Credible Practice of Models and Simulations for Healthcare

Presented by: Jerry Myers

NASA - Glenn Research Center

On behalf of the Committee on Credible Practice of Modeling & Simulation in Healthcare

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CFMS

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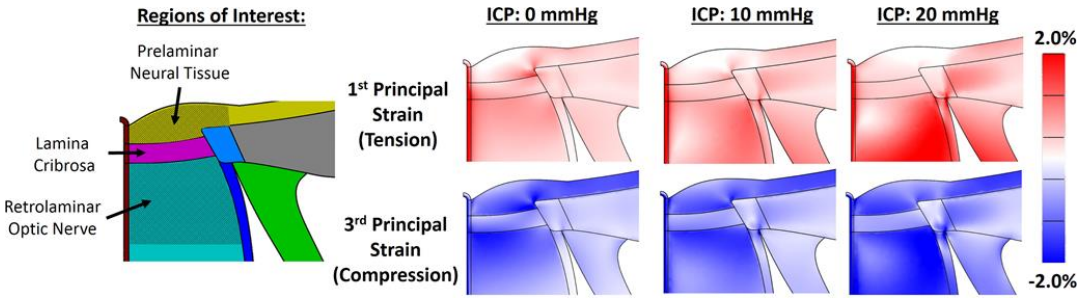
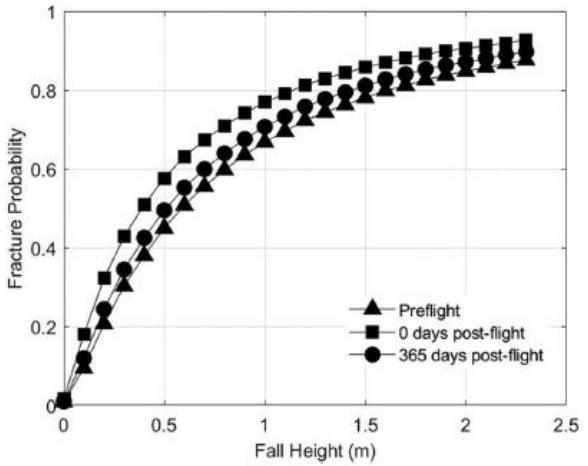
Obligatory images of astronauts doing stuff in microgravity

BACKGROUND

- Computational modeling and simulation (M&S) methods have substantial potential to support research and development, clinical decisions, and education in healthcare.
- Government agencies and industry are making substantial investments into R&D activities in simulation-supported medical research, and decision-making.



Feola, A. J. et al. Invest. Ophthalmol. 2016



Lewandowski & Myers,J. Biomech. Eng. 2019

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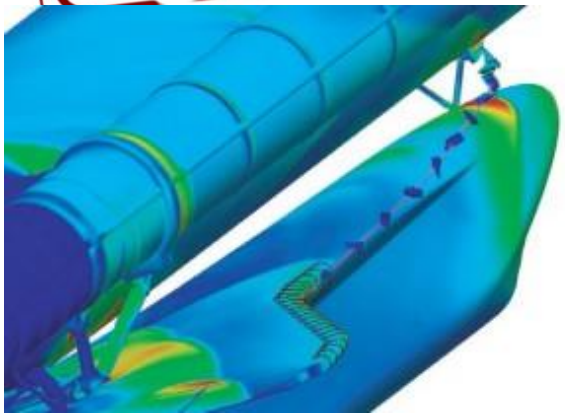
Columbia Accident – Influence of Computational Models



Space Safety Magazine - Winter 2013

- Debris Assessment Team (DAT) was restricted to using a mathematical modeling tool called ***Crater*** to predict the depth to which debris penetrated Thermal Protection System (TPS) tile.
- Crater was classified as a “conservative” tool due to historical use with predicting damage from ice impacts.
- Crater was validated as accurately predicting damaged for small debris impacts, on the order of 49cm^3 - estimated size of actual foam impact : 19665cm^3.
- DAT used a qualitative extrapolation of the test data and engineering judgment that a foam impact angle of up to 21° would not penetrate the shuttle.
- *Crater, as the only predictive tool available, was correctly applied, but it was given weight in the decision making process far outside the boundaries of its Credibility.*

