Committee on Credible Practice of
Modeling & Simulation in Healthcare
https://simtk.org/home/cpms

Establishing Credible Practice Guidelines for Simulation-Based Medicine

Jacob Barhak[I], Ahmet Erdemir[II], Anthony Hunt[III], Joy Ku[IV], and Lealem Mulugeta[V]

I. Independent Consultant
II. Cleveland Clinic, Computational Biomodeling (CoBi) Core
III. University of California, San Francisco, Bioengineering and Therapeutic Sciences
IV. Stanford University, Simbios
V. Universities Space Research Association, Division of Space Life Sciences

14th International Meeting on Simulation in Healthcare
San Francisco, CA January 27, 2014

Presentation Outline

- Background on the Committee
- Committee's definition of "Simulation"
- The Committee's charge
- Current goals and activities of the Committee
- Real-world Examples of credible practice
- Future work
- Open discussion

BACKGROUND

- Computational modeling and simulation (M&S) methods have substantial potential to support research, clinical decision and education in healthcare

- Government agencies and industry are making substantial investments on R&D activities in simulation-based medicine and notable discoveries are being made

- ***Common practice guidelines <u>do not</u> exist*** to ensure these tools are appropriately applied

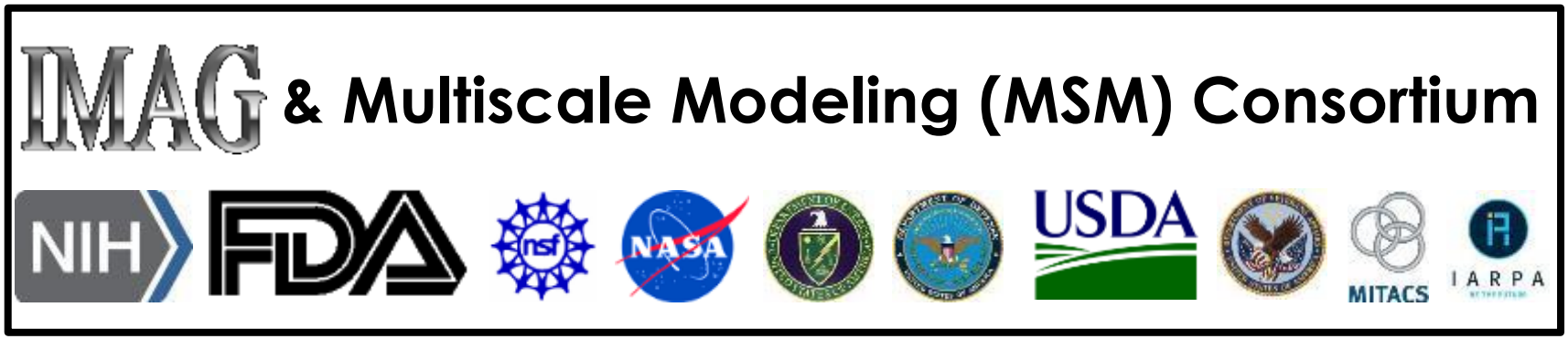
CFMS

BACKGROUND

To bridge this gap, the

Committee on Credible Practice of Modeling & Simulation in Healthcare

was established under



Definition of Simulation

Credible Practice of Modeling & **Simulation** in Healthcare

computational solution of models *to quantify descriptive and predictive metrics of system(s) of interest; including related post-processing efforts to calculate these metrics from raw analysis results*

CFMS

CHARGE: OVERVIEW

GUIDELINES & PROCEDURES	For credible practice in computational medicine by leveraging readily available techniques, and to define novel translational workflows to enhance credibility practice.
+	
DEMONSTRATE WORKFLOWS	By conducting studies for the implementation of novel credibility assessment procedures, and by disseminating examples of credibility assessment.
+	
CONSISTENT TERMINOLOGY	To unify the use of M&S vocabulary for clear communication across a variety of disciplines and stakeholders in the field.
+	
PROMOTE GOOD PRACTICE	By bridging synergistic activities of establishing confidence in simulation-based medicine conducted by M&S communities, as well as conducting outreach activities.
=	
END PRODUCT	I. "Guidelines for Credible Practice of M&S in Healthcare" II. Proposed model certification process III. Identify new areas of research to advance I & II

CHARGE: IMPLEMENTATION STRATEGY

None of us are experts in everything.
We need to learn from each other.

Credible practice of modeling and simulation in healthcare requires *ongoing* **inclusive communications** to establish *adaptive* **workflows** that can be utilized **broadly**.

CFMS

CHARGE: IMPLEMENTATION STRATEGY

COMMITTEE EXECUTIVE MEMBERS (EXECUTE & CHARGE)

Ahmet Erdemir, Ph.D. - Co-Chair
Cleveland Clinic

Gary An, MD
University of Chicago

Jacob Barhak, Ph.D.
Independent

Joy Ku, Ph.D.
Stanford University

Marc Garbey, Ph.D.
University of Houston

Lealem Mulugeta, M.Sc. -Co-Chair
Universities Space Research Assoc.

