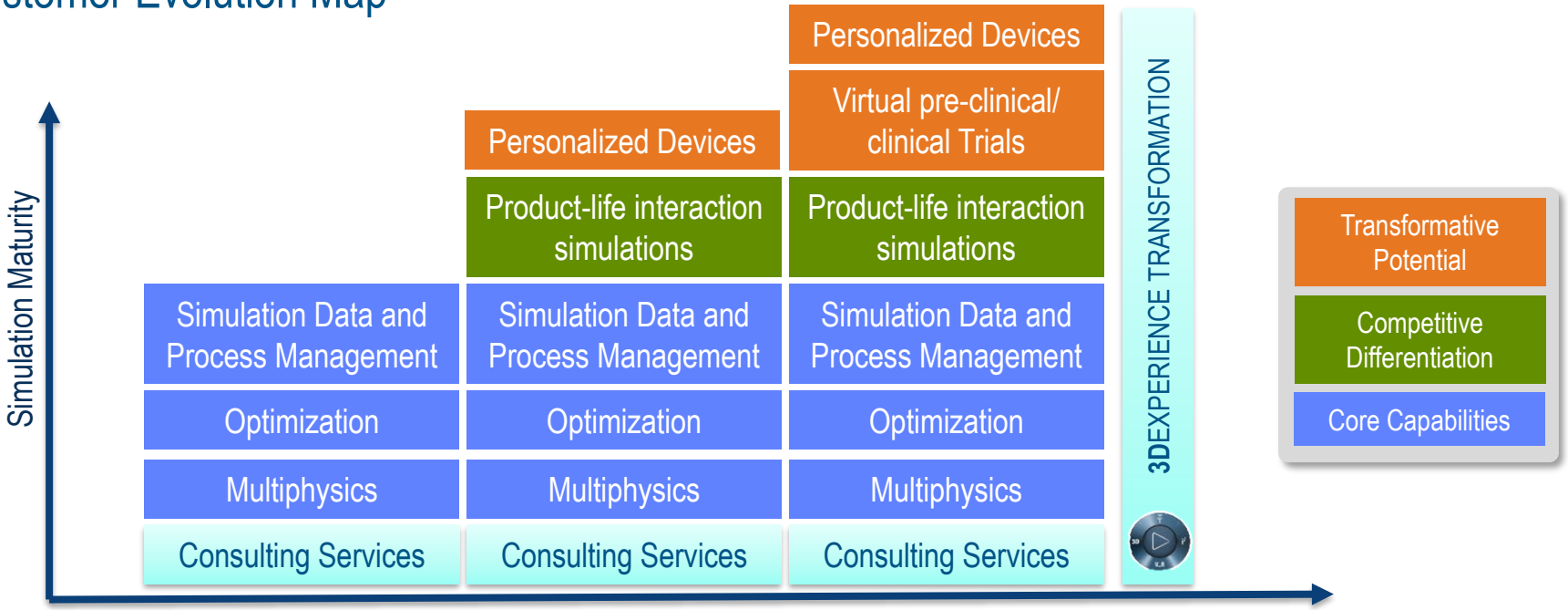
- **Computer models of patients** are used to support the approval or clearance of new medical devices. These models of patients, such as the *Virtual Family* set of virtual anatomical models (VF), have been used in over 120 submissions to the FDA. Most of these submissions have used the VF to demonstrate that an implanted medical device will not cause the heating of tissue when a patient undergoes MRI.
- **Population modeling methods** enable a more comprehensive understanding of the differences and similarities for a wide range of data sets, which may also lead to improved medical device designs for more people. An example of this type of tool is *The Musculoskeletal Atlas Project*, a population model of the musculoskeletal system, which was supported in part through *FDA extramural support*.
- **Virtual clinical trials** treated computational approaches to design virtual patients or simulate a clinical study itself. Virtual patients may be incorporated in clinical study designs, allowing for smaller clinical studies or enrichment of the clinical study with virtual patients having conditions with low prevalence in the clinical study cohort. FDA researchers are developing methodologies for conducting in silico imaging clinical trials. In one such project, Virtual Imaging Clinical Trials for Regulatory Evaluation (VICTRE), an all-digital imaging pipeline will be made available open source for simulating three-dimensional breast imaging systems, now approved only through burdensome clinical trials.