8 Factors of Model Credibility

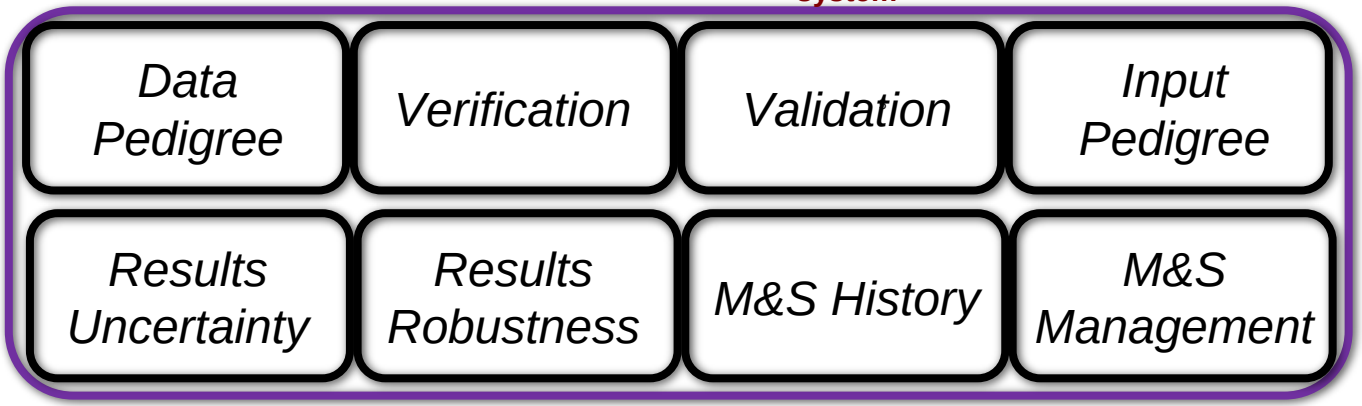
NASA-STD-7009A – Credibility of Models and Simulation

Appropriate data informing concept implementation

Concept implemented correctly

Concept represents real world system

Appropriate data informing boundary / initial conditions



How variations are propagated

How small variations affect output

How model has changed

How has the model helped decisions

Development cycle, reviews, & configuration management

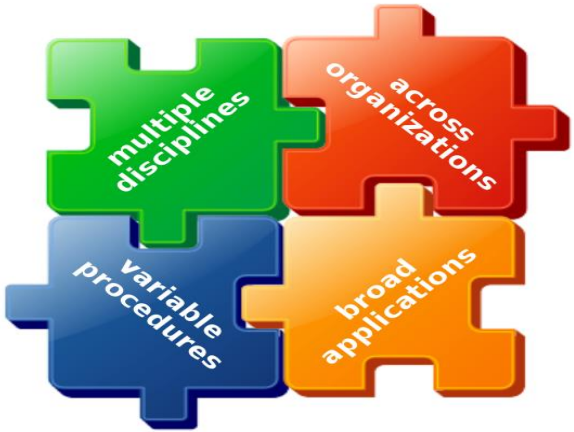
Factor Score
4
3
2
1
0

CREDIBLE PRACTICES OF M&S IN HEALTHCARE

IMAG & Multiscale Modeling (MSM) Consortium

NIH FDA NSF NASA USDA MITACS IARPA

CFMS Committee on Credible Practice of Modeling & Simulation in Healthcare



Goal: Guide reliable application of M&S in healthcare practice and research

- Establish credible practice guidelines
- Consistent terminology
- Demonstrate workflows
- Extensible to new areas of research
- Generally promote good practice

