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INSTITUTE FOR BIOLOGICAL INTERFACES OF ENGINEERING

Advancing Regulatory Science through Integrative Engineering with COMSOL Modeling

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COMSOL CONFERENCE
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- **Really, there are sciences in regulatory affair?**

- **Regulatory affair**
  - The affairs handled by the U.S. Food and Drug Administration (FDA) - an agency within the Department of Health and Human Services overseeing Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations, for
  - Protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices, and the safety and security of most of our nation’s food supply, all cosmetics, dietary supplements and products that give off radiation.
- **Regulatory science**
  - According to the FDA, regulatory science is the science of developing tools, standards, and approaches to assess the safety, effectiveness, quality, toxicity, public health impact, and/or performance of FDA-regulated products.

- **Why should we care? Unfortunately, it concerns all of us!**

- **Science of developing tools, standards, and approaches?**
  - **Clearly, regulatory science has been equated to the development of tools, standards, and approaches.**

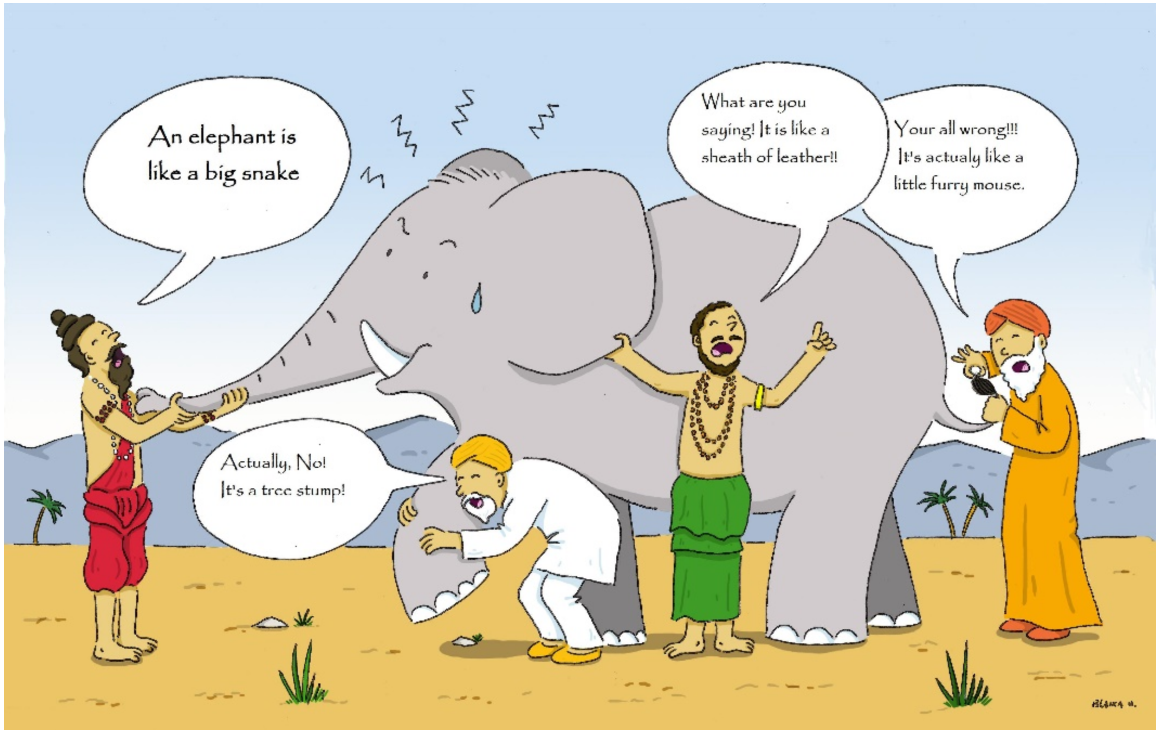
- **Will a tool, standard or approach developed based on incomplete scientific premises help improve the regulatory processes and pathways?**

- **What do I mean by incomplete scientific premises?**

- **Our limited scientific understanding of the world shaped by our training in a compartmentalized discipline**

  - A compartmentalized discipline is a field of study or a trade, in which a set of rules, codes, ways of doing things is imparted from teachers to students
  - The origin of disciplines is likely the result of our cognitive dealing with the world we live in, through a ***reductive process***
  - Reductive thinking helps reduce a complex issue to small independent pieces by neglecting and discarding as much as possible factors and issues that we have no knowledge or comprehension of at the moment
  - The benefits: in each discipline, specialized knowledge, procedures, and practices can be imparted to students or trainees
  - The problems: it ignores the interwoven issues that signifies the real-world problems

- **A classic example of incompleteness - Blind men and an elephant**



- **While we have been laughing at it since childhood, we are still victims of this exploratory approach in our scientific endeavors even to this day**

- **Today, pretty much all investigative approaches are reductive and compartmentalized, hence insufficient for dealing with the complex biomedical problems**

- **To change that, we need to breakaway from this incompleteness**
  - **By promoting a new way of scientific exploration through seeking convergence upon integration of knowledge, understanding, ways of exploration, etc. from transdisciplinary fields including the life sciences, physical sciences, engineering, social and behavioral sciences, etc. to address complex problems**

