Cardiovascular Test Methods: Part II
Design Validation Testing (F2477, F2914)

PERU Workshop on Medical Device Regulation: Policy and Technical Aspects

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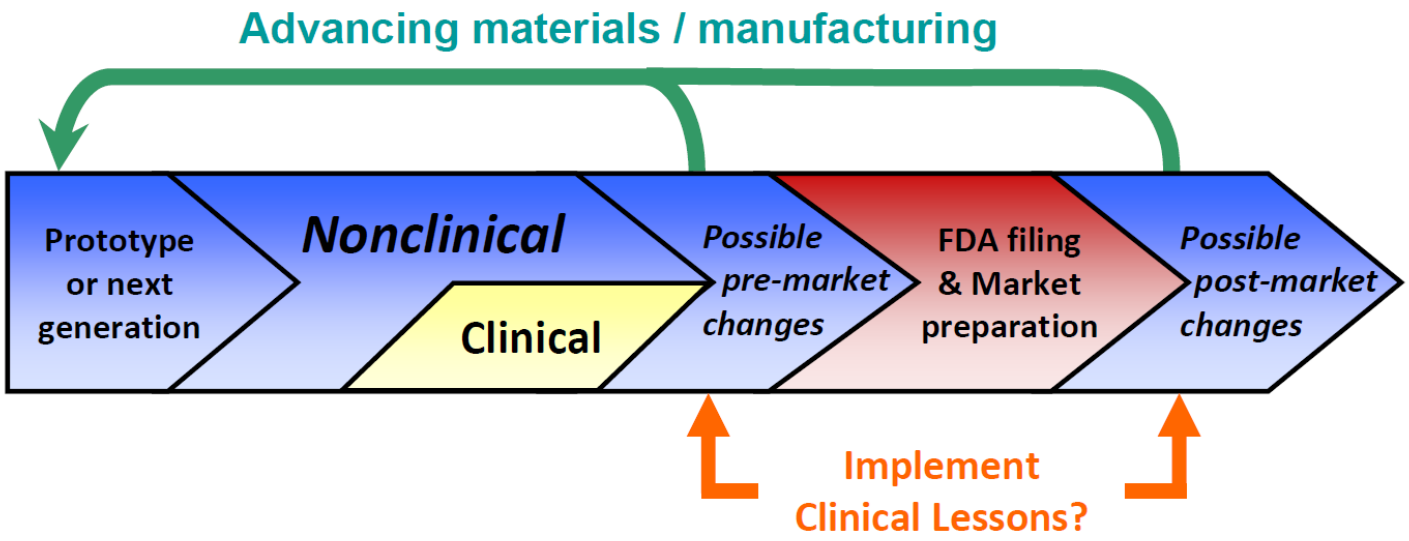
Design->Evaluation->Market

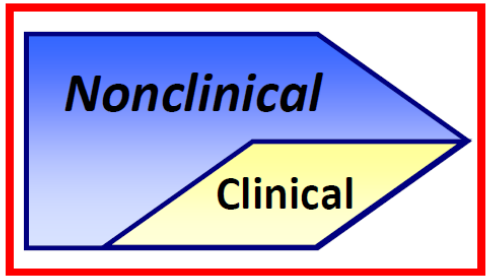


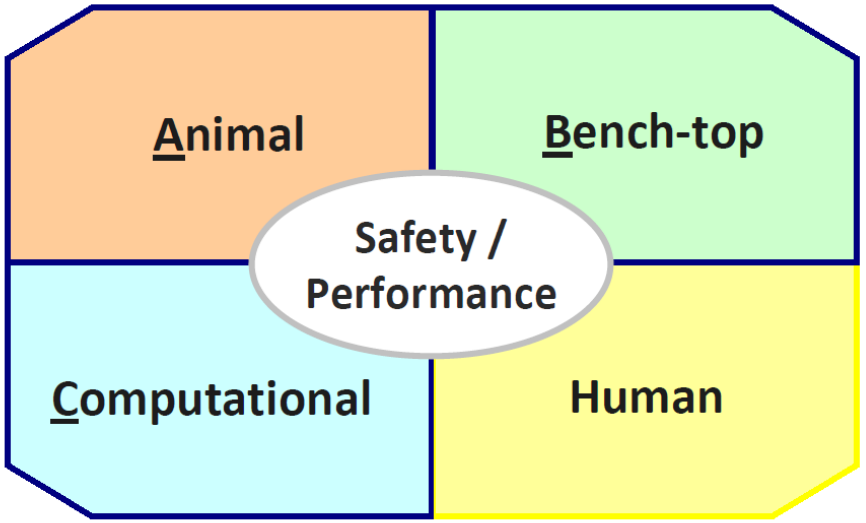
Manufacturers, regulatory agencies, physicians, engineers and patients

How can we best learn from the past and make better products?