Ten Rules from a Multidisciplinary Perspective

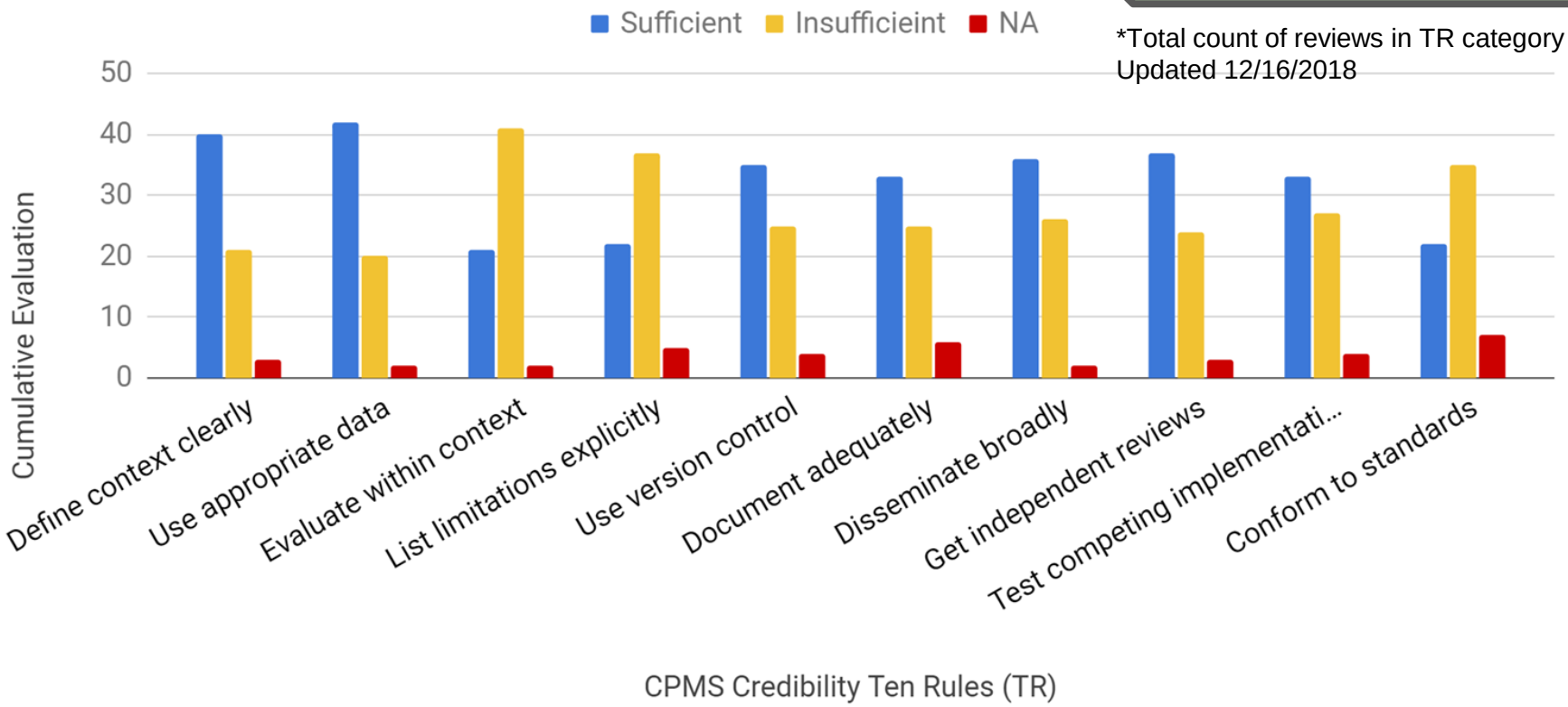
Rule		Description
1.	Define context clearly	Develop and document the subject, purpose, and intended use(s) of the model or simulation
2.	Use contextually appropriate data	Employ relevant and traceable information in the development or operation of a model or simulation
3.	Evaluate within context	Perform verification, validation, uncertainty quantification, and sensitivity analysis of the model or simulation with respect to the reality of interest and intended use(s) of the model or simulation
4.	List limitations explicitly	Provide restrictions, constraints, or qualifications for or on the use of the model or simulation for consideration by the users or customers of a model or simulation
5.	Use version control	Implement a system to trace the time history of modeling and simulation activities including delineation of each contributors' efforts
6.	Document appropriately	Maintain up-to-date informative records of all modeling and simulation activities, including simulation code, model mark-up, scope and intended use of modeling and simulation activities, as well as users' and developers' guides
7.	Disseminate broadly	Share all components of modeling and simulation activities, including simulation software, models, simulation scenarios and results
8.	Get independent reviews	Have the modeling and simulation activity reviewed by nonpartisan third-party users and developers
9.	Test competing implementations	Use contrasting modeling and simulation implementation strategies to check the conclusions of different strategies against each other
10.	Conform to standards	Adopt and promote generally applicable and discipline specific operating procedures, guidelines, and regulations accepted as best practices

Erdemir, A. et al. J. Transl. Med. 2020.

How Prominent Are These Principles?