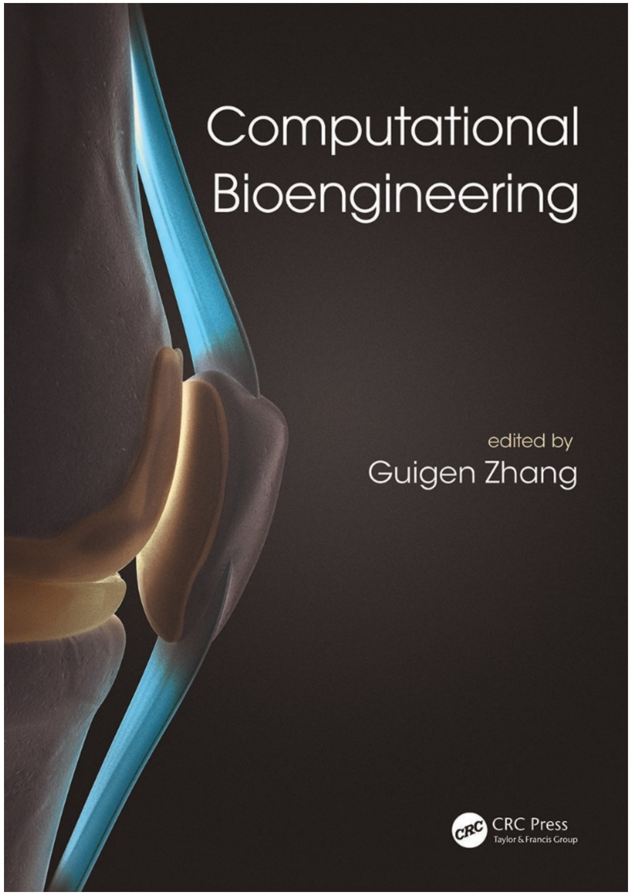
Introduction to

Integrative Engineering

A Computational Approach to Biomedical Problems

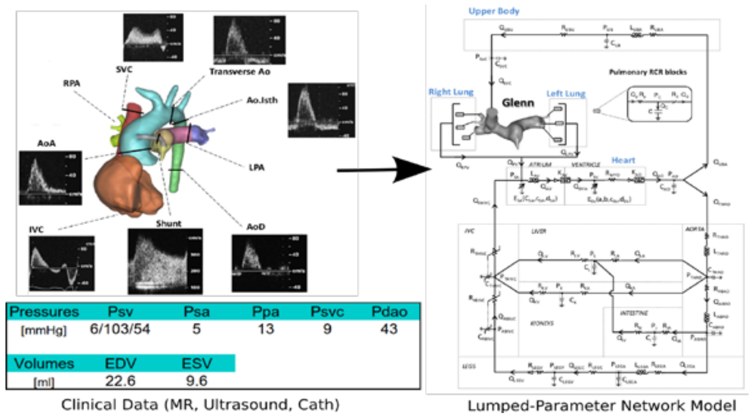
Guigen Zhang

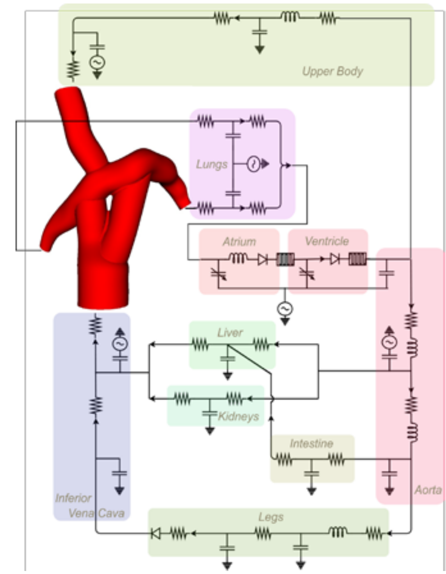
- **Computational Methods**
  - **On the science and engineering front, the problems need to be examined with a holistic consideration of all relevant governing principles.**
  - **COMSOL® software is particularly suited for solving, non-reductively and non-destructively, complex problems that are not only of mechanical, but also of electrical, thermal, chemical, and biological in nature, which behave according to the governing laws of thermodynamics, chemistry, physics and biology.**



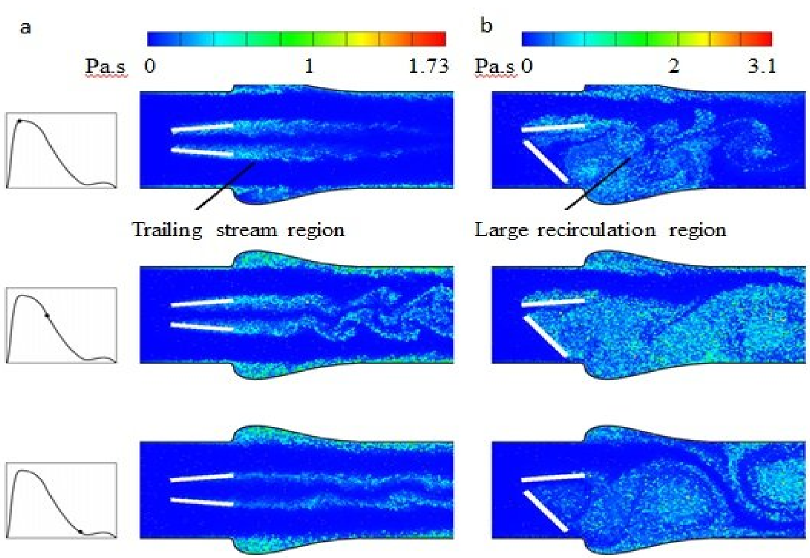
Examples – Cardiovascular related problems