William Lytton, M.D.
Kings County Hospital
Downstate Med. Center

Tina Morrison, Ph.D.
FDA

Jerry Myers, Ph.D.
NASA

Lu Tian, Ph.D.
Stanford University

COMMUNICATION ⇕ **ACCOUNTABILITY**

ADVISORY COUNCIL (REVIEW & ADVISE)

Jeffrey Bischoff, Ph.D.
Zimmer

David Eckmann, M.D., Ph.D.
University of Pennsylvania

Ronald Germain, M.D., Ph.D.
NIH

Anthony Hunt, Ph.D.
University of California, San Francisco

Martin J. Steele, Ph.D.
NASA

Donna R. Lochner
FDA

James Thomas, M.D.
Cleveland Clinic

Vasilis Marmarelis, Ph.D.
University of Southern California

Grace Peng, Ph.D.
NIH

Pras Pathmanathan, Ph.D.
FDA

Wing Kam Liu, Ph.D.
Northwestern University

Marlei Walton, Ph.D.
Wyle Science, Technology and Engineering Group

Interagency Modeling and Analysis Group (**IMAG**) & Multiscale Modeling Consortium (**MSM**)

CPMS

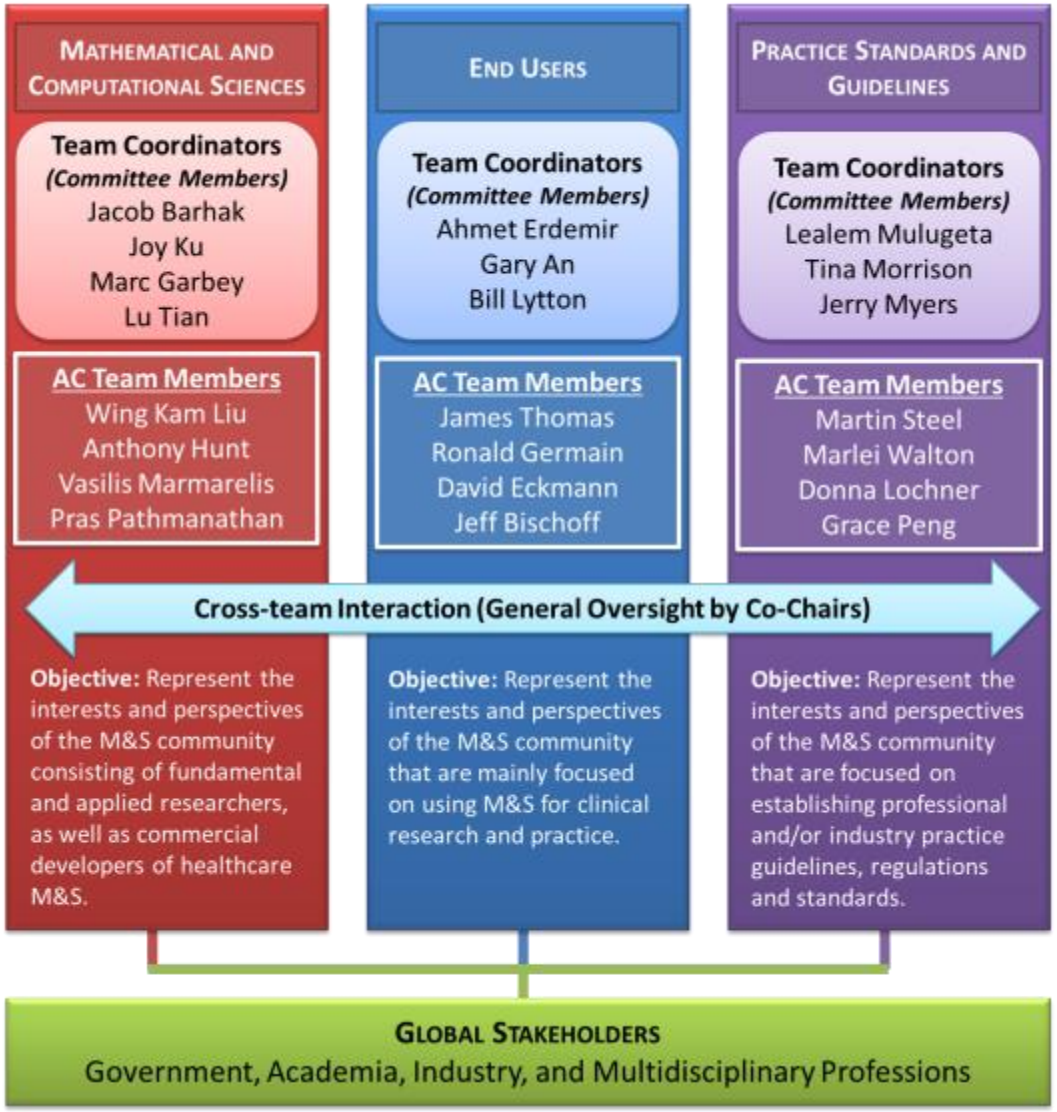
For full credentials of the CPMS members: http://wiki.simtk.org/cpms/CPMS_Members

CHARGE: IMPLEMENTATION STRATEGY

The Committee is divided into three Task Teams that represent the fundamental areas that are significant to our primary aims.

This team-based structure helps to:

- Establish a balanced representation of the interests and perspectives of the different stakeholders
- Bridge synergistic activities in simulation-based medicine throughout the M&S communities



GOAL: ESTABLISH CREDIBLE PRACTICE GUIDELINES

The Committee's primary deliverable by the end of the first two year term (03/2015) is to establish, "*Guidelines for Credible Practice of Modeling and Simulation in Healthcare*"

Goal Oriented Activity: The CPMS Task Teams were charged to identify ten key elements or simple rules of credible practice in order to establish a foundation from which the "*Guidelines for Credible Practice of Modeling and Simulation in Healthcare*" can be developed.