2018 IMAG Meeting Reviewed 35 MSM member Credibility Plans

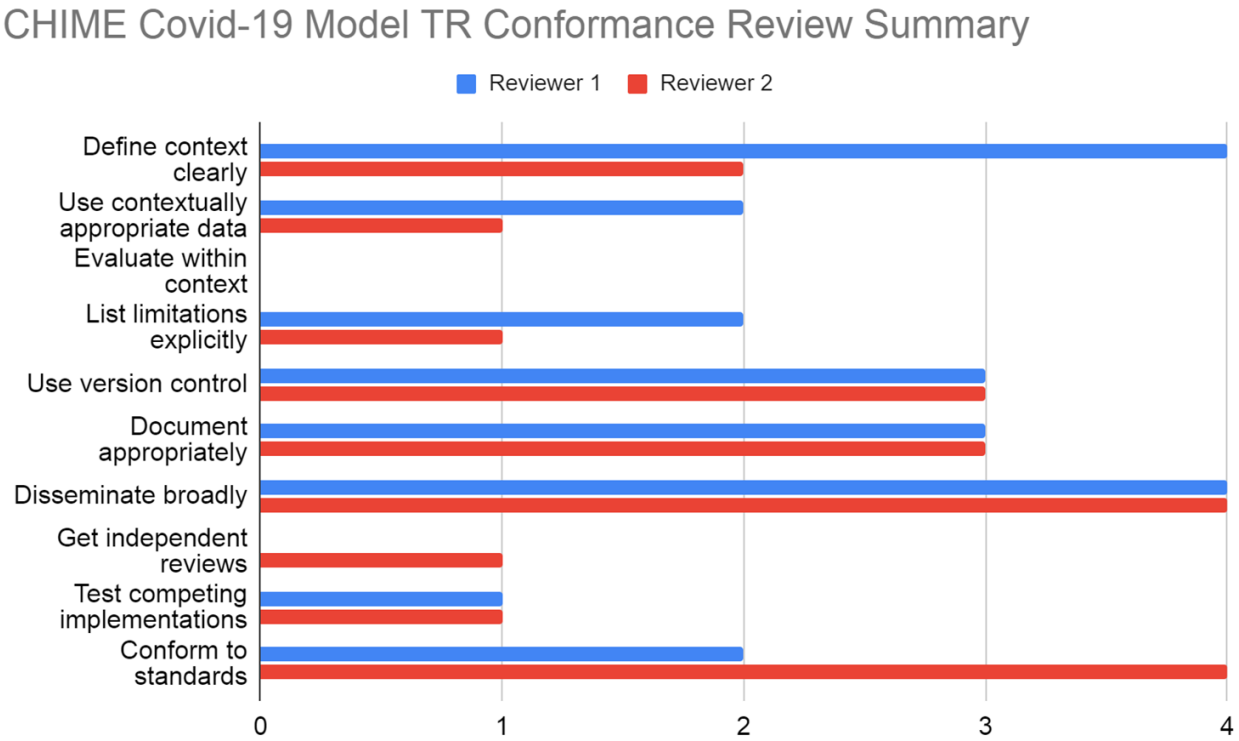
*Total count of reviews in TR category = 64
Updated 12/16/2018



Preliminary Conformance Rubric: Outreach

Outreach Capability	Outreach to application-domain experts who may not be M&S practitioners	Outreach to M&S practitioners who may not be application-domain experts	Outreach to application-domain specific M&S practitioners	Outreach to application-domain specific M&S practitioners	None or very limited
Conformance Level	*Comprehensive*	*Extensive*	*Adequate*	*Partial*	*Insufficient*
	4	*3*	*2*	*1*	*0*
Description Level	Can be understood by non-M&S practitioners familiar with the application domain and the intended context of use	Can be understood by M&S practitioners not familiar with the application domain and the intended context of use	Can be understood by M&S practitioners familiar with the application domain and the intended context of use	Unclear to the M&S practitioners familiar with the application domain and the intended context of use	Missing or grossly incomplete information to properly evaluate the conformance with the rule