Vascular blood flow and heart valves





Multiscale modeling of cardiovascular flow

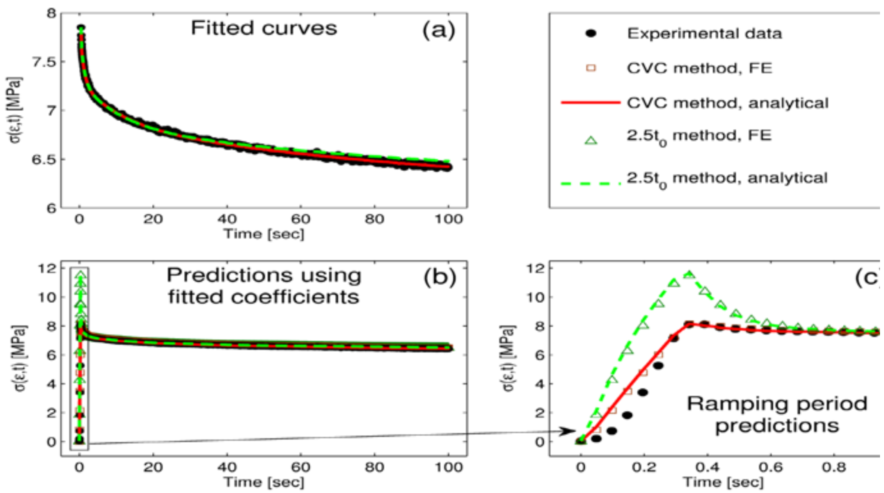


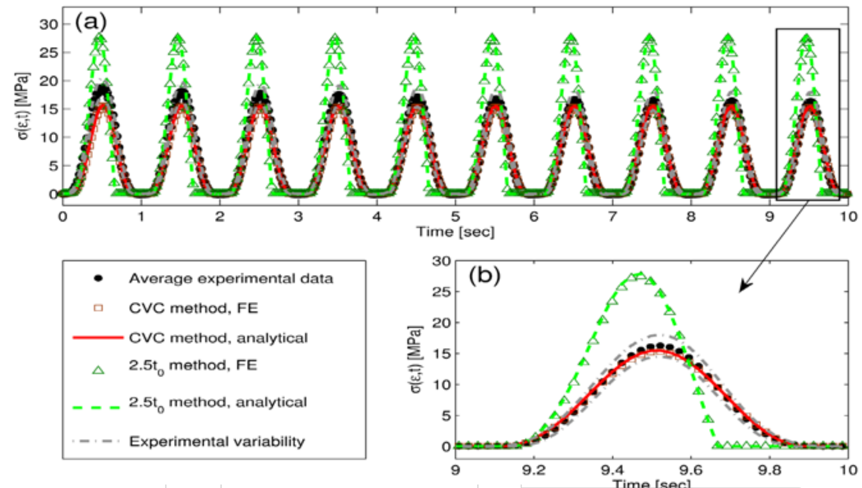
Fluid modeling of heart valves

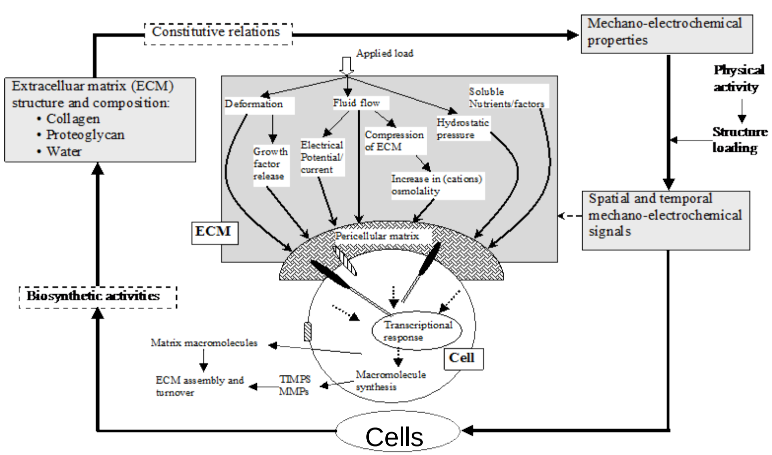
Examples – Soft tissue related problems

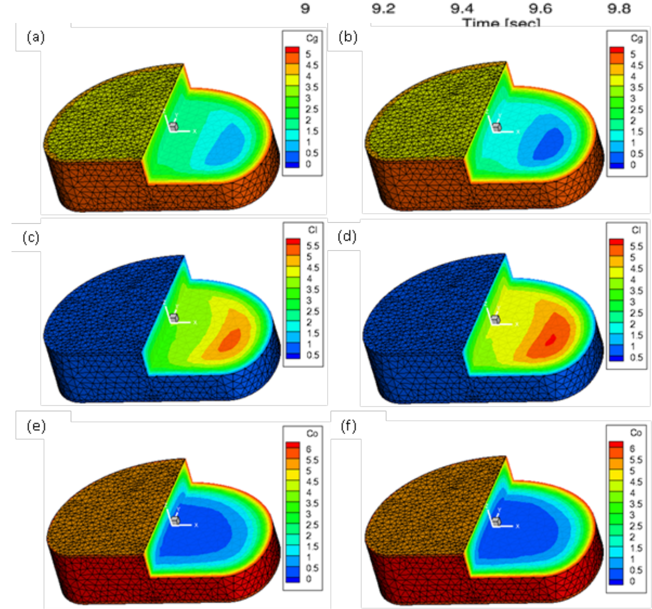
Connective tissues and intervertebral discs

Viscoelasticity of connective tissues







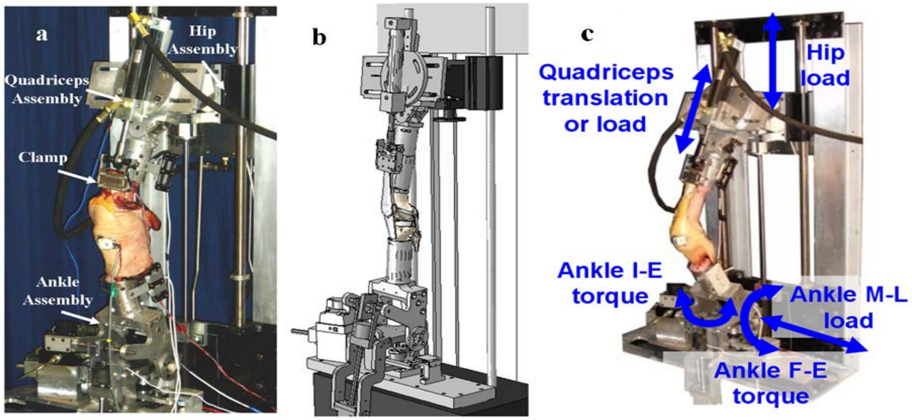


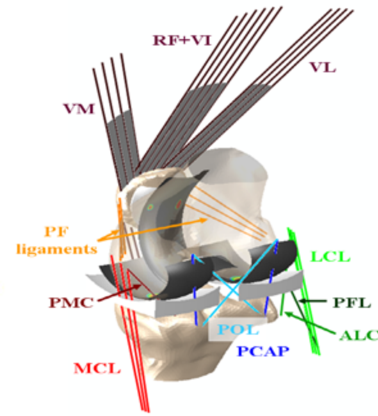
Transport in human intervertebral disc

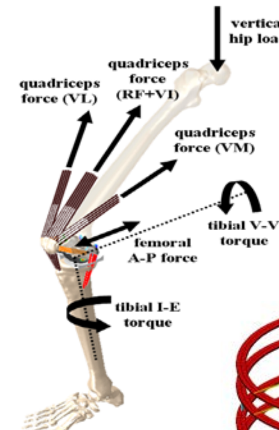
Examples - Hard tissue related problems

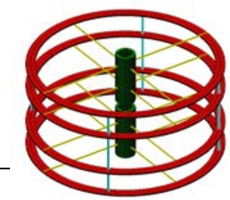
Joint prosthesis, bone remodeling, and fixation device

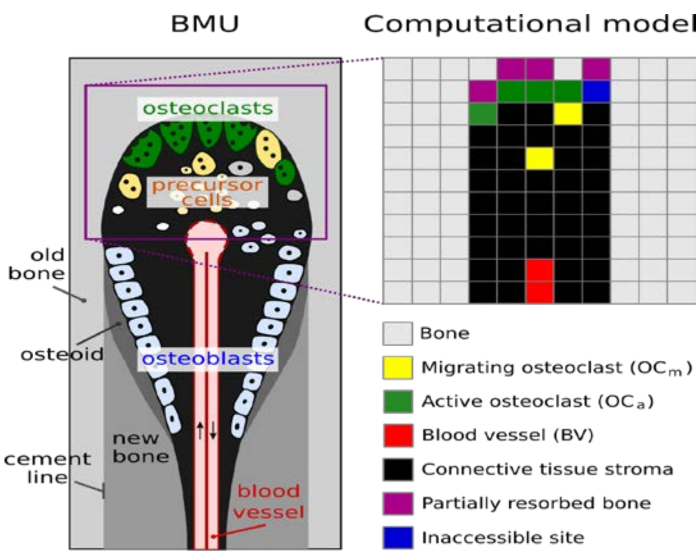
Predicting the performance of joint arthroplasty