Full details of this activity is available at:
http://wiki.simtk.org/cpms/Ten_Simple_Rules_of_Credible_Practice

CFMS

ONGOING: TEN SIMPLE RULES OF CREDIBLE PRACTICE

To initiate the Ten Simple Rules task, the following 26 simple rule candidates were initially generated and surveyed internally by the Committee.

- Use version control
- Use credible solvers
- Explicitly list your limitations
- Define the context the model is intended to be used for
- Define your evaluation metrics in advance
- Use appropriate data (input, validation, verification)
- Attempt validation within context
- Attempt verification within context
- Attempt uncertainty (error) estimation
- Perform appropriate level of sensitivity analysis within context of use
- Disseminate whenever possible (source code, test suite, data, etc)
- Report appropriately
- Use consistent terminology or define your terminology
- Get it reviewed by independent users/developers/members
- Learn from discipline-independent examples
- Be a discipline-independent/specific example
- Follow discipline-specific guidelines
- Conform to discipline-specific standards
- Document your code
- Develop with the end user in mind
- Provide user instructions whenever possible and applicable
- Practice what you preach
- Make sure your results are reproducible
- Provide examples of use
- Use traceable data that can be traced back to the origin
- Use competition of multiple implementations to check and balance each other

ONGOING: INTERNAL SURVEY RESULTS ANALYSIS

#	Consolidated & Rephrased Rules
1	Plan and develop the M&S with clear definition of the intended purpose or context, and with end-user input
2	Document the your code and the M&S (domain of validity/invalidity, intended use, user guide, etc), and make your code readable
3	Use version control
4	Test the M&S Appropriately within Context (V&V, UQ, sensitivity analysis (SA), test cases)
5	Use appropriate data
6	Disseminate whenever and whatever possible
7	Explicitly list the limitations of the M&S
8	Adopt and promote standard operating procedures
9	Use competition of multiple implementations to check and balance each other
10	Make it easy for anyone to reproduce and/or falsify your results
11	Use traceable data that can be traced back to the origin
12	Define your evaluation metrics in advance
13	Have the M&S reviewed by independent users/developers/members

These results will be analyzed and reported in more detail in an upcoming presentation at the 2014 ASME V&V Symposium in May.

Full details are available at:
http://wiki.simtk.org/cpms/Ten_Simple_Rules_of_Credible_Practice/Summary_of_Results

UPCOMING: COMMUNITY AND MODEL SURVEYS

Simulation-Based Healthcare Community Survey: To ensure that we capture the perspectives and interests of the global stakeholder community, we are preparing to launch a public survey of the new 33 simple rule candidates (increase due to internal survey results)

Survey of Models: To complement the survey, we are also conducting a survey of computational models to develop a better understanding of the needs and successes of different types and applications of M&S in healthcare

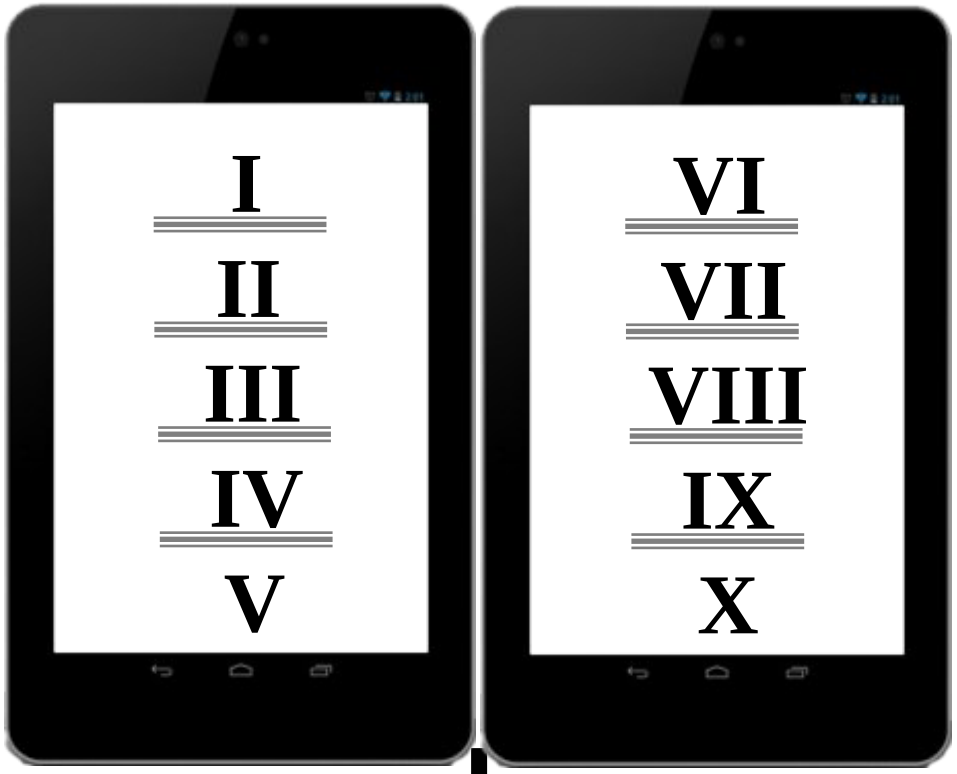
How can the SSH Community Participate?