Application to Early Covid Model Assessment



April 2020

CHIME: U Penn – https://penn-chime.phl.io/

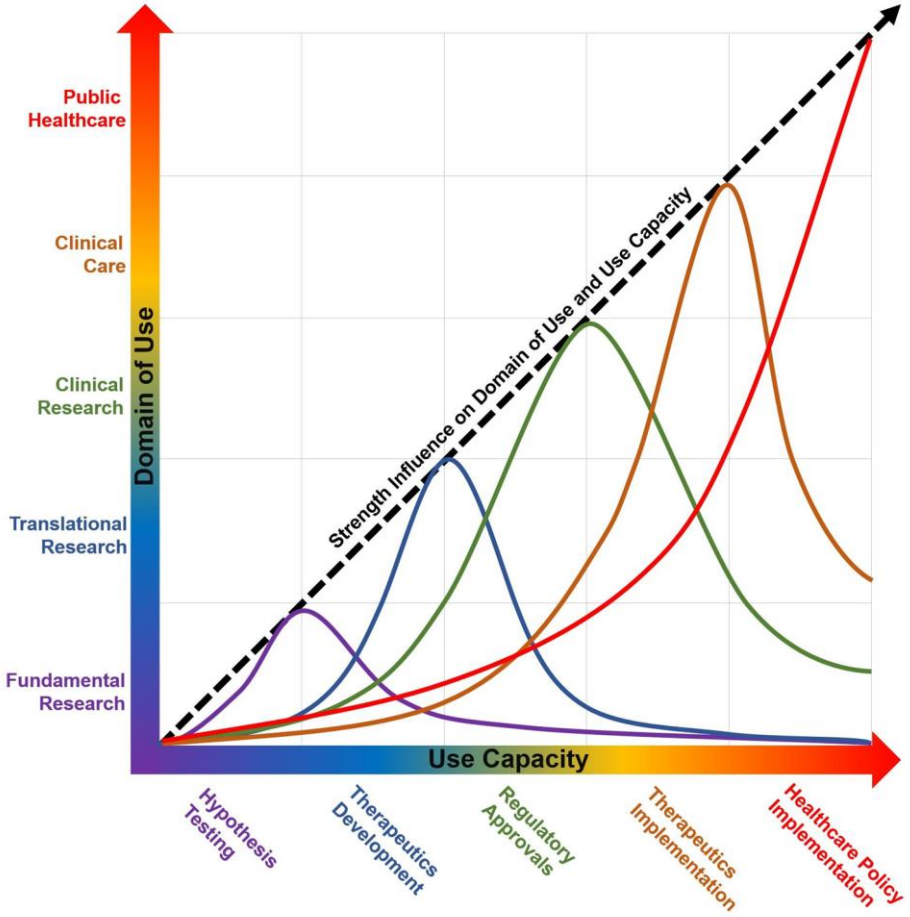
- Reviewer comments
  - Model “validated by epidemiologist” – no details provided on extent or when.
  - Prediction capacity compared to early versions of the Imperial College COVID-19 model.
  - Unclear uncertainty and robustness evaluation

Keep In mind...

TR describes evaluation of Credible Practice Activities

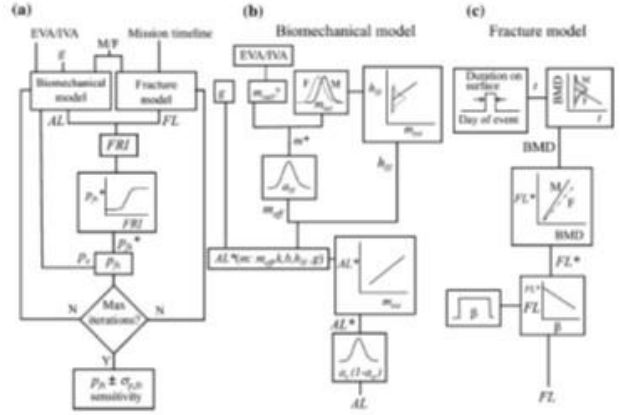
Decision makers should consider the credible practice factors in their unique decision making application

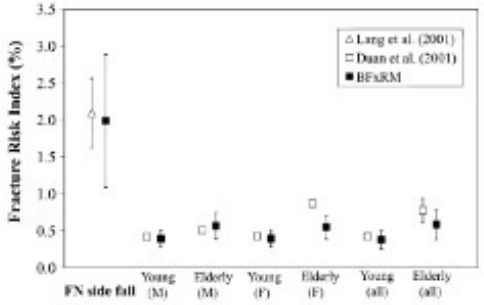
- Domain of Use
- Use Capacity
- Strength of Influence



TR Example: Predictive Bone Fracture Risk Model for Astronauts

https://imagwiki.nibib.nih.gov/resource_credibility_assessment/cpms-tsr-example-predictive-bone-fracture-risk-model-astronauts