The CDRH recognizes the great potential of computational modeling and simulation as an efficient and effective method for the evaluation of medical devices and believes the MDDT process can be used to support regulatory submissions.

Examples of MDDTs currently being reviewed by FDA include Vextec's computational durability software for predicting fatigue failure of medical devices and SIMULIA's Abaqus Knee Simulator for predicting the performance of artificial implants.

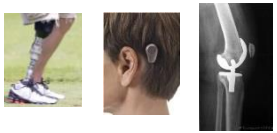
# Value of Simulation for Medical Devices

## Customer Evolution Map




**Class I**

**Class II**



**Class III**

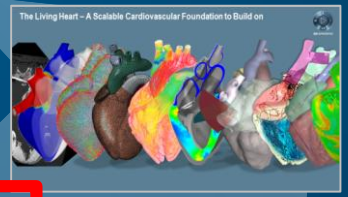
# Can we Simulate a Patient?

- Can we create virtual patients to design and test new medical devices?


- Can we create virtual patients to test and target new drugs?

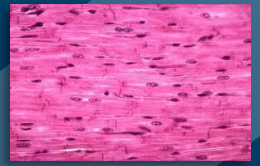

- Can we create virtual patients to guide clinical procedures?

# Human Heart is Multiscale



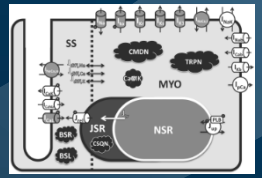

Patient Populations

Whole Heart Physiology



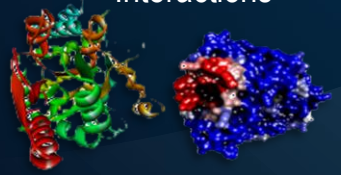
Tissue Mechanics

Cellular Biophysics

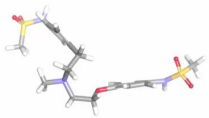


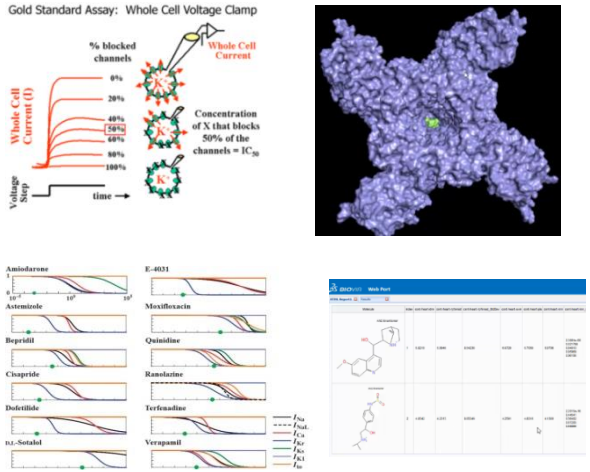

Biochemical Pathways

Molecular Interactions



# Current Drug Safety Paradigm






***Model-based and Data-driven***

***Limitations with current pre-clinical paradigm:***

- ***Narrow focus on hERG and QT prolongation***
- ***Do not predict endpoint of clinical concern (TdP) reliably***
- ***May lead to early termination of drug development***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The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative — Update on progress


Thomas Colatsky [a], Bernard Fermini [b], Gary Gintant [c], Jennifer B. Pierson [d], Philip Sager [e], Yuko Sekino [f], David G. Strauss [a], Norman Stockbridge [a]