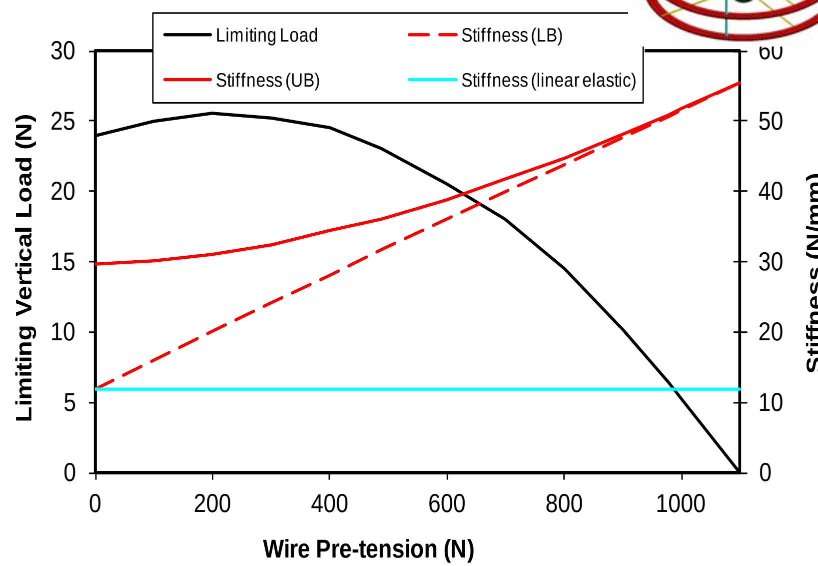








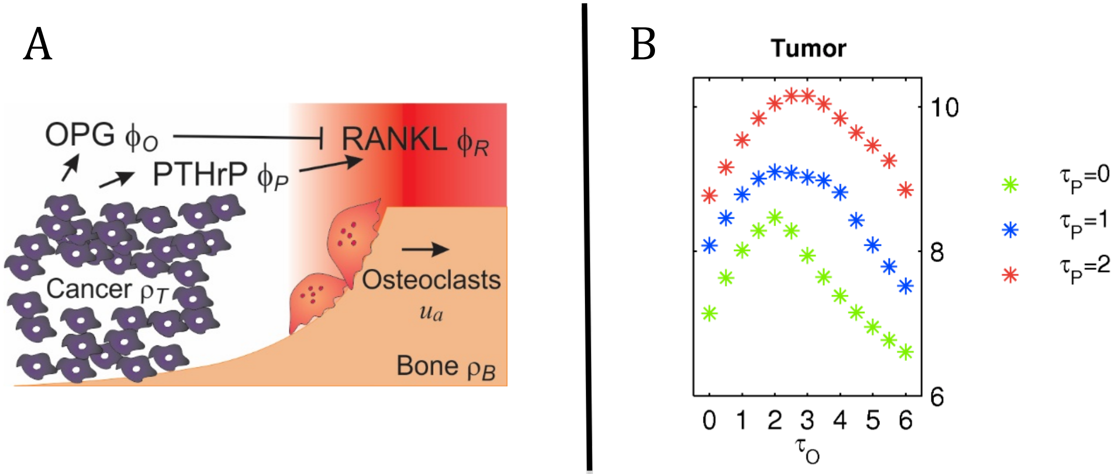




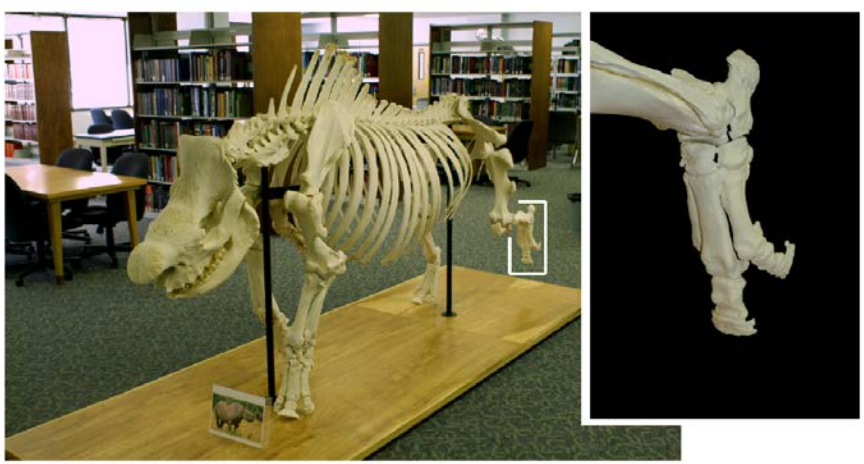
Basic multicellular units and bone remodeling

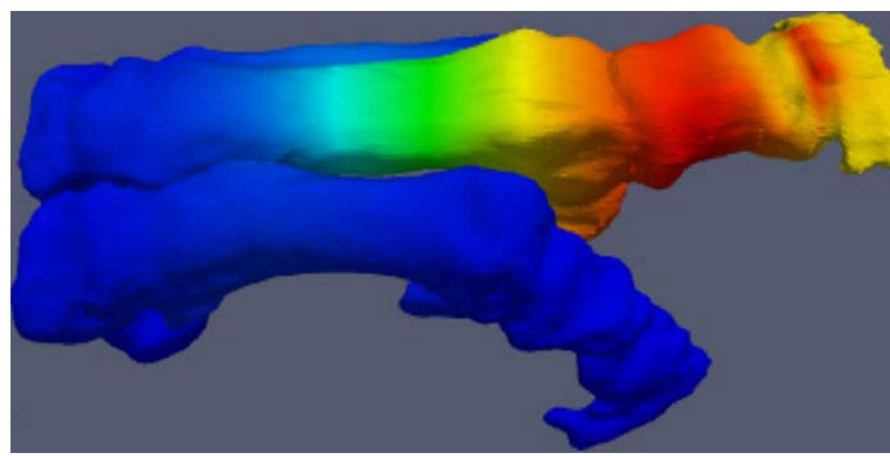
Nonlinearity in tensioned wires

Examples – Cancer metastasis, etc.



Modeling of cancer metastases

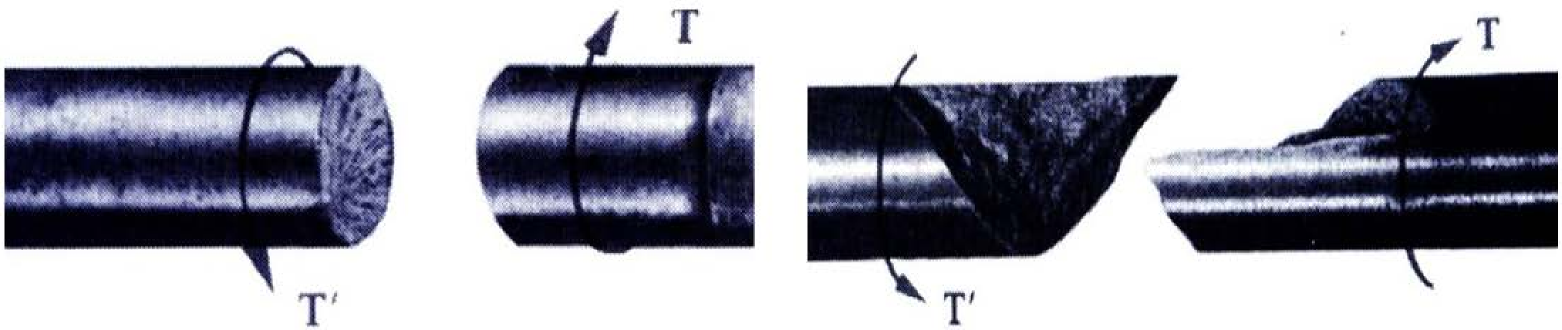


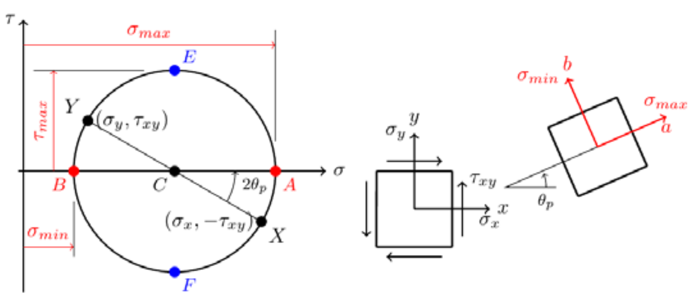


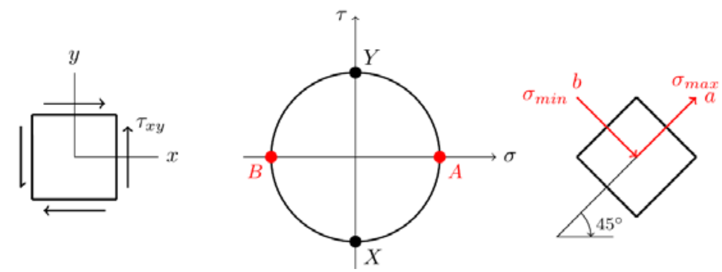
Patient specific modeling

- **Modeling based science to aid decision making**

Loading modes, stress states and Mohr's circle
--- Seeing beyond what meets the eyes







- **Modeling based science to aid decision making**

von Mises or max tensile stress?