CPMS TSR Example: Predictive Bone Fracture Risk Model for Astronauts

Submitted by JerryMyers on Mon, 03/02/2020 - 12:33

Investigators

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1. Define context(s)

other

Conformance Level

Extensive

Primary goal of the model/tool/database

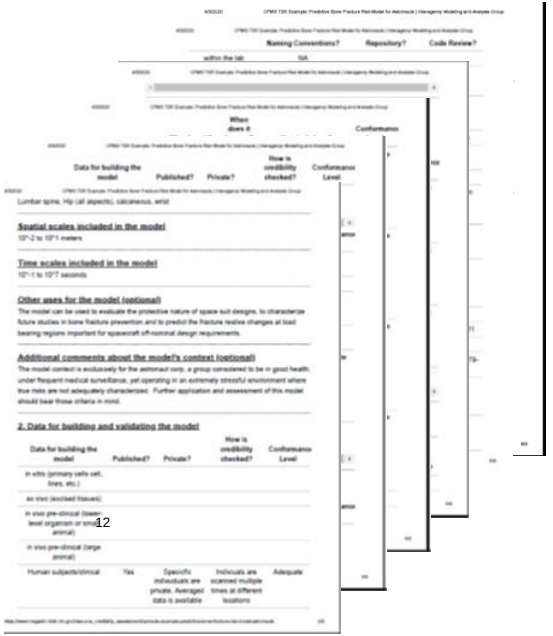
Lacking phenomenological data on fracture risk in space, we have developed a predictive tool based on biomechanical and bone loading models at any gravitational level of interest. The tool is a statistical model

that forecasts fracture risk, bounds the associated uncertainties, and performs sensitivity analysis. The model is intended to be extensible to all genders, all races and all age groups applicable to astronaut demographics. The model is intended to addresses, in-flight and post-flight risks based on assumptions regarding astronaut mission and personal activities utilizing the best available information for space flight induced bone loss and return from flight recovery in bone gravity load bearing regions (hips, lumbar spine) and areas endangered from falls (wrist, hips). To make the model tractable with current space flight planning, the model uses a series of characteristic loading scenarios to characterize the risk. Characterization of this risks allows for mission trades with other medical conditions, as well as defining mission parameters and engineering requirements.