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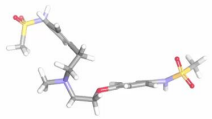
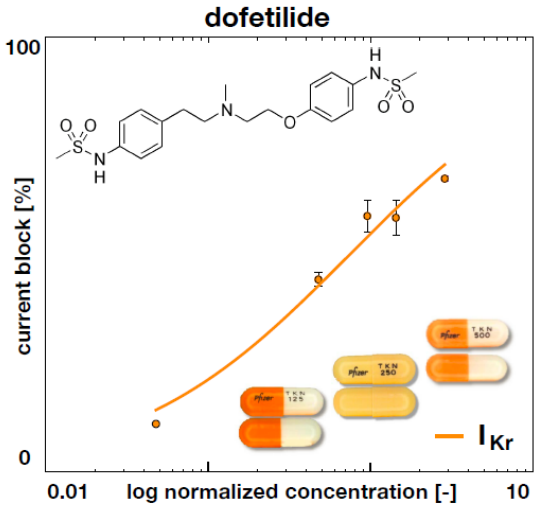
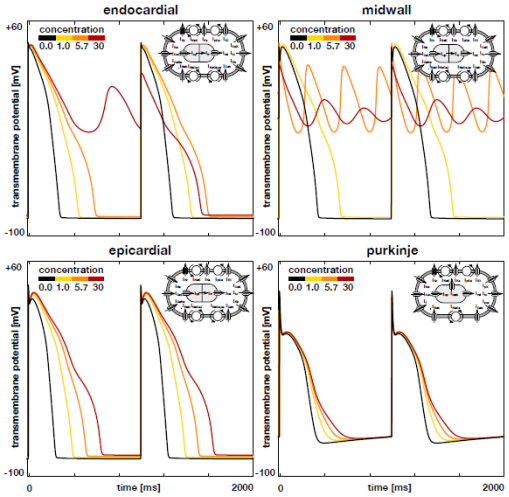
Received 31 March 2016, Revised 1 June 2016, Accepted 4 June 2016, Available online 7 June 2016.

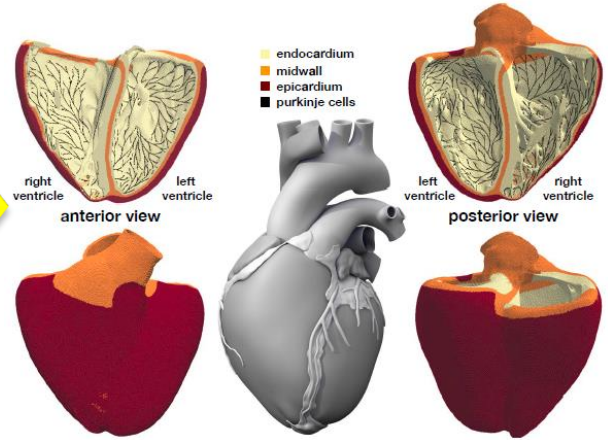

***Can we use Multiscale Modeling to better understand and predict the proarrhythmic potential of a drug ?***

# Multiscale Modeling





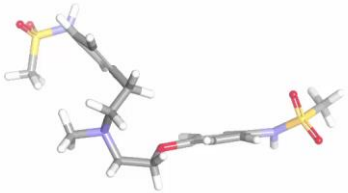




***Measure the effect of drug on cardiac ion channels (Experiment)***

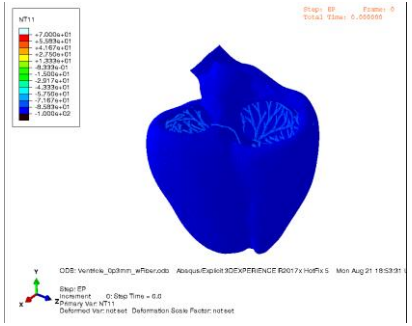
***Predict the effect of drug on cardiac cells (Simulation)***

***Determine the spatial location of cardiac tissue (Data)***

# Multiscale Modeling

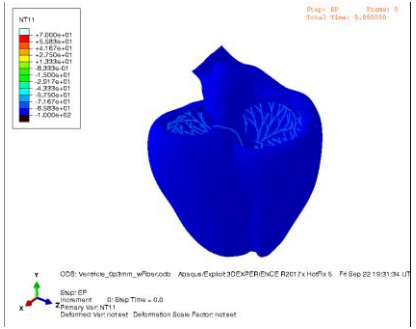


## 0x



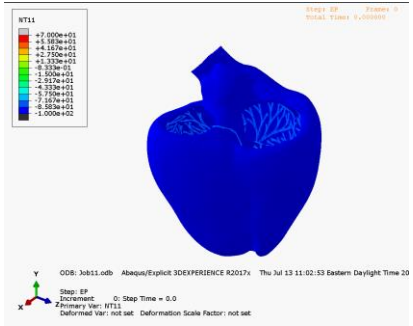
- ❑ *Periodic excitation*
- ❑ *Sinus rhythm*
- ❑ *No risk*

