Simulation in the Life Sciences

A Look Ahead

Mechanics = study of forces acting on bodies, including our own...
3DEXPERIENCE for Digital Healthcare

Data Feeds and Knowledge Base

V+R Virtual Human Modeling and Simulation

Model-based and Data-driven Insights

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
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?

**Prevalence of Chronic Disease in the U.S.**

- ** Millions of Americans**
  - 118 (1995)
  - 125 (2000)
  - 133 (2005)
  - 141 (2010)
  - 149 (2015)
  - 157 (2020)
  - 164 (2025)
  - 171 (2030)

**Novel Device Approvals**

- 4-fold Increase in # of Novel Device Approvals

- Number of Novel Devices

- Calendar Year

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

- 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

Sources of Evidence

1. Bench
2. Animal
3. Computer
4. Computer
5. Clinical Trial
6. Computer

Model's ability to represent aspects of device performance
- Good
- Fair
- Poor
Can we build a physically realistic simulation of a human heart?

The Living Heart Project

Mission:
Advance the development of safe & effective cardiovascular products and treatments by uniting engineering, scientific, & biomedical experts to deliver validated models and translate simulation technology into improved patient care.
Cardiac Behavior is Multiphysics

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

\[ \phi + \text{div}(q(\phi)) = f(\phi, r) \]

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

\[ \sigma_{af}(t, E_{ff}) = \frac{T_{max}}{2} \frac{C_{a}^3}{C_{a}^3 + E_{ff}} \left( 1 - \cos \left( \omega(t, E_{ff}) \right) \right) \]

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

\[ \frac{\partial u}{\partial t} + u \cdot \nabla u = -\frac{\nabla P}{\rho} + \nu \nabla^2 u \]
The Living Heart Model on the 3DEXPERIENCE Platform

Cloud-based Virtual Testing of Cardiovascular Devices

Realistic Physiology
The Living Heart Model on the 3DEXPERIENCE Platform

Cloud-based Virtual Testing of Cardiovascular Devices

Real World Device Simulation

INTEGRITY • SENSITIVITY • EFICACY • ORGAN RESPONSE
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

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 are a related computational approach 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.
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**

- Molecular Interactions
- Biochemical Pathways
- Cellular Biophysics
- Tissue Mechanics
- Whole Heart Physiology
- Patient Populations
Current Drug Safety Paradigm

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

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


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

Pascini E¹, Britton D¹, Lu HB², Rohrbach P³, Herrman AN², Gallacher DJ², Greco RJ², Bueno-Orovio A¹, Rodríguez B¹

@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 Pascini 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 Pascini, Oliver Britton, Alfonso Bueno-Orovio, Blanca Rodríguez).

**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 3DEXPERIENCE Platform

Responsive to tDCS

Unresponsive to tDCS

Transcranial Direct Current Stimulation (tDCS)

Anode placed over left DLPFC
Cathode placed over left TPJ

35 cm² electrodes
Stimulation intensity: 2 mA
Duration: 20 minutes
Course: 2 sessions daily for 5 days

Venkatasubramanian et al American Journal of Psychiatry 2005
Venkatasubramanian et al Neuroimaging 2005

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

Ganesan Venkatasubramanian, Gaurav Vivek Bhalaria, Rinkhim Agrawal, Sunil Vasu Kalnady
Department of Psychiatry, National Institute of Mental Health and Neurosciences, India

Responsive to tDCS

Unresponsive to tDCS

Transcranial Direct Current Stimulation (tDCS)
Patient Care on the 3DEXPERIENCE Platform

Structural MRI scan data

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

tDCS simulation results mapped back in MRI space for clinical analysis

tDCS simulation results showing differing loci of electric current in responder and non-responder
Patient Care on the 3DEXPERIENCE Platform

3DEXPERIENCE® Lab

DIGITAL ORTHOPAEDICS

Comprehensive Clinical Decision Support System for Foot & Ankle Diseases

- Clinical expertise available and for specific clinical information.
- Suggestion of additional investigation.
- Guided diagnosis
- Potential treatment comparison
- Root-cause analysis of the disease.
- Optimization of surgery plan
- Improved treatment success rate.
- Complete solution for the surgeon:
  - Tissue, patient-specific simulation
  - Product patient-specific surgical guides.
- Improvement of knowledge base and algorithms.
- R&D support for medical device industry.

Diagnosis
Surgical planning
Outcome-based knowledge improvement

Add Value


© Dassault Systèmes | Confidential Information
Patient Care on the 3DEXPERIENCE Platform

OUR SOLUTION:
3D PRINTED SURGICAL SIMULATORS
Patient Care on the 3DEXPERIENCE Platform

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 3DEXPERIENCE platform → end-to-end innovation

**PATIENT CARE**
Patient Monitoring/Engagement
Chronic Disease Management
Data-driven knowledge

**CLINICAL TREATMENT**
Device/Procedure Selection
Outcome Prediction
3D Printing

**MEDICAL DIAGNOSIS**
Personalized models
Data-driven insights
Informed choices

**SERVICE ECOSYSTEM**

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

**MEDICAL DEVICE DESIGN**
Device performance/reliability
Treatment efficacy/safety
Accelerate Clinical Trials

Simulation on the 3DEXPERIENCE platform → end-to-end innovation