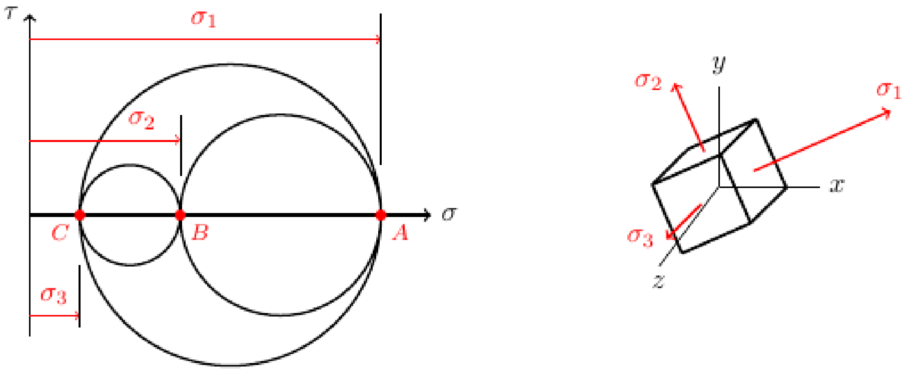


Figure A.9: 3D Mohr's circles and the first, second and third principal stresses.

$$\tau_{max_{(xy)}} = \frac{(\sigma_1 - \sigma_2)}{2},$$

$$\tau_{max_{(yz)}} = \frac{(\sigma_2 - \sigma_3)}{2},$$

$$\tau_{max_{(xz)}} = \frac{(\sigma_1 - \sigma_3)}{2}$$

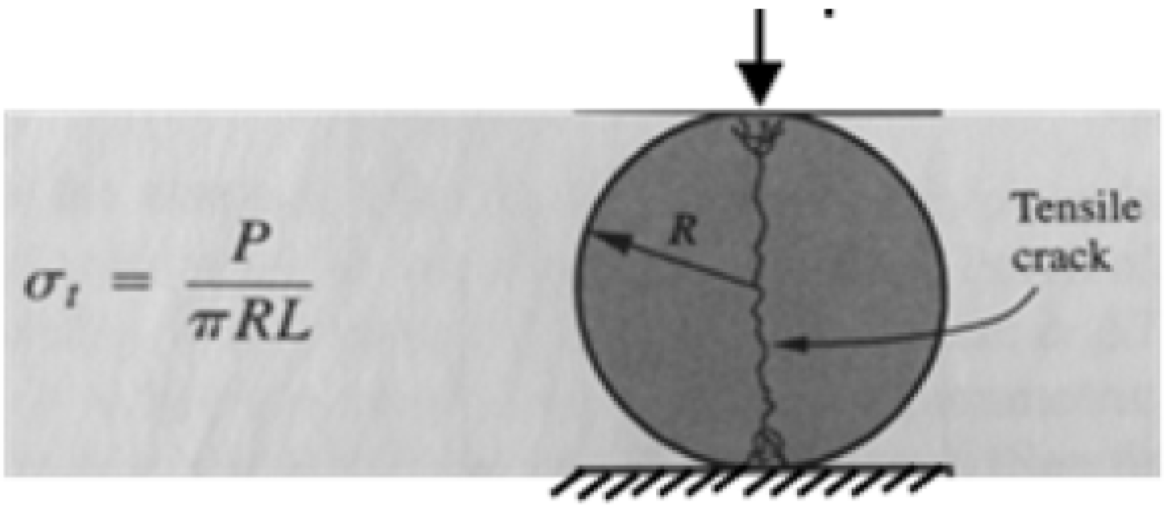
von Mises stress is not stress in a vector sense. Instead, it is a scalar representation of the *distortion energy* (caused by the maximum shear stresses) within a material using a quantity that carries the units of stresses:

$$\sigma_{vM} = \sqrt{\frac{(\sigma_1 - \sigma_2)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_1 - \sigma_3)^2}{2}}$$

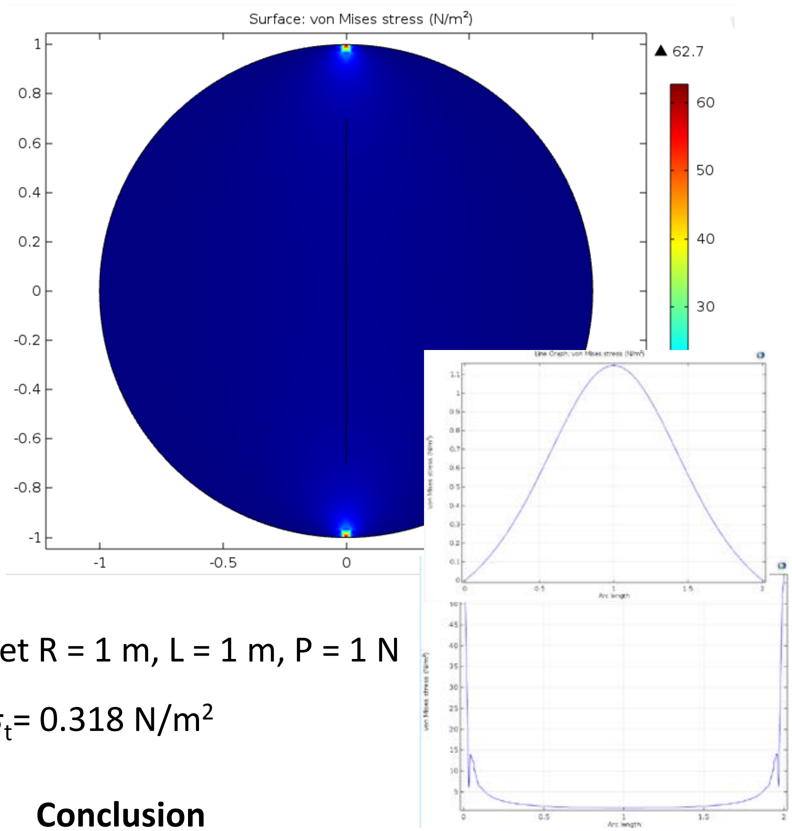
- **A classroom example on decision making**

The Brazilian test for brittle materials

1. The tensile strength of brittle materials such as rocks and concrete can be evaluated by performing a compressive test, known as the Brazilian tensile test. When the specimen crack along the center vertical line (see figure 1), the tensile strength is taken to be $\sigma_t = P/\pi RL$, where R is the radius and L the length of the specimen, and P is the load applied. Build a 2D model to evaluate the accuracy of this equation and compare the 2D plane-strain and plane-stress results to see which 2D case represents the actual situation better.