- We strongly encourage the SSH community to participate in and promote the survey
- Contribute M&S examples that may help us better understand the needs and successes of different types and application of M&S within the SSH community

CFMS

UPCOMING: TEN SIMPLE RULES, GUIDELINES & CERT.

COMMUNITY GENERATED TEN SIMPLE RULES



"GUIDELINES FOR CREDIBLE PRACTICE OF M&S IN HEALTHCARE"

PROPOSED MODEL CERTIFICATION PROCESS

CFMS

EXAMPLE: FRACTIONAL FLOW RESERVE - CT

Description

Intended use: Computes Fractional Flow Reserve (FFR) from non-invasive computed tomography images.

Limitations: Clinical studies assess only the accuracy of the FFR_{CT} quantity for coronary arteries

Credibility Assessment

Used clinical studies specifically designed to evaluate the efficacy of the model for non-invasive cardiac diagnostic relative to the traditional invasive FFR

- HeartFlow NXT Study (2013) – 254 patients
- DeFACTO Study (2012) – 252 patients
- DISCOVER-FLOW Study (2011) – 103 patients

Appropriate Application

- Determining FFR_{CT} for clinical decision-making purposes in terms of coronary artery disease
- Suitable for teaching purposes centered around FFR (and FFR_{CT})

Inappropriate Application

- Computing FFR_{CT} for diagnosing of other parts of the vasculature
- Utilizing quantities from the simulation other than FFR_{CT} (e.g., pressure, wall shear stress) for clinical decisions

EXAMPLE: BONE FRACTURE RISK MODEL

Description

Intended use: Probabilistic risk assessment of bone fracture due to bone changes due to zero-gravity exposure – analyses may be run for spaceflight or terrestrial scenarios

Limitations:

- Small n - "Attributable" data for model development
- Uses DXA BMD, which has a limited correlation to bone strength or [resistance to fracture], and bone quality

Credibility Assessment

Compared to two published data sets that are considered to be among the latest state of knowledge in bone loss and risk of fracture

- *Development and Validation of a Predictive Bone Fracture Risk Model for Astronauts, Annals of Biomedical Engineering, 2009, Vol. 37, Number 11, 2337-2359*

Appropriate Application

Provide supporting evidence for:

- Bone fracture risk due to spaceflight related bone loss in terrestrial and spaceflight environment
- Injury criteria definition: additional for fitness of duty evaluations for spaceflight, and injury loading thresholds
- Changes to inflight injury likelihood resulting from exercise or pharmaceutical countermeasures to bone loss

Inappropriate Application

- As a sole source of evidence to make decisions regarding bone fracture risk – credibility level is not sufficient for this
- Predict changes in bone volumetric density or architectural changes – μQCT and finite element methods are required for this

EXAMPLE: GROSS CARDIOVASCULAR PHYSIOLOGY

Description

Intended use: Education model to teach medical students about the general response of the cardiovascular system to various physiologic stresses, and administration of various interventions

Limitations: Assumes average adult male between the ages of 25 and 55, weighing 180 lbs, and 5' 9" tall

Credibility Assessment

- Verification against simple test cases
- Face/qualitative validation against literature data by physicians and physiologists for general trends in physiologic responses
- Numerical stability and sensitivity analysis were not performed
- Historical development data and versions were not documented

Appropriate Application

- A teaching tool to provide very high level insight of how the cardiovascular system may respond to various stressors and interventions built into the simulation environment
- The educator should emphasize the simulations should be used as a supplement and not a replacement of their core curriculum

Inappropriate Application

- Conducting simulation scenarios that violate the primary assumptions
- Simulations of other physiologic systems
- Attempting to use the model for research or clinical purposes; credibility assessment is not sufficient for these kinds of applications, and it was developed for teaching purposes

Note: This is a generalized example based off of a real use case of an educational model

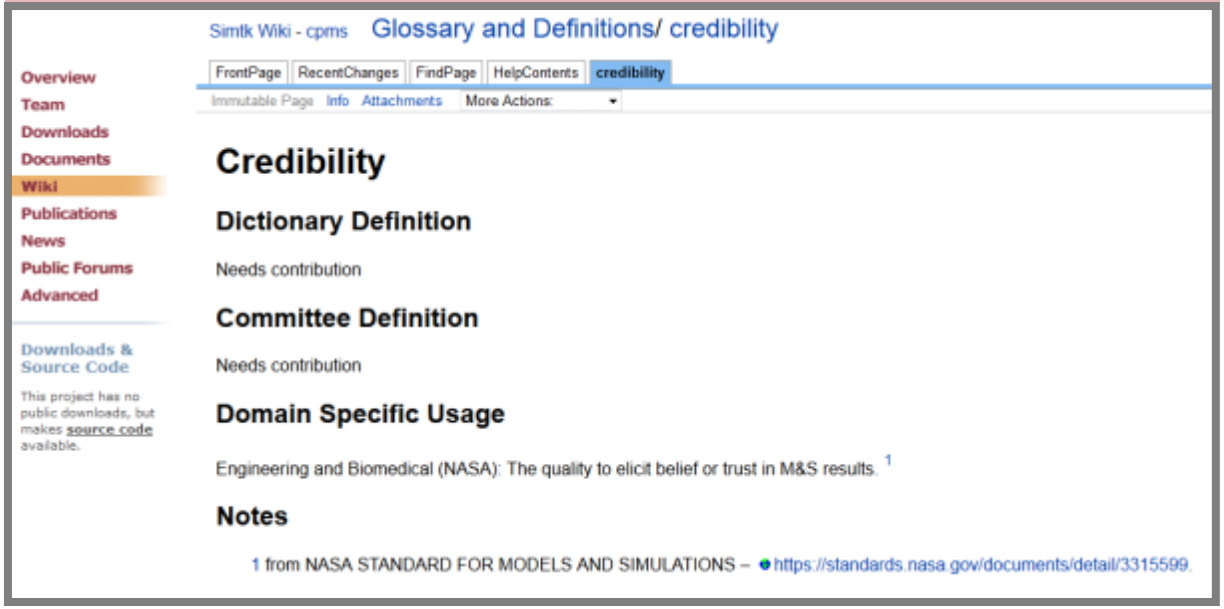
GOAL: A COMMON LANGUAGE ACROSS DISCIPLINES