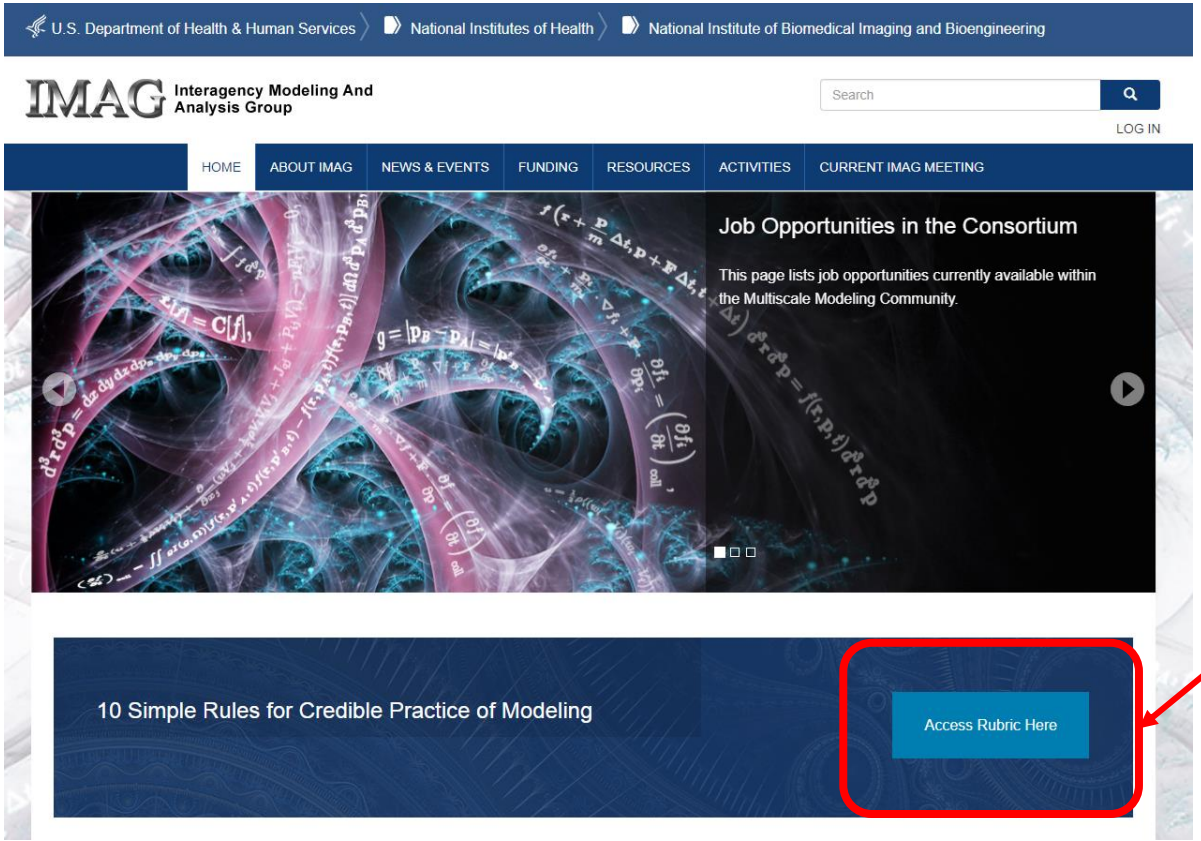
Biological domain of the model

Skeletal fracture

Structure(s) of interest in the model



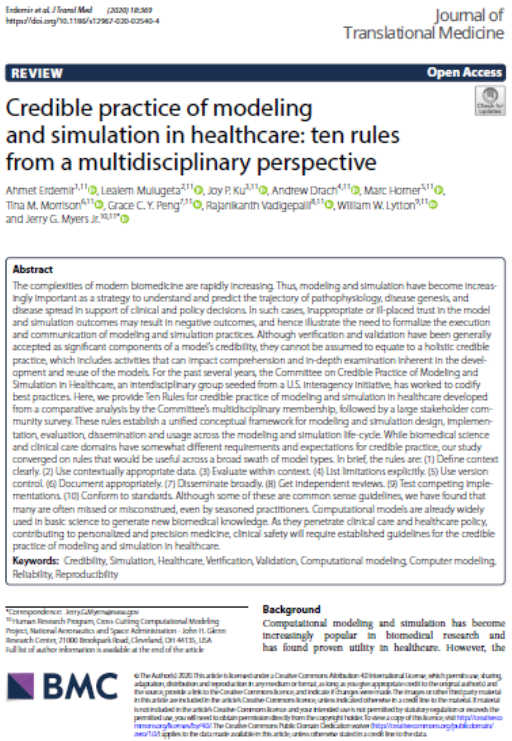
Form is free to use...



https://www.imagwiki.nibib.nih.gov/

Accessed by this button

Many Thanks From the CPMS Members



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Journal of Translational Medicine

REVIEW Open Access

Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective

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Abstract

The complexities of modern biomedicine are rapidly increasing. Thus, modeling and simulation have become increasingly important as a strategy to understand and predict the trajectory of pathophysiology, disease genesis, and disease spread in support of clinical and policy decisions. In such cases, inappropriate or ill-placed trust in the model and simulation outcomes may result in negative outcomes, and hence illustrate the need to formalize the execution and communication of modeling and simulation practices. Although verification and validation have been generally accepted as significant components of a model's credibility, they cannot be assumed to equate to a holistic credible practice, which includes activities that can impact comprehension and in-depth examination inherent in the development and reuse of the models. For the past several years, the Committee on Credible Practice of Modeling and Simulation in Healthcare, an interdisciplinary group seeded from a U.S. Interagency initiative, has worked to codify best practices. Here, we provide Ten Rules for credible practice of modeling and simulation in healthcare developed from a comparative analysis by the Committee's multidisciplinary membership, followed by a large stakeholder community survey. These rules establish a unified conceptual framework for modeling and simulation design, implementation, evaluation, dissemination and usage across the modeling and simulation life-cycle. While biomedical science and clinical care domains have somewhat different requirements and expectations for credible practice, our study converged on rules that would be useful across a broad swath of model types. In brief, the rules are: (1) Define context clearly. (2) Use contextually appropriate data. (3) Evaluate within context. (4) List limitations explicitly. (5) Use version control. (6) Document appropriately. (7) Disseminate broadly. (8) Get independent reviews. (9) Test competing implementations. (10) Conform to standards. Although some of these are common sense guidelines, we have found that many are often missed or misconstrued, even by seasoned practitioners. Computational models are already widely used in basic science to generate new biomedical knowledge. As they penetrate clinical care and healthcare policy, contributing to personalized and precision medicine, clinical safety will require established guidelines for the credible practice of modeling and simulation in healthcare.