Answer No. 1



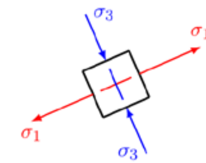
Set R = 1 m, L = 1 m, P = 1 N

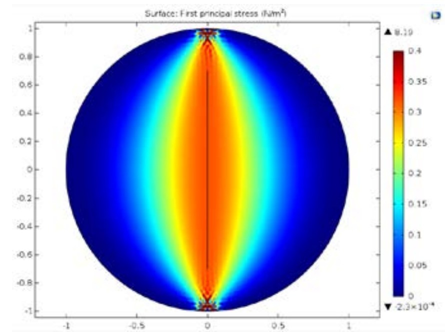
σ_t= 0.318 N/m^2

Conclusion

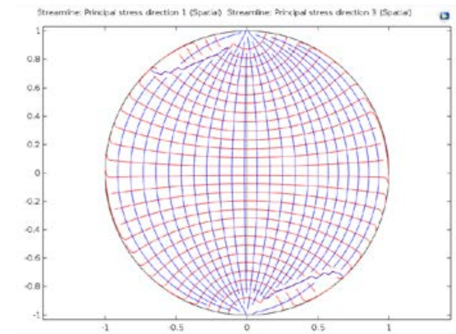
Judging from the modeling results (the von Mises stress shown above), the given equation is not reproduced ...

Answer No. 2

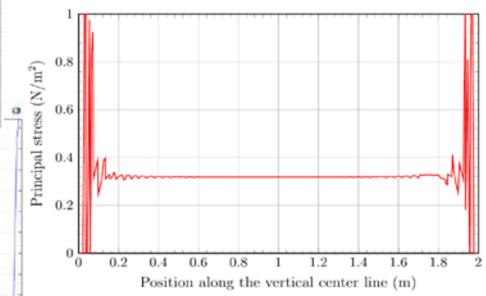




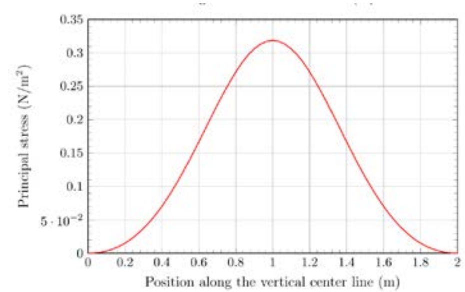
Max tensile stress



Stress trajectories



Max tensile stress: v-center-cut



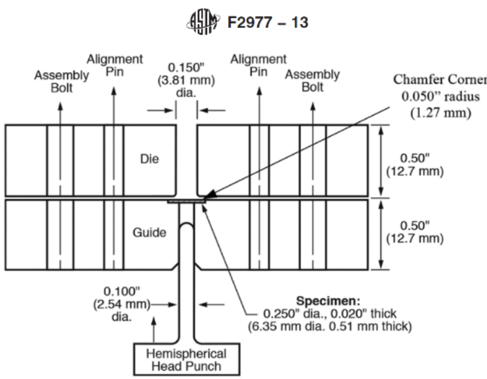
Max tensile stress: h-center-cut

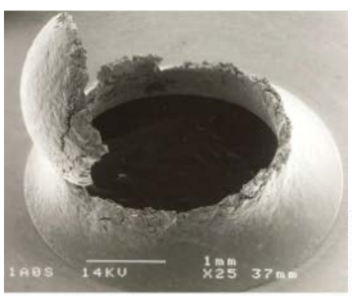
Conclusion

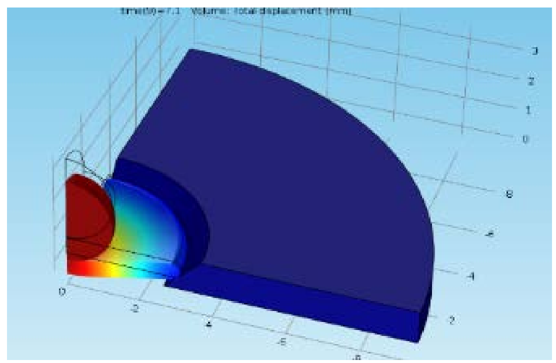
The modeling results predict the highest tensile stress along the vertical center line with the stress value in very good agreement with that given by the equation.

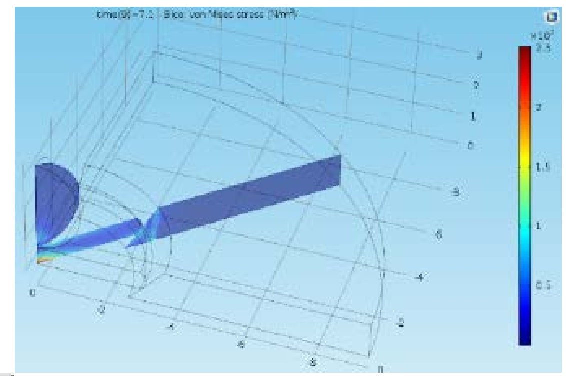
The underlying message: if done right, computational modeling (cost effective, quick turn-around, insightful, etc.) can predict very well the failure modes and failure stresses.

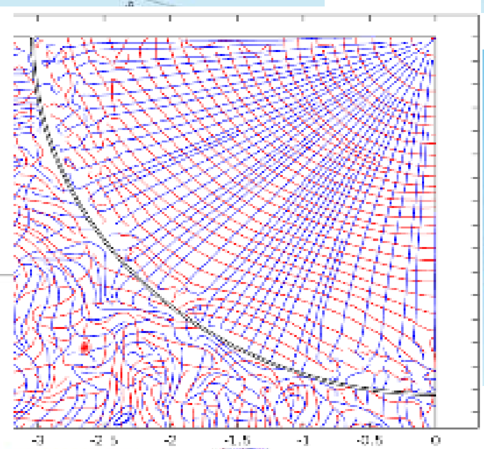
A Case Study of an existing standard: A small punch-out test (ASTM F2977-13), designed to provide a simpler way to assess material failure, is found to possess a very complicated stress condition as shown in Fig.1, causing unnecessary ambiguity in failure modes including tensile, shearing or combined modes of failure.