## 1x



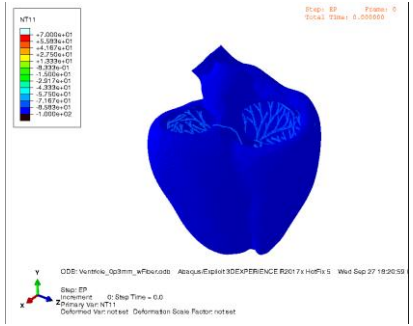
- ❑ *Delayed repolarization*
- ❑ *Periodic rhythm*
- ❑ *Low risk*

## 5.7x



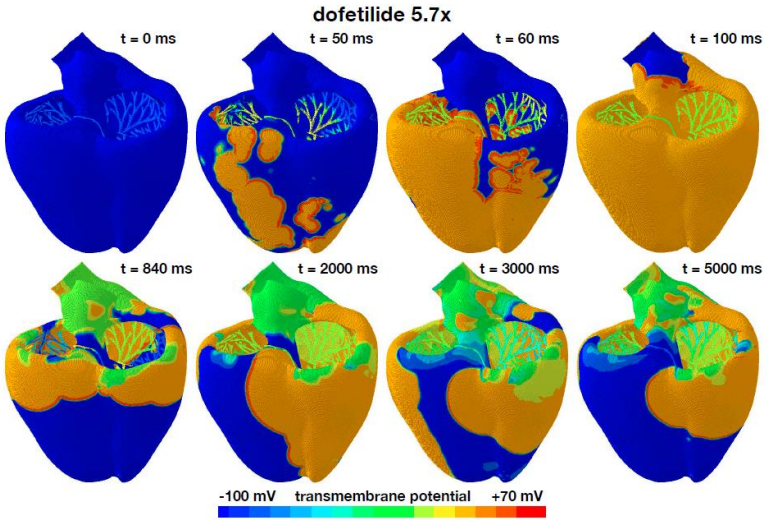
- ❑ *Asynchronous excitation*
- ❑ *TdP detected*
- ❑ *High risk*

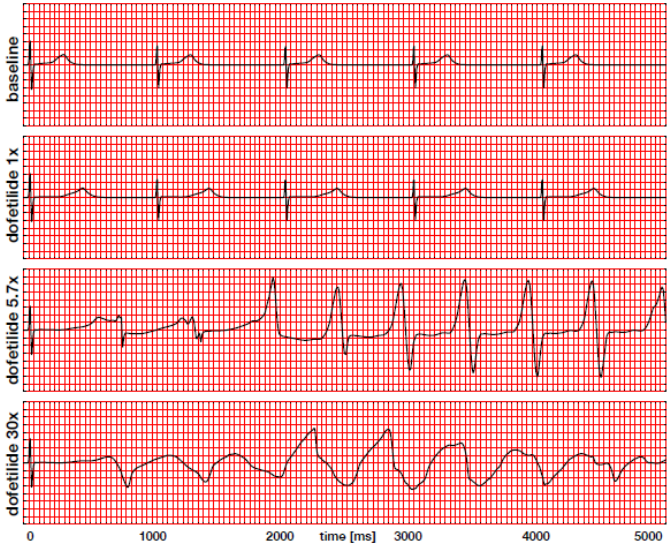
## 30x



- ❑ *Chaotic excitation*
- ❑ *Ventricular fibrillation*
- ❑ *Extremely high risk*

# Multiscale Modeling of Drug-induced Arrhythmia




*3D profile of electrical excitation*

- *Mechanistic (actionable) effect of drug*
- *Patient-specific (anatomy, physiology, genetics)*

*Virtual electrocardiogram (ECG)*

- *Facilitate collaboration with clinicians*
- *ML for patient-specific pathology*

# Simulation Proves Superior to Animal Models

Front Physiol. 2017 Sep 12;8:668. doi: 10.3389/fphys.2017.00668. eCollection 2017.