Keywords: Credibility, Simulation, Healthcare, Verification, Validation, Computational modeling, Computer modeling, Reliability, Reproducibility

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Background

Computational modeling and simulation has become increasingly popular in biomedical research and has found proven utility in healthcare. However, the

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Backup

Rules Overview

Rule 1 – Define context clearly - document the subject, purpose, and intended use(s) of the model or simulation

- Domain of Use
- Use Capacity
- Strength of Influence

Rule 2 – Use contextually appropriate data - Employ relevant and traceable information

- Data used in development, operation, and evaluation of the M&S traceable to their original source
- Data's relevance to the stated COU is well articulated
- The Domain of Use SME understands which and how the data is applied
- **F**indable, **A**ccessible, **I**nteroperable, **R**eusable (FAIR)

Rules Overview cont.

Rule 3 – Evaluate within context - accomplished with respect to the reality of interest and intended use

- Verification - determine computational M&S accurately represents the underlying mathematical model and its solution.
- Validation - determine the degree to which the model is an accurate representation of the real world from the perspective of its COU
- Uncertainty quantification - characterize the pertinent variability in the model and comparator and to quantify their effect on the simulation outcomes
- Sensitivity analysis - establish the degree to which the uncertainty in the model output(s) can be attributed uncertainty in the model inputs

Rules Overview cont.

Rule 4 – List limitations explicitly - Restrictions, constraints, or qualifications

- Assumptions that are application-specific, limits generalizability
- Clearly identify the conditions under which their M&S cannot be relied upon

Rule 5 – Use version control - Implement a system to trace the time history of M&S activities

- Version control for all model, software, data, and documentation files
- Tracking changes between versions
- Associating specific modifications to the creator/developer
- Including annotations/comments/notes with each version

Rules Overview cont.

Rule 6 – Document appropriately - Maintain up-to-date informative records of all activities, including simulation code, model mark-up, scope and intended use, and users guide

- Providing the information needed for to assess the credibility of the M&S activity planned and probably COU's
- Providing the information needed to understand the nuances of reproducing and using/reusing the associated code and model.

Rule 7 – Disseminate broadly - Publish all components of M&S activities

- Sharing of knowledge via publications and the sharing of M&S assets
- Methods sections of scholarly publication is generally not sufficient to embed all the details needed to meet rule 6 and 7

Rules Overview cont.

Rule 8 – Get independent reviews - M&S activity reviewed by nonpartisan third-party users and developers

- Independent “third-party” reviews by end-users or peers evaluating the activity in its entirety - Evaluate rules 2-6, 9 & 10 wrt 1.
- Mechanism should be a thoughtful, impartial evaluation predicated on accepted guidelines and requirements
- Peer reviews of manuscripts should not be the sole form of third-party review

Rule 9 – Test competing implementations - Use contrasting M&S execution strategies to check conclusions

- Understanding of model behavior WRT familiar standards of performance
- Insight deriving from weighing the pros and cons of competing approaches

Rules Overview cont.

Rule 10 – Conform to standards - Adopt applicable procedures, guidelines, and regulations accepted as best practices within supporting disciplines

- When consistently applied, represent a means of providing requirements, specifications, and guidelines that establish that the M&S materials and products fit the intended purpose
- May vary depending on the institution or discipline
- Importance will vary with the development stage of the M&S application
- Improved insight into and adoption of M&S follows from adherence to standards which promote transparency

Summing it up...

- Biomedical sciences and clinical disciplines are diverse and multidisciplinary
- Intentions of M&S vary dramatically
- Are Credible Practices Being Implemented?
  Ten Simple Rules represent a tightly linked cohort, in a customizable framework that can be tailored to the domain of application, state of development, and stakeholder community
- Most importantly viewed as a communications tool bridging the implemented and the expected practices to support M&S decision making.
- Many researchers and developers follow and communicate many aspects of these TSR
- Few demonstrate all aspects - There is room for improvement!!!

What Constitutes Credible Practice?

- Started with 26 proposed rules of good practice from the Committee
- Committee estimated proximity to clinical applications:
  - mathematics and computation
  - vested interest in the end-use of M&S
  - standards, guidance, evaluation and regulation
- August 15, 2014 to April 15, 2015 - An international public survey with spectrum of perspectives in healthcare M&S
- Ranking of committee and survey findings identified the top 10 “rules”
- Tested and refined these rules in the IMAG community and open access.
- Submitted for publication this year.

NASA Credibility Levels of Evidence

	M&S Development			M&S Use (Operations)			Supporting Evidence	
Level	**Data Pedigree**	**Verification**	**Validation**	**Input Pedigree**	**