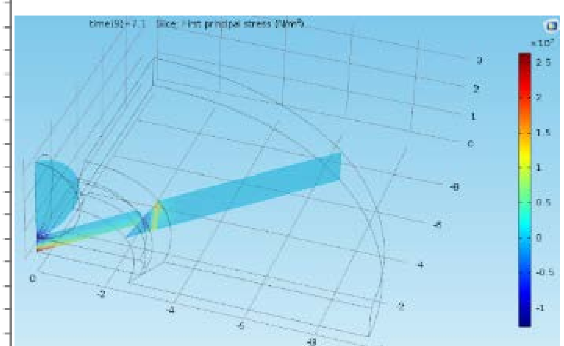


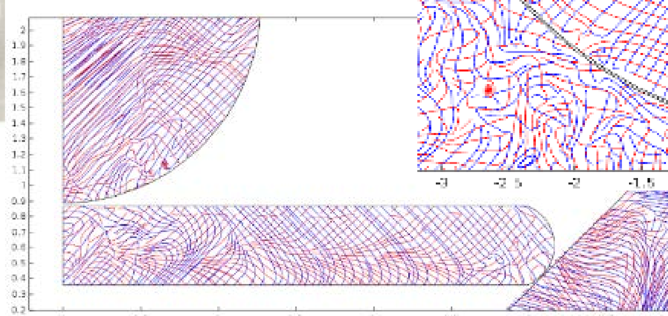






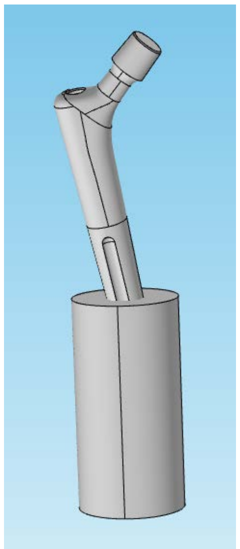
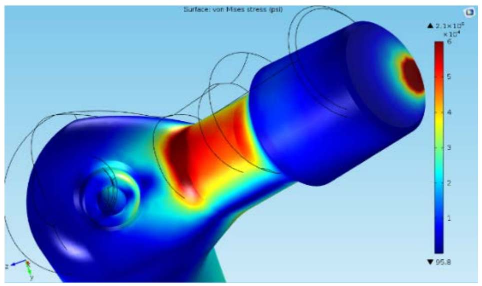
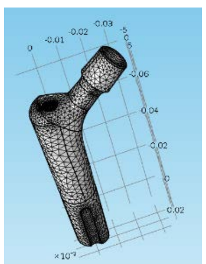
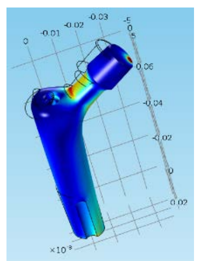
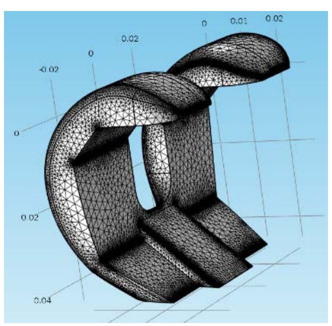
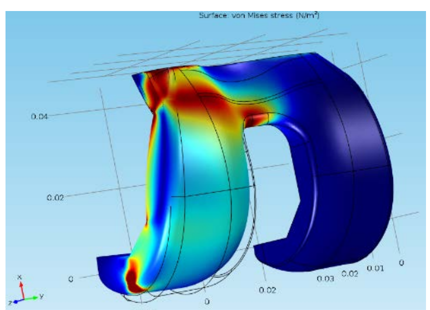


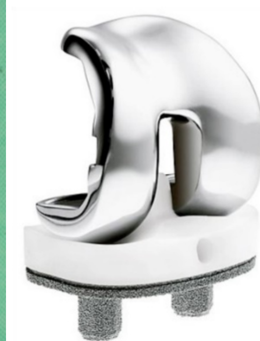


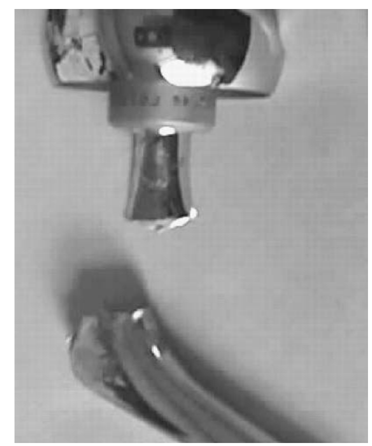


A standard that invites uncertainty!

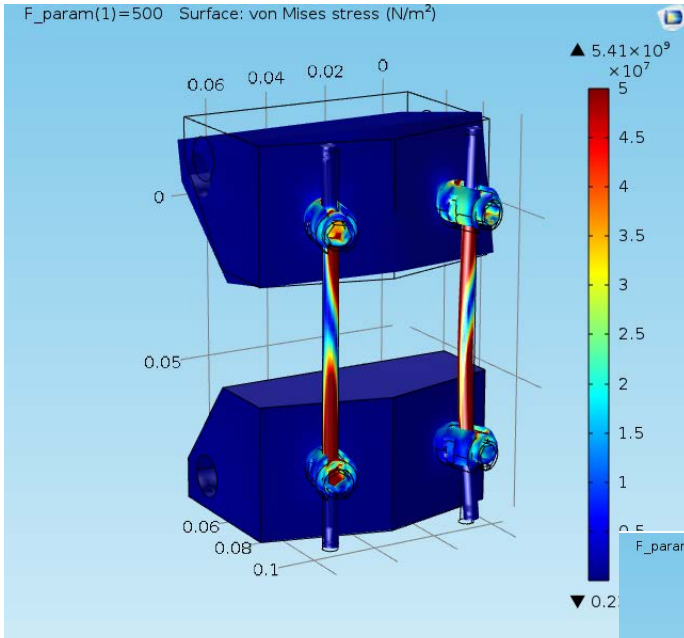
For standards, they need to be developed with clinical-relevant predictive power to inform decision making