Goal Oriented Activity: A glossary of terms is being generated on the Committee's to help unify the use of M&S vocabulary across a variety of disciplines and stakeholders in the field

We strongly encourages all stakeholders (e.g. SSH community) to help establish these terms and definitions by visiting: http://wiki.simtk.org/cpms/Glossary_and_Definitions

CFMS

Example



GOAL: ADOPTION OF GUIDELINES BY STAKEHOLDERS

Goal Oriented Activity: We are taking every opportunity to engage and strongly encourage the global stakeholder community, such as the Society for SSH, to actively contribute to these efforts to ensure that the guidelines established capture the primary interests of the computational medicine community

Open discussions and contribution to activities via:

- Wiki pages
- Discussion forum
- Meeting minutes
- Subversion repository access of all presentations, abstracts and posters

URL: https://simtk.org/home/cpms

Future Work

- Launch public survey to the global community (~3 months) – Projected launch date: ??/2014
- Analyze data, and publish results in PLOS Computational Biology in the form of "*Ten Simple Rules of Credible Practice of M&S in Healthcare*" – Estimated submission date: ??/2014
- Develop and publish the "*Guidelines for Credible Practice in Modeling & Simulation in Healthcare*" based off of the Ten Simple Rules – Estimated completion date: 03/2015

CFMS

Open Floor Discussion

- What are the areas that are most important to you in simulation-based healthcare?
- Have we've missed something?
- What are the challenges you face in applying simulations effectively to educate the healthcare practitioners?
- Are there any use cases you want to discuss with us?

Please take advantage of the survey, public forum and wiki site to continue this conversation with us. The guidelines will ultimately belong to you, so we want to hear from you!

CFMS

Backup Slides

DEFINITIONS

Credible Practice of Modeling & Simulation in Healthcare

dependable *with a* ***desired certainty level*** *to guide research or support decision making within a prescribed application domain and intended use; establishing* ***reproducibility*** *&* ***accountability***

CFMS

DEFINITIONS

Credible **Practice** of Modeling & Simulation in Healthcare

*any activity involving **development**, **solution**, **interpretation** and **application** of computational representation of biological, environmental and man-made systems and their interaction thereof*

CFMS

DEFINITIONS

Credible Practice of **Modeling** & Simulation in Healthcare

specifically ***computational modeling****;* ***virtual representation*** *of system(s) of interest in a usable form in order to provide* ***descriptive*** *and* ***predictive*** *metrics for timely and systematic exploration of the system(s)*