**Human In Silico Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity.**

Passini E[1], Britton OJ[1], Lu HR[2], Rohrbacher J[2], Hermans AN[2], Gallacher DJ[2], Greig RJH[3], Bueno-Orovio A[1], Rodriguez B[1].

Author information

**Abstract**

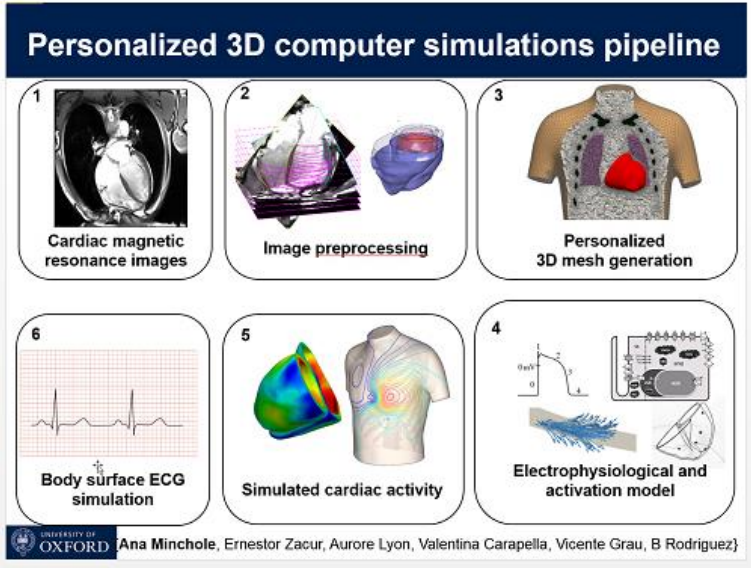
Early prediction of cardiotoxicity is critical for drug development. Current animal models raise ethical and translational questions, and have limited accuracy in clinical risk prediction. Human-based computer models constitute a fast, cheap and potentially effective alternative to experimental assays, also facilitating translation to human. Key challenges include

## The Virtual Assay software is the winner of the Safety Pharmacology Society Technological Innovation Award 2017

Posted: 2nd October 2017

Elisa Passini received the Technological Innovation Award at the Safety Pharmacology Society Meeting 2017 for "Virtual Assay: a User-Friendly Framework for In Silico Drug Trials in Populations of Human Cardiomyocyte Models" (Elisa Passini, Oliver Britton, Alfonso Bueno-Orovio, Blanca Rodriguez.)

**Computational Cardiovascular Science** team at the Department of Computer Science, University of Oxford, in collaboration with Oxford Computer Consultants and supported by a EPSRC Impact Acceleration Award. It's a user-friendly software for In Silico drug trials, using populations of human cardiac cellular models based on well-understood human cardiac physiology. The



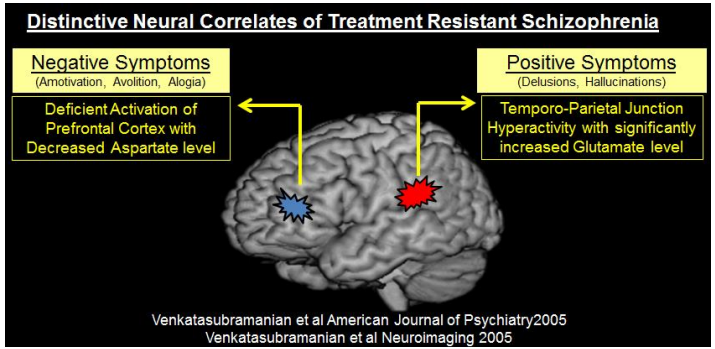
# Can we Simulate a Patient?