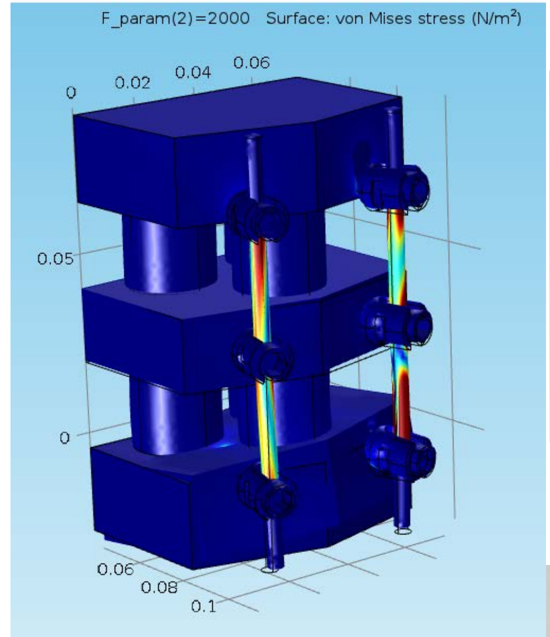







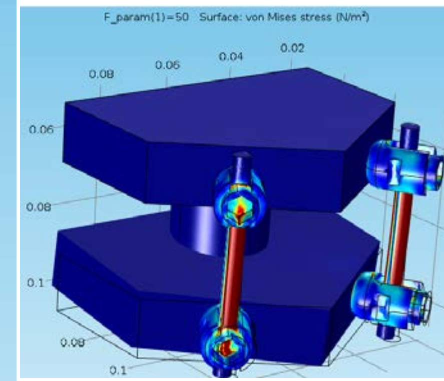



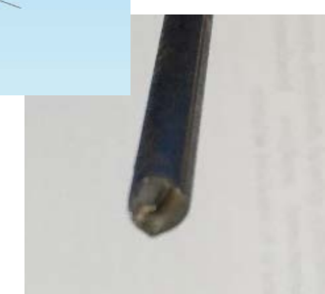


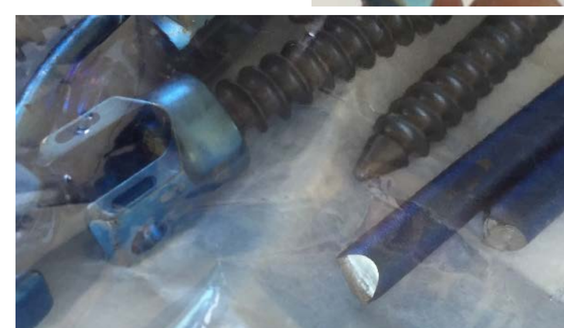

Making it clinically relevant: ASTM 1717-14; ISO 12189

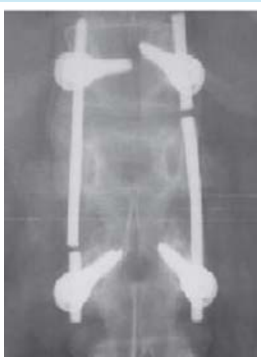


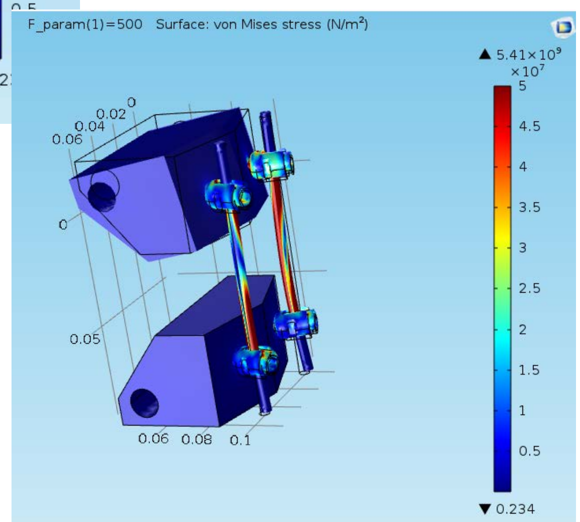






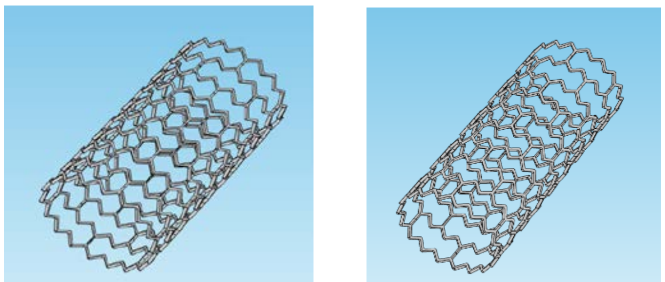




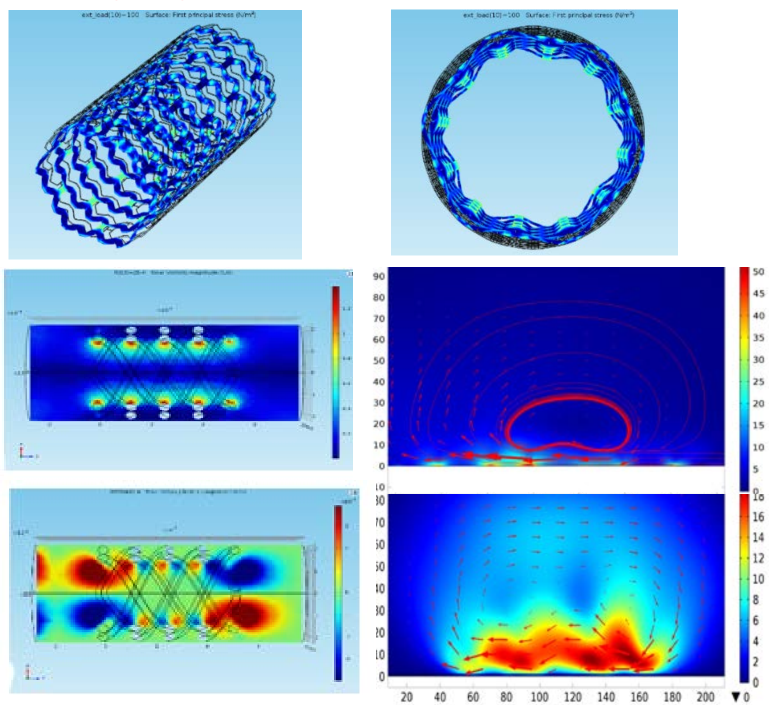


The untapped power of modeling capabilities

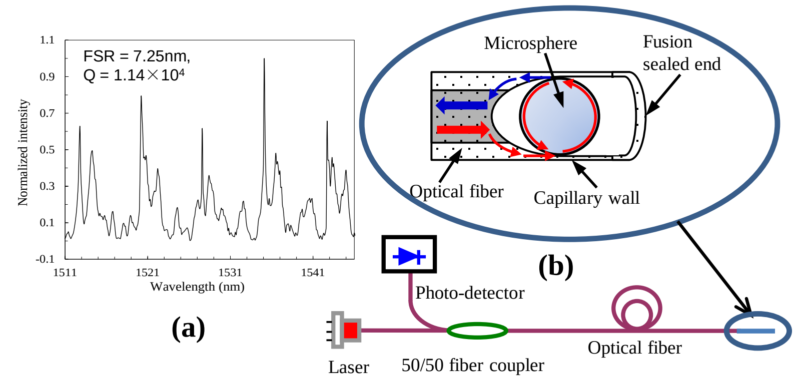
Parametrizing computational models

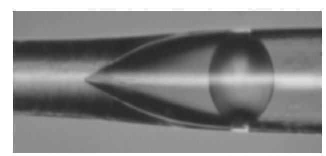


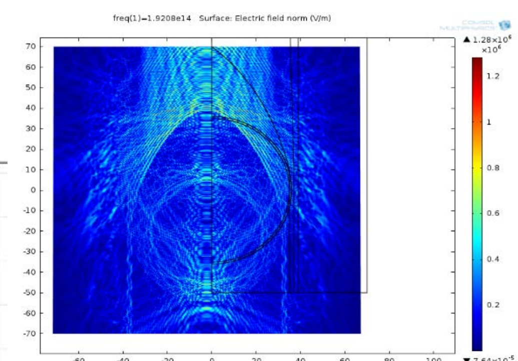
A holistic perspective

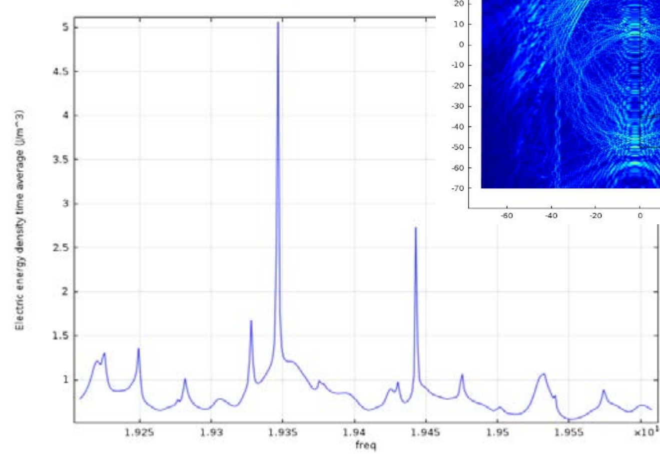


Integrated fiber optic WGM needlescopic sensor









Conclusions:

- In addition to developing relevant tools, standards, and approaches, regulatory science should be regarded as the **science of the highest level – the science of making right regulatory approval decisions, assuring public safety, and promoting innovation**

- Such a science calls for seeking convergence based on information gained from life and clinical sciences, physical sciences, computer science, engineering, social and behavioral sciences, etc.

- COMSOL Multiphysics can play a crucial role to facilitate it!

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Thank You!