CFMS

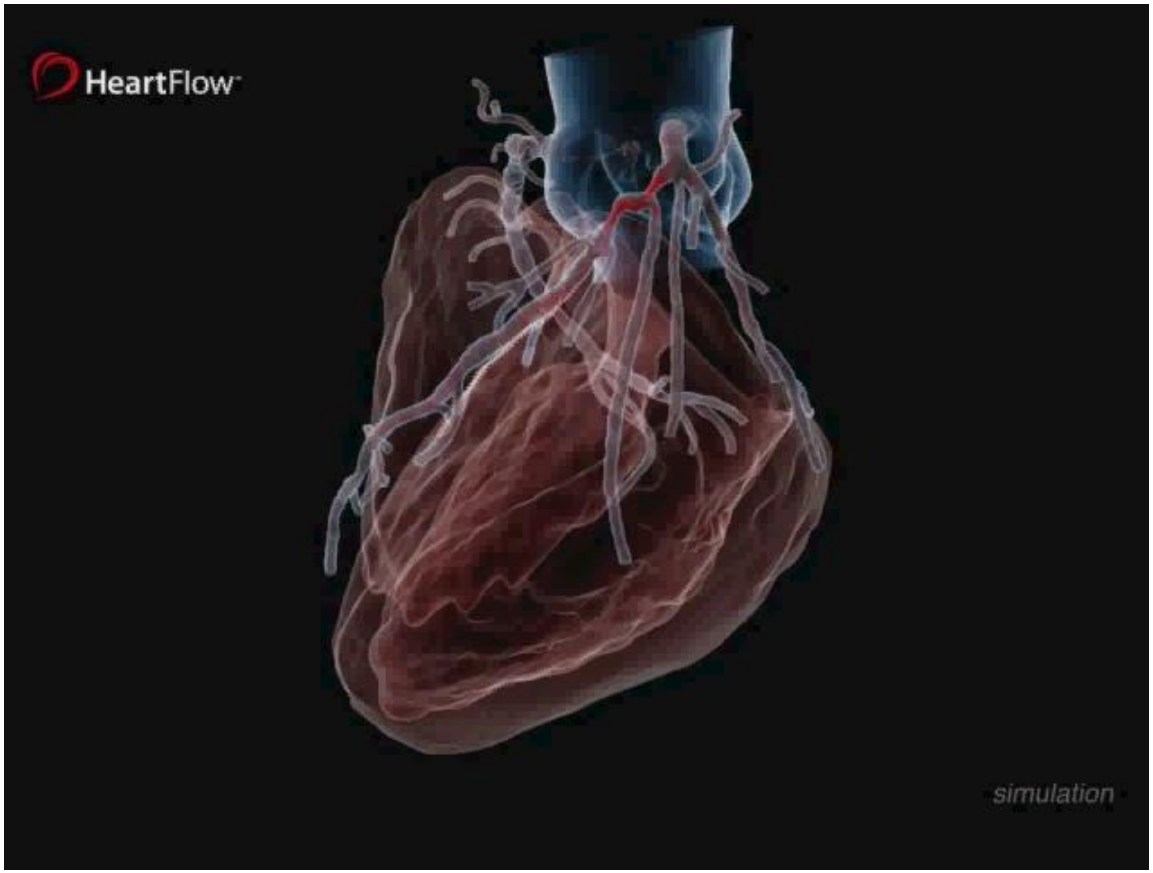
DEFINITIONS

Credible Practice of Modeling & Simulation in **Healthcare**

*any activity involving **development**, **maintenance**, **advancement**, or **administration** of **medical care**; including research, diagnosis, risk assessment, prevention, therapy, rehabilitation, surgery, intervention design, and regulation*

CFMS

Modeling for Coronary Artery Disease Diagnostics

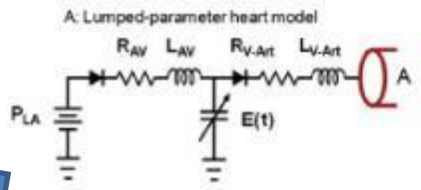


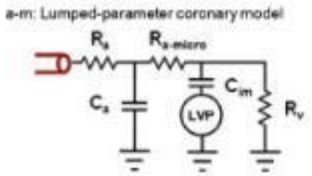
- Fractional Flow Reserve (FFR)
  - Current gold standard in assessing coronary artery disease
  - Invasive procedure
- Heartflow's FFR_{CT} technology computes FFR from non-invasive computed tomography images

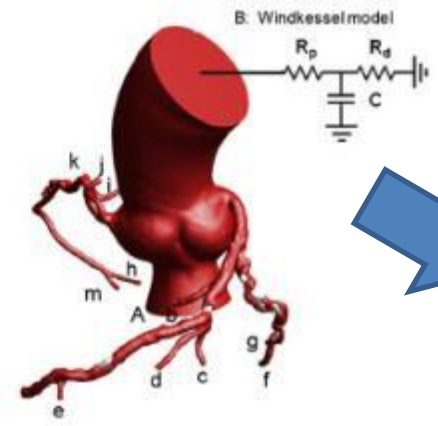
Video from http://heartflow.com

Overview of FFR_{CT}

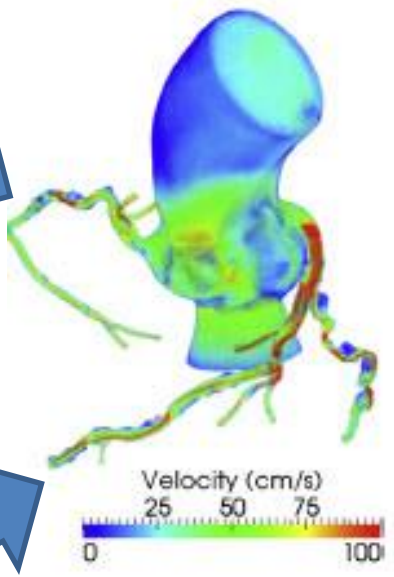
computed tomography angiography imaging



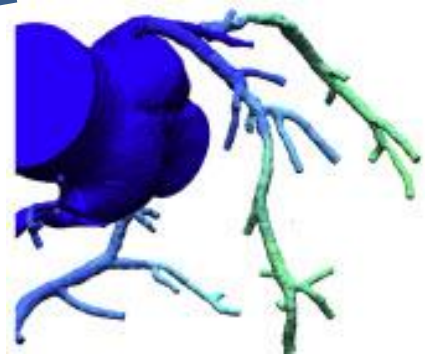




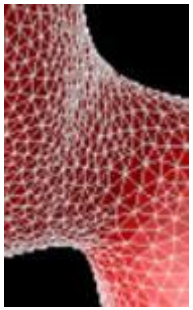
model conditions at inlets and outlets of geometric model



computational fluid dynamics used to compute velocities and pressures, from which FFR_{CT} can then be derived