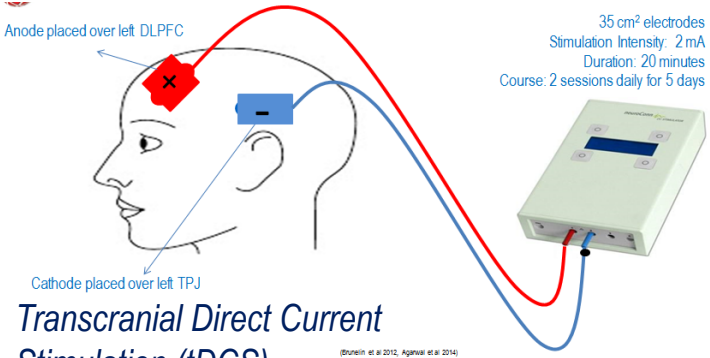
- Can we create virtual patients to design and test new medical devices?


- Can we create virtual patients to test and target new drugs?


- Can we create virtual patients to guide clinical procedures?

# Patient Care on the **3D**EXPERIENCE Platform



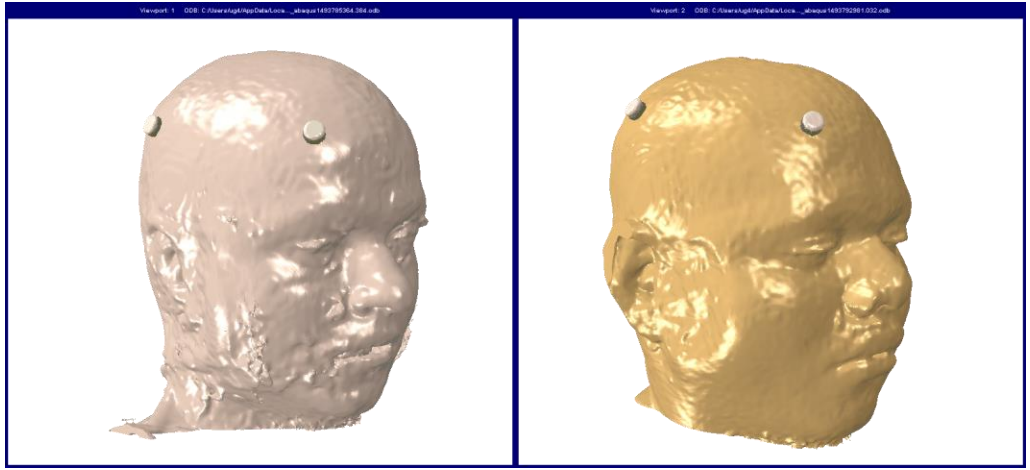




*Transcranial Direct Current Stimulation (tDCS)*

(Brunelin et al 2012, Agarwal et al 2014)

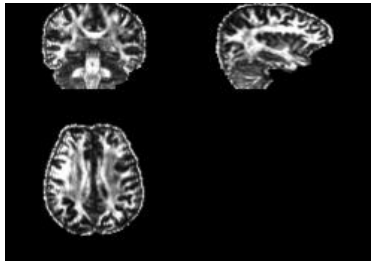
Personalized Neuromodulation: Application of Numerical Computation to Simulate Transcranial Direct Current Stimulation (tDCS) in Schizophrenia

Ganesan Venkatasubramanian, Gaurav Vivek Bhalerao, Rimjhim Agrawal, Sunil Vasu Kalmady
*Department of Psychiatry, National Institute of Mental Health and Neurosciences, India*



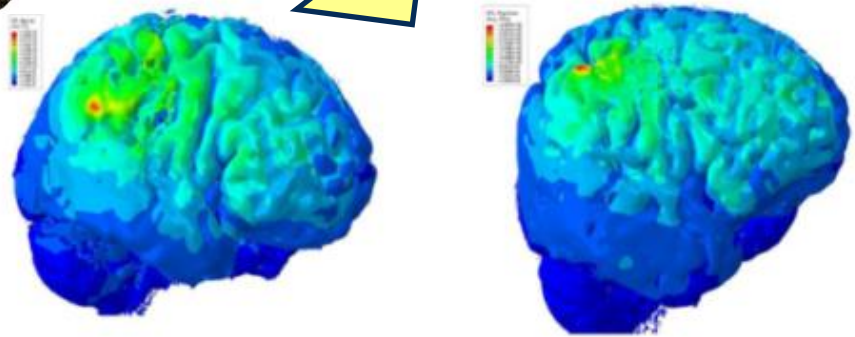
*Responsive to tDCS* *Unresponsive to tDCS*