Models Used for Evaluation

In general, there are four models device manufacturers use (and the FDA reviews) in the pre-market setting to demonstrate safety and performance of a cardiovascular device:





Models and Their Advantages

Adapted from Victor Krauthamer

	Cost	Time	Ability to vary parameters	Evaluation involving harm	Simplifying assumptions	Relevance to Clinical Use	Evaluating disease state	Experimental control	Ability to interpret data and predict clinical use
Animal	moderate	moderate	limited	restricted	moderate	species variability	difficult	relatively high	limited
Bench	low	short	limited	yes	many and always	limited	simplified states	high	limited
Human	very high	long	not easy	no, unethical	minimal	direct	yes	low	not easy
Computer	relatively low	short - to - moderate	high	yes*	many and always	variable	yes*	high	yes*

Computer modeling in medical devices, as compared to other industries, is nascent and there is great potential for refinement/improvement because the other models are fairly mature

Safety and Effectiveness

- There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the *probable benefits to health* from use of the device for its intended uses and conditions of use, *outweigh any probable risks*.
- There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, *will provide clinically significant results*.

Characteristics important for device evaluation: Device Functional Properties

Develop risk analysis and evaluation strategy to assess the technical and clinical considerations for the *delivery system* and the *implant*

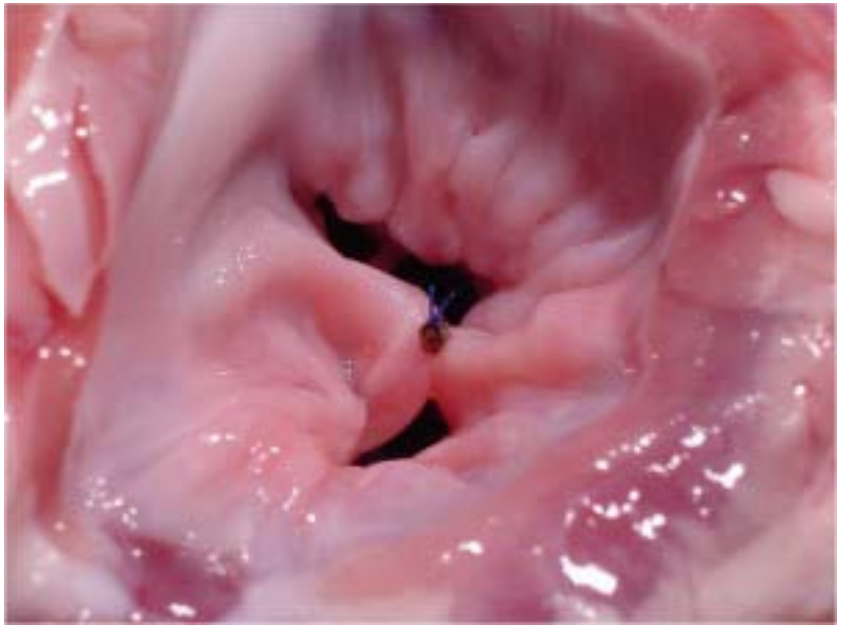
Device/Procedure Related Function(s)	Potential Failure Mode(s)	Potential Effect(s) of Failure		Preclinical Tests
		Device	Clinical	

Advantages of Animal Models

ANIMAL MODEL

– Anatomical and physiological similarities may enable some short term safety evaluation. E.g., Deployment inaccuracies

– Importantly, they provide histological information that is not readily available in humans



Limitations of Animal Models

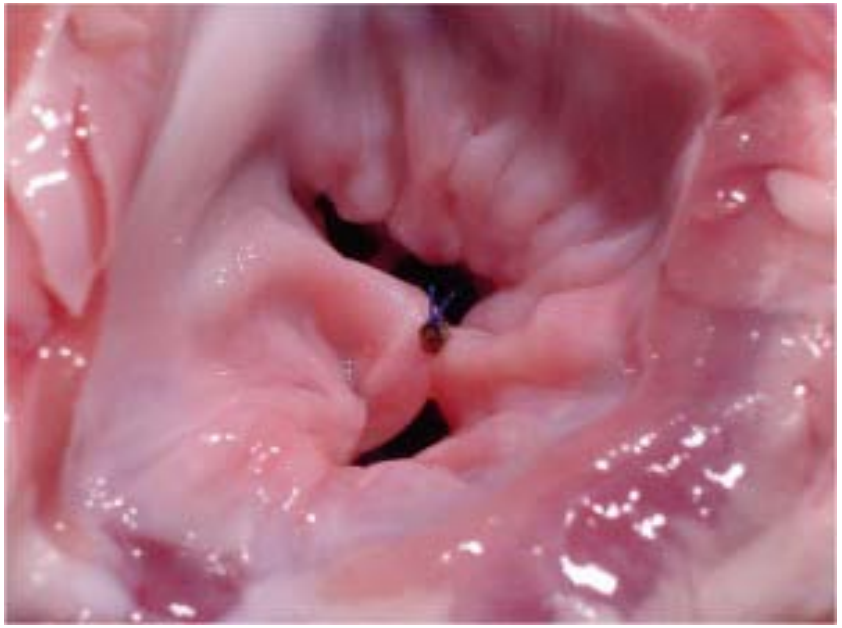
ANIMAL MODEL

– Anatomical and physiological differences limit utility of some pre-clinical testing

– Modes of deformation (e.g. SFA) are not the same

– Healing time course is accelerated compared to humans

– Inferences derived may be species-dependent



Advantages of Bench-top Models

BENCH-TOP MODEL

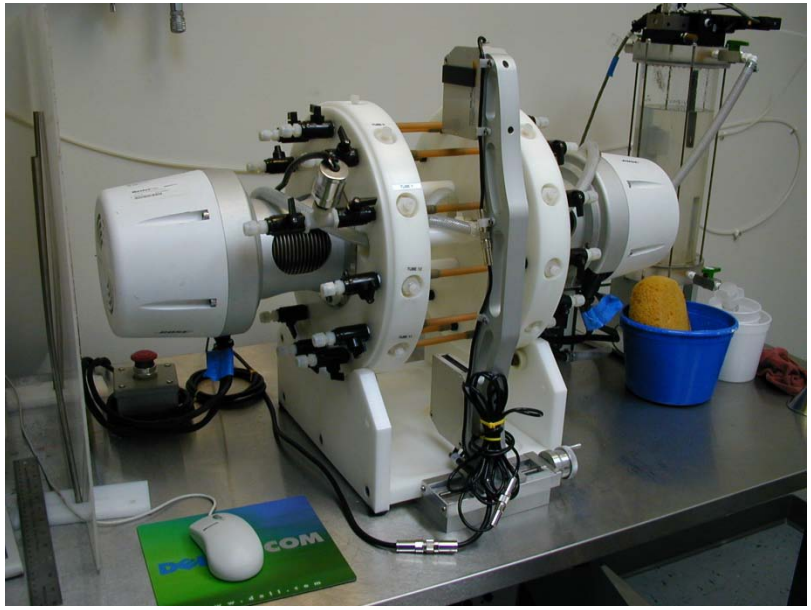
– Characterize a *specific mechanical function of the device that* may be difficult to examine *in vivo or with a computer model*

– Deform the device under “worst-case” conditions that may not be readily reproduced in the clinical setting

– Understand mechanical limitations

– Test the “actual” manufactured device, with material inclusions, surface treatments, residual stresses, etc.

– Evaluate the initiation and nature of the fracture and wear using imaging techniques



Pulsatile Durability of Stents (ASTM F2477)

Traditional fatigue testing of complete stent devices is addressed by ASTM F2477 “Standard Test Methods for in vitro Pulsatile Durability Testing of Vascular Stents,”

This standard specifies methods for fatigue of complete devices through hydrodynamic pulsation. The method involves placing complete devices into mock arteries and subjecting them to 400 million cycles of internal pressure pulsation, forcing them to radially expand and contract in each cycle.

Two Pulsatile Test Methods

The test can either be performed between pressure limits, simulating diastolic and systolic pressures, or displacement controlled, reproducing the minimum and maximum diameters that a stent would see in vivo under worse case conditions.

In both cases, silicone tubing is carefully selected to provide the appropriate mechanical behavior.

F2477 has details for BOTH test methods.

Accelerated Durability Testing

Tests are typically performed at frequencies of up to 50 cycles per second, resulting in test durations of over three months, more typically at six months.

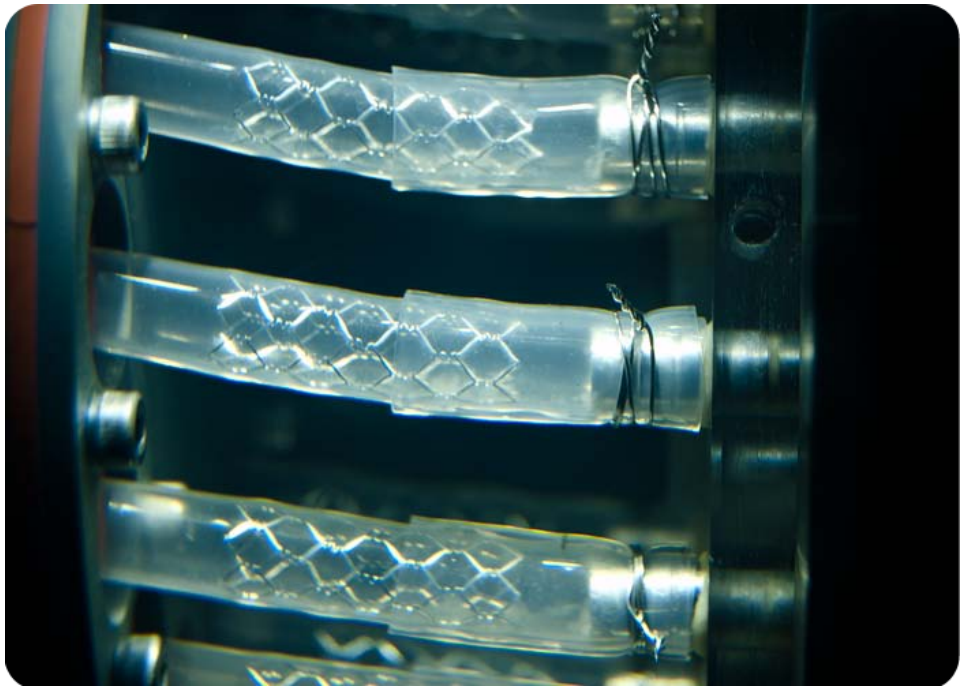
Test Speed	1 month	3 months	6 months
1 Hz	2,592,000	7,776,000	15,552,000
20 Hz	51,840,000	155,520,000	311,040,000
50 Hz	129,600,000	388,800,000	777,600,000
100 Hz	259,200,000	777,600,000	1,555,200,000

Application to New Device Types

Adaptations of F2477 have been made for testing more general endovascular devices.

Application to Custom Test Methods

Many custom tests follow the basic principles of F2477.



Potential Limitations of the Models

BENCH-TOP MODEL

– Simple loading modes and amplitudes may not replicate the *in vivo biomechanical environment*
– No tissue or blood interaction with the device
– Limited or no incorporation of disease state (e.g., plaque or lesions)
– Device not responsive to biological reactions or vessel adaptations
– Limited knowledge gained if the device does not fail
– Test outcomes may not predict clinical performance

Some Advantages of the Models

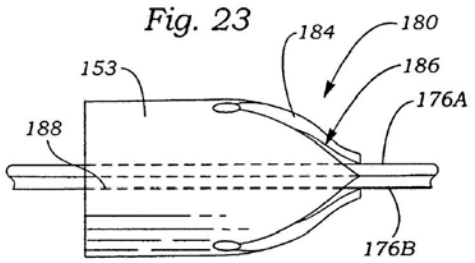
COMPUTATIONAL MODEL

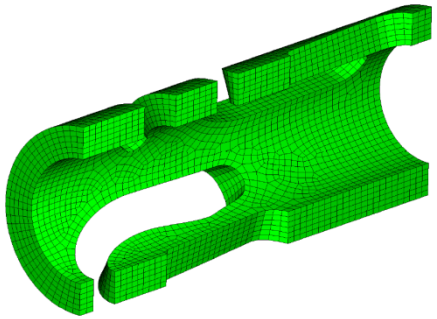
– Examine the structural performance of an entire device family or generations of devices under various loading conditions (whether they're physiologic or not)

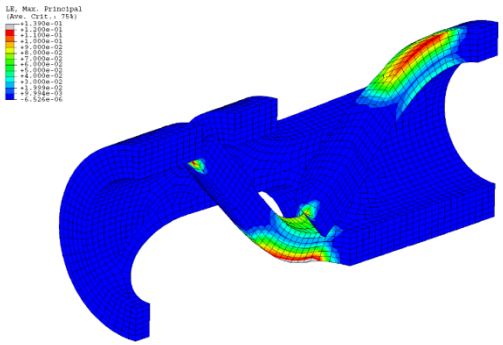
– Evaluate the stress/strain distributions of a single or combined loading modes (e.g., pulsatile and bending)

– Investigate the "hot spots" or potential failure zones on the device

– Investigate the durability of the device under a variety of loading scenarios (safety factors!)







Types of Computational Modeling

- Computational Solid Mechanics
  - Stents, Heart Valve Frames, Occluders, Vena Cava Filters
  - Spine and Joint Implants
- Computational Fluid Dynamics and Acoustics
  - Blood Pumps, Heart Valves, Endovascular Grafts
  - Drug Eluting Stents, Virus and Aerosol Transport
  - Ultrasound Propagation
  - Heat Transfer and Thermal Bioeffects
- Computational Toxicology
  - (Q)SAR models to predict human risk
- Computational Electromagnetics
- Virtual Clinical Trials

Computational Solid Mechanics

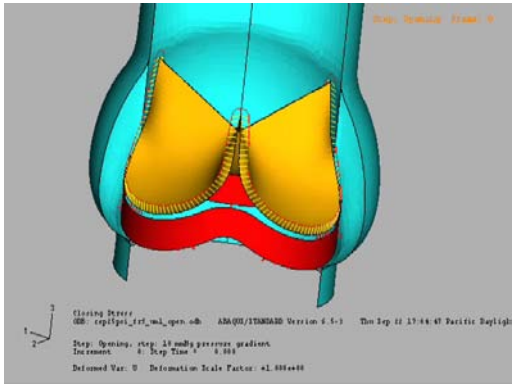
Stents / Heart Valve Frames / Occluders / Vena Cava Filters / Annuloplasty Rings / Dental Implants / Spine & Joint Implants / Bone Plates & Screws / Surgical Tools

- Determine the implant size in a device family that is expected to perform the worst under simulated *in vivo* conditions
  - Reduces the amount of physical testing
  - Calculate Safety Factors for static and cyclic loads
- Evaluate the effect of manufacturing tolerances
- *Predicate Comparison*
- Demonstrate a modification (e.g., dimensional) is minor and has minimal affect on performance

Computational Fluid Mechanics

Ventricular Assist Devices / Total Artificial Heart / Blood pumps / Heart Valves / Endovascular Grafts / Drug Eluting Devices

- Characterize the flow field by identifying regions of high shear stress, wall shear stress, or areas of low flow or flow stagnation
  - Especially in regions that cannot be visualized on the bench
- Determine blood damage, thrombosis potential, and drug transport using fluid flow properties



Computational Electromagnetism

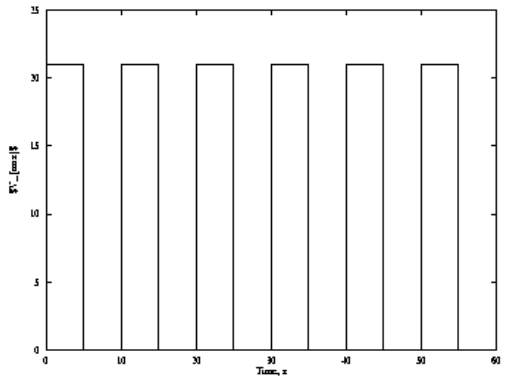
Passive and Active Cardiology Implants / Peripheral Implants / Joint and Spinal Implants / Deep Brain Stimulators / MR-guided Interventional Devices

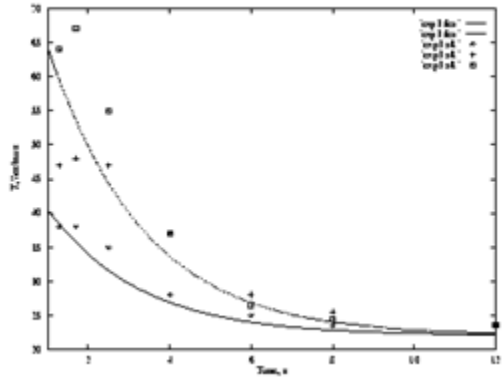
- Simulate the radiofrequency energy absorbed by patients undergoing magnetic resonance imaging (MRI)
  - Especially worst-case conditions that cannot be replicated in an animal model and cannot be tested ethically in humans
- Radiofrequency-induced currents and heating of (external) devices for electrophysiological recordings
- Simulate the electric/magnetic field generated by a device during use to provide evidence of effectiveness

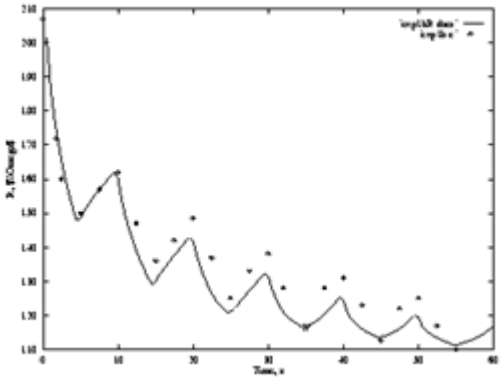
Physiological Closed-Loop Controllers & Algorithms

Anesthesiology Devices / Artificial Pancreas / Neurodiagnostic Tools

- Use the simulation as an alternative validation method to demonstrate device performance and robustness
- *In silico* simulation model (control algorithm) of diabetes replaces *in vivo* animal testing for evaluating artificial pancreas
- Signal modeling (EEG source localizing software) for brain activity analysis



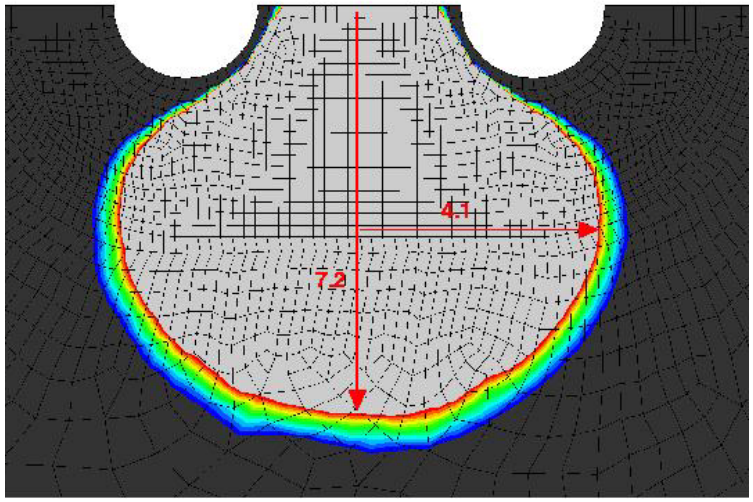


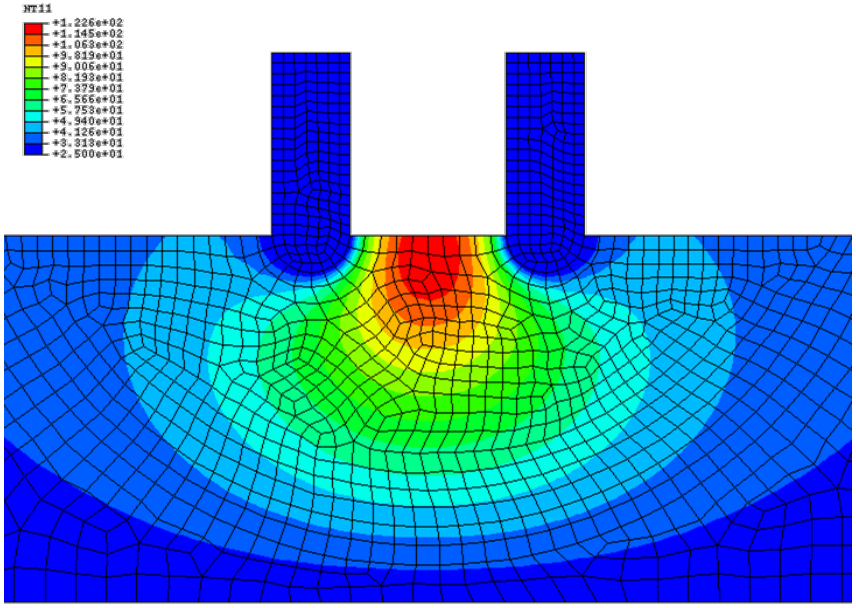


Computational Thermal Mapping

Ablation Devices

- Determine the thermal field distributions generated by tissue ablation devices (e.g., High Intensity Ultrasound, radiofrequency)
- Assess potential damage to surrounding tissue, organs and bones





Potential Limitations of the Models

COMPUTATIONAL MODEL

- Not all factors and scales can be added to the model (yet)
- Physiologically relevant boundary conditions and input data are not always known
- Device cannot respond to biological reactions and adaptations
- Cannot accurately model complex time-dependent materials
- Lack robust validation for biomedical applications
- May be computationally expensive to examine complex loading and boundary conditions of an entire device family

Harness the power of the ABC Models

Many issues arise (e.g., ethical) if we were to evaluate all devices in randomized controlled, double-blinded studies.

Therefore, in the Division of Cardiovascular Devices, we encourage the use of the ABC Models (animal, bench, and computer) to evaluate a device

For most types of devices, we have learned much from the clinical studies to influence the nonclinical evaluation

- Gain some *safety information before the clinical evaluation;*
- Therefore, single-arm, relatively low number of patients is acceptable.

Ideally, a comprehensive evaluation plan should utilize the **advantages of the ABC models to demonstrate safety and** performance of the device.

What have we learned about using ABC models?

The Bridge between Bench-top to Bedside

- The bridge is bi-directional
  - Clinical lessons greatly influence design and evaluation.
  - The ABC models yield safety data (especially for new or modified devices) before the clinical evaluation.
- Understanding the Anatomical and Physiological / Pathophysiological variations are crucial for design and evaluation.
- Boundary conditions for the ABC models can be further advanced by clinical data and knowledge.

Safety and Effective Clinical Trials

Animal, Bench and Computational models can improve medical device design and increase access to safe and effective therapies for patients.

Appropriately balanced and clinically relevant conditions and the development of new tests and methodologies can push the evaluation of devices forward.

Estimating In Vivo Load Conditions

How does one select durability test conditions to simulate what a cardiac implant might encounter in the body?

What to do when the implant has a complex geometry, non-standard boundary conditions with little or no precedent?

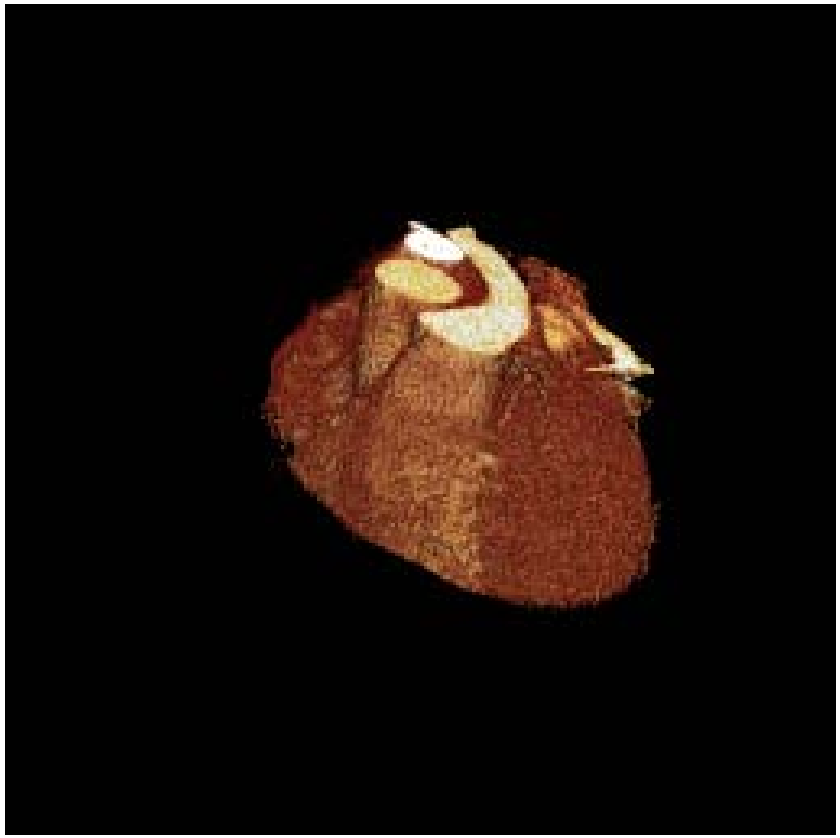
Benefits of using medical imaging data and FEA

- Combine data to provide clearer picture
- Interpret data based on assumptions
- Evaluate, refine and develop theories

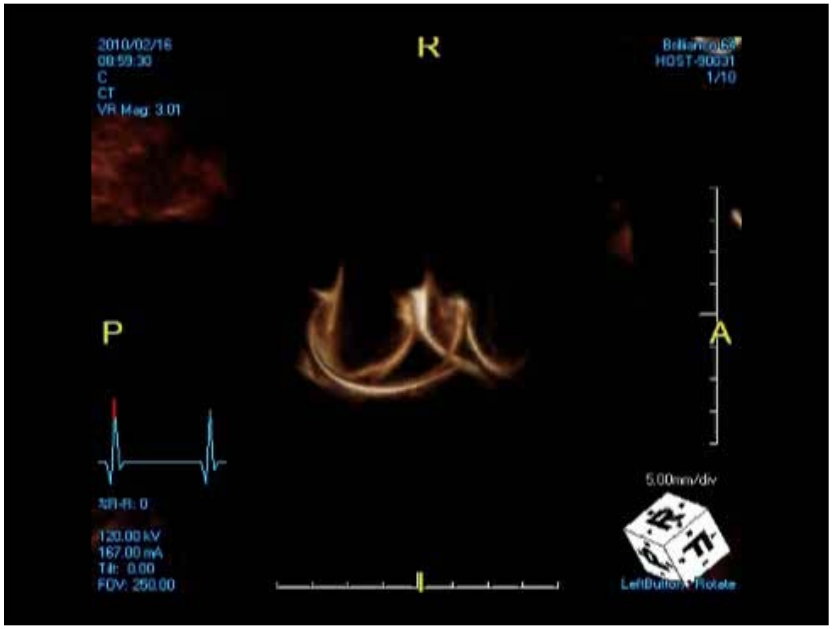
In situ Deformation of Aortic Valve

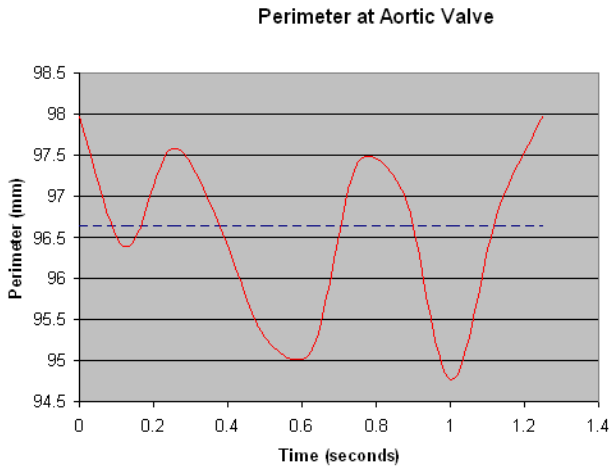
Patient imaging data is under-utilized for device design and performance validation

For many new devices and concepts, loading conditions are not known in advance



Spectral Analysis of Aortic Valve Frame





The valve frame experiences three cycles of contraction for every heart beat.

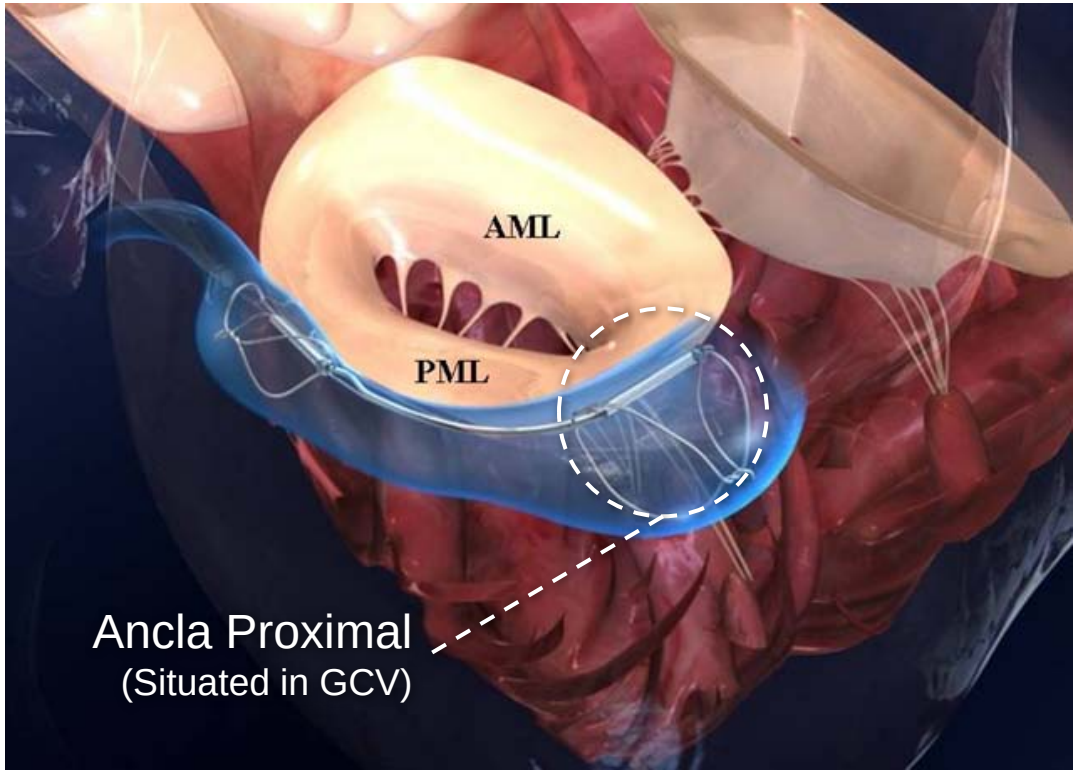
Imaging studies can quantify clinically relevant loading conditions and provide essential data and for selecting bench-top testing parameters.

Determining Complex Loading Conditions

This percutaneous device is used to treat mitral valve disease.

The loading conditions on the device are complex and difficult to quantify.

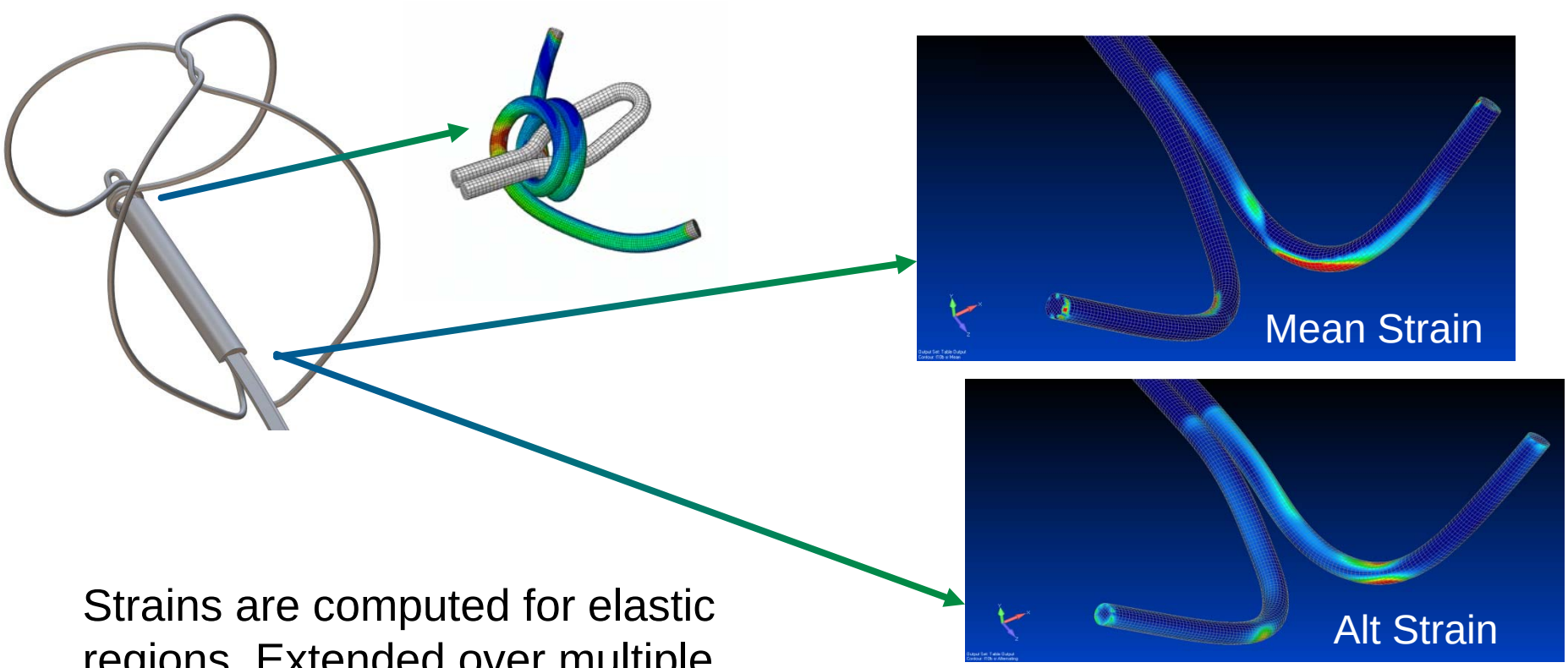
AEF and medical imaging were used to study these conditions and reduced them to simple engineering terms.



Biplane Cine with FEA Results

The implant geometry can be determined by projections the characteristics of individual frames in space.

In vivo Fatigue Strain Estimates



Strains are computed for elastic regions. Extended over multiple frames, mean and alternating *in vivo* strains may be calculated.

A Vision for Modeling and Simulation in Device Design and Development

Digital Patients: Designers download anatomic and physiologic computer models of (dozens, hundreds, thousands, …) of patients with a given disease.

Virtual Clinical Trials: New device concepts are "deployed" in digital diseased patients and performance is simulated leading to more effective bench testing, animal studies and (actual) clinical trials.

Discover "Soft Failures"

Personalized Medicine: Physicians use simulation to predict safety and effectiveness of a given medical product for an individual patient.

Computational Modeling is a powerful tool for *Regulatory Decision-Making*

Summary

- The ABC models yield safety data (especially for new or modified devices) before the clinical evaluation.
- Boundary conditions for the ABC models can be further advanced by clinical data and knowledge

Medical imaging data and analysis is a gold mine for information about implant mechanics

Acknowledgements

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