construct geometric model of main vessels of interest

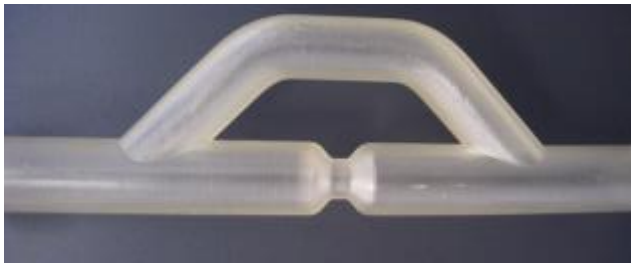


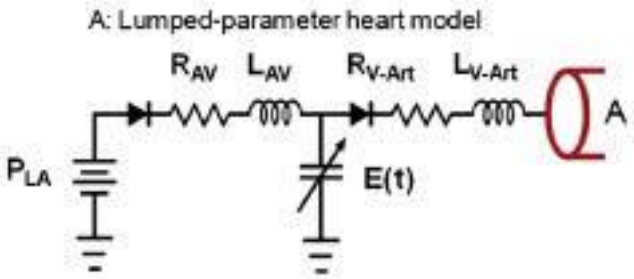
discretize model into mesh for computation

Taylor, CA, Fonte, TA, Min, JK, "Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve," 2013, JACC, 61(22):2233-2241

Building Confidence in the Model

- Started out with simple, "easy-to-test" *in vitro* model over 10 years ago
- Methods developed and tested to address limitations in the interim
- Assessing what model can be used for
  - Original idea: prediction of surgical bypass surgeries
  - Recent clinical studies assess technology for coronary artery flow, not necessarily applicable to other parts of the vasculature

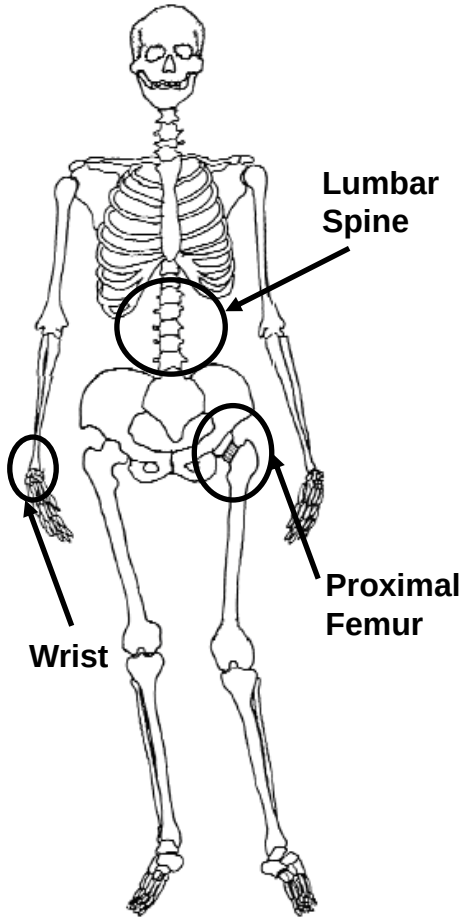




(to add: graph of results from

Bone Fracture Risk Model

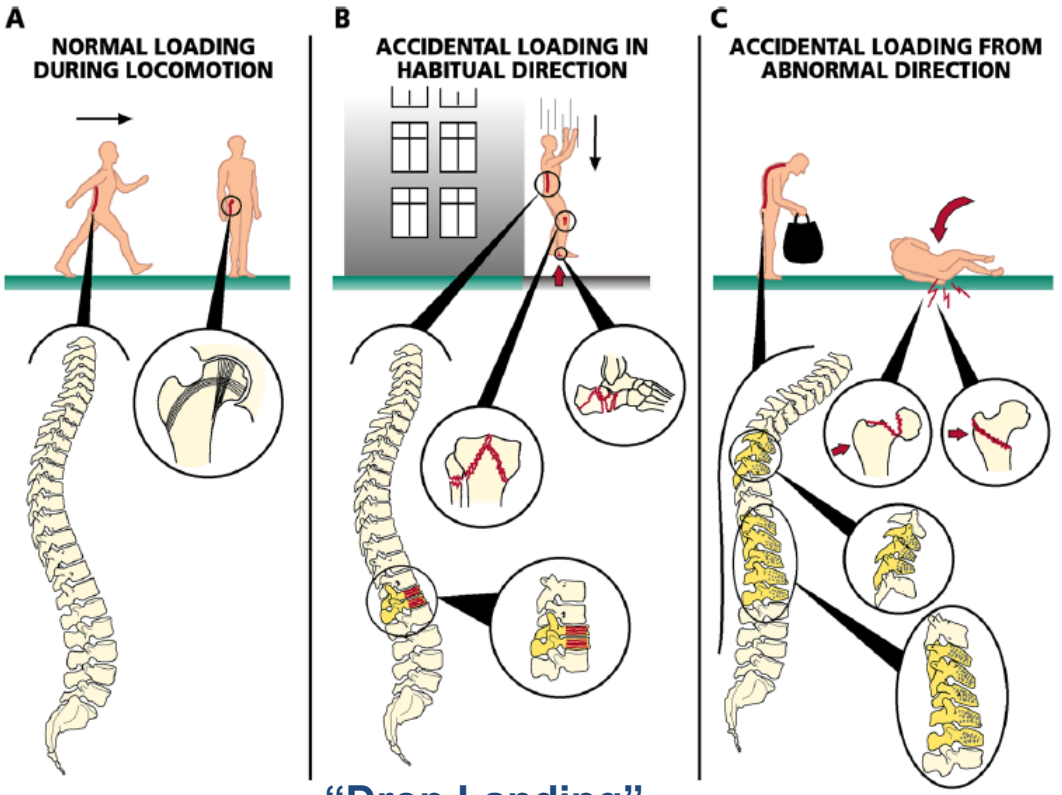
- What can we do to estimate astronaut risk of fracture?
- Real and Present Concern: Skeletal Fracture
  - Weakened bones
  - Unique and off-nominal loading states
- Lack of In Flight Injuries
  - Predictive data is limited
- Fracture risk
  - Likelihood (unknown)+ Severity (known)
- Our Question is:
  - What is the fracture likelihood in space (ISS, Orion) and on planetary activities (Moon and Mars)?
  - Can such assessments be extended to the BMD recovery period after return?