# Patient Care on the **3D**EXPERIENCE Platform

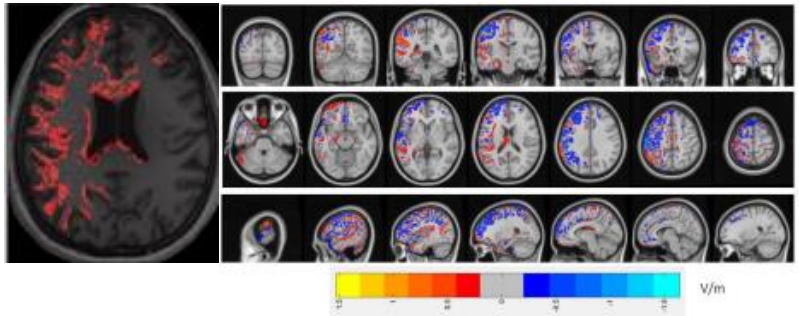


*Structural MRI scan data*

*Finite Element Model including Brain, Skull, Flesh, CSF, etc.*




*tDCS simulation results showing differing loci of electric current in responder and non-responder*

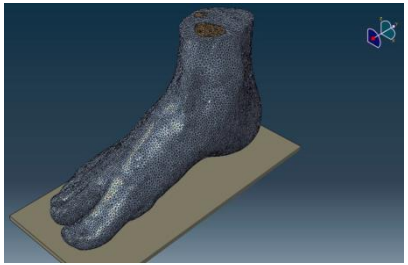


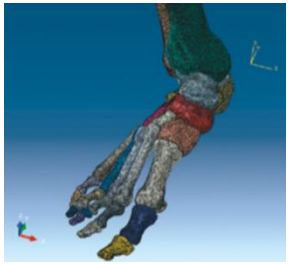

*tDCS simulation results mapped back in MRI space for clinical analysis*

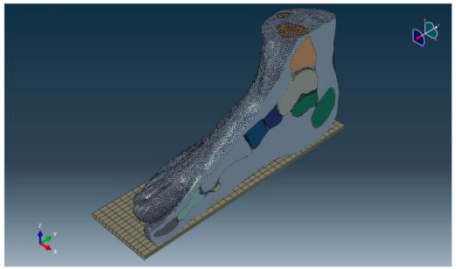
# Patient Care on the **3D**EXPERIENCE Platform

3DEXPERIENCE® Lab

DIGITAL ORTHOPAEDICS







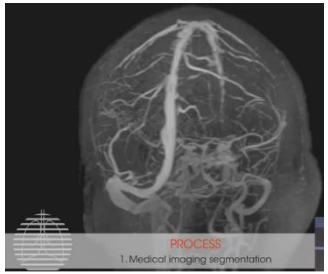
Comprehensive Clinical Decision Support System for Foot & Ankle Diseases

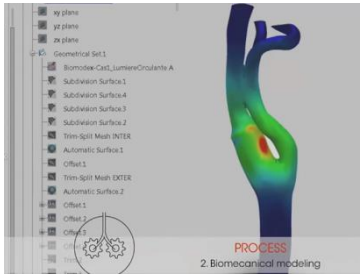
| TECHNO PLATFORM | Diagnosis | Surgical planning | Outcome-based knowledge improvement |
|---|---|---|---|
| ADDED VALUE | • Clinical expertise available and for Specific clinical information.<br>• Suggestion of additional investigation.<br>• Guided diagnosis<br>• Potential treatment comparison | • Root-cause analysis of the disease. Optimization of surgery plan<br>• Improved treatment success rate.<br>• Complete solution for the surgeon:<br>• Service: patient-specific simulation<br>• Product: patient-specific surgical guides. | • Improvement of knowledge base and algorithms.<br>• R&D support for medical device industry. |

# Patient Care on the **3D**EXPERIENCE Platform

3DEXPERIENCE® Lab

BIOMODEX®



# Patient Care on the **3D**EXPERIENCE Platform

3DEXPERIENCE® Lab

BIOSERENITY

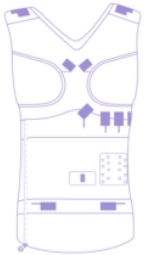

Textile

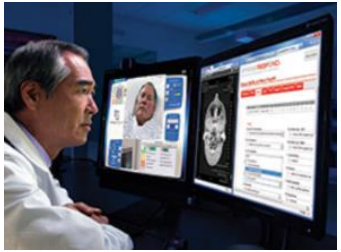
Remote Diagnostics

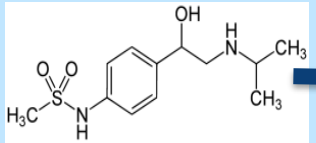
Mobile Application

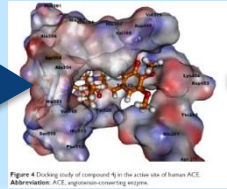
Internet of Things

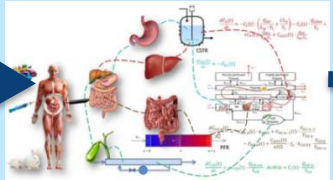
Artificial Intelligence

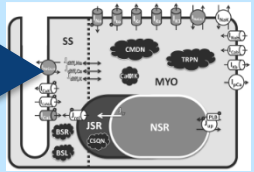


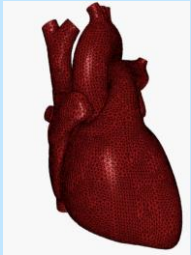




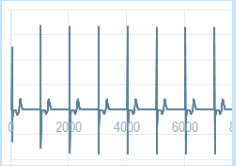



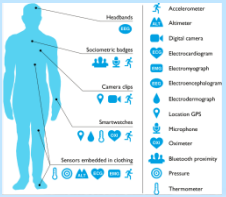


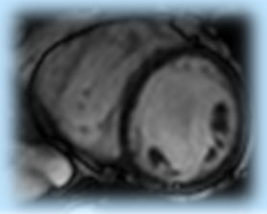



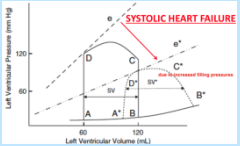
## Precision Medicine and Personalized Treatment…


## …using a Model-Based and Data-Driven Foundation





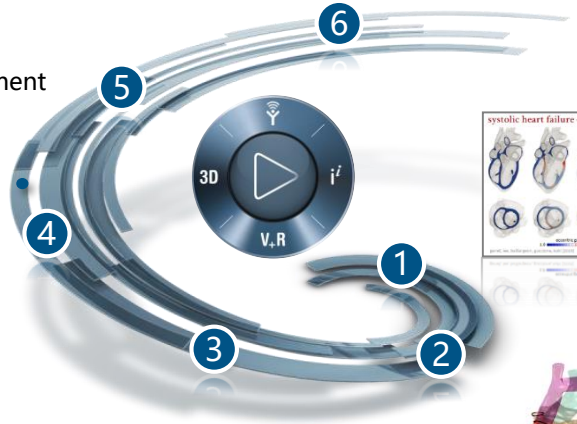
# Simulation on the **3D**EXPERIENCE platform → end-to-end innovation

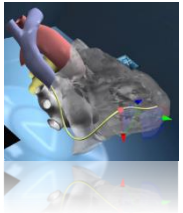
## PATIENT CARE

Patient
Monitoring/Engagement
Chronic Disease Management
Data-driven knowledge

## SERVICE ECOSYSTEM

3DEXPERIENCE Lab
FEOPS insights for excellence
ilumens
BIOMODEX
BIOSERENITY
The Living Heart Project



## CLINICAL TREATMENT

Device/Procedure Selection
Outcome Prediction
3D Printing


## SCIENTIFIC DISCOVERY

Anatomical effects
Normal/Abnormal physiology
Short- and long-term behavior


## MEDICAL DIAGNOSIS

Personalized models
Data-driven insights
Informed choices

## MEDICAL DEVICE DESIGN

Device performance/reliability
Treatment efficacy/safety
Accelerate Clinical Trials

IF WE™