CFMS

The Loading Environment

Micro-g Translation



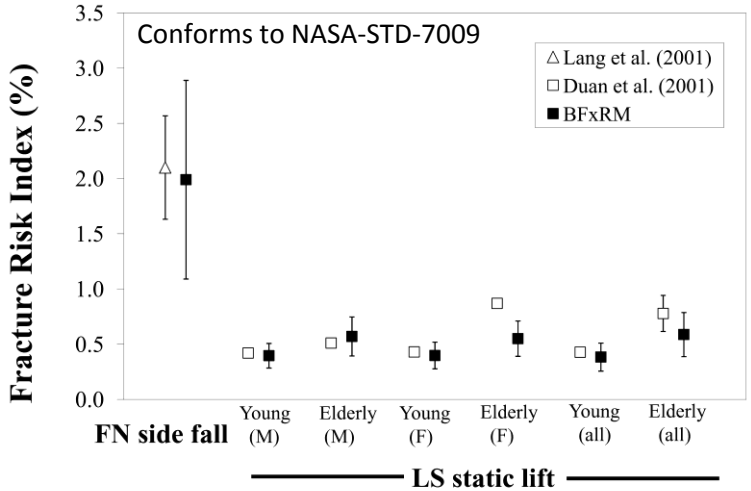
Stance
Walking
Ladder/Stair
Ascent/Decent

"Drop Landing"

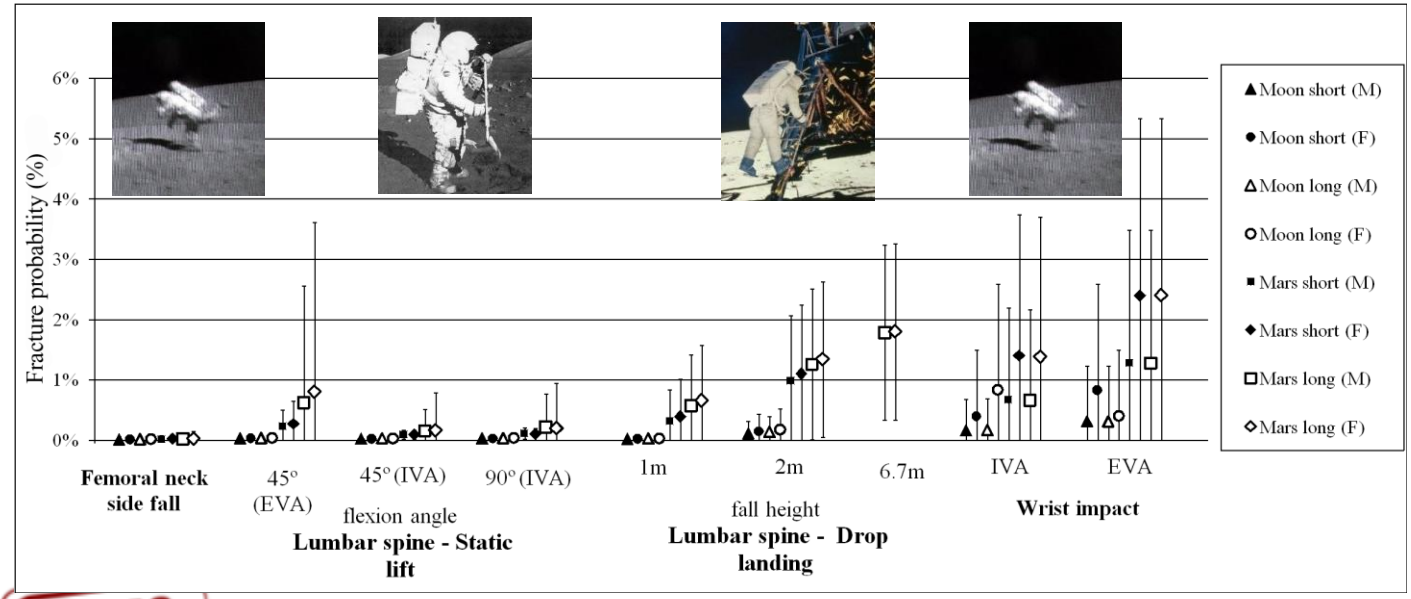
Lateral/Posterolateral
Fall Impacting the Hip
Or
Abnormal Lifting

CFMS

Model Validation and Predictive Results



- Although femoral neck fracture is of high concern
  - Least likely location of fracture
- Wrist most likely fracture location



Highest sensitivities: EMU properties

Nelson et al., Development and Validation of a Predictive Bone Fracture Risk Model for Astronauts, Annals of Biomedical Engineering, Vol 37, Number 11, 2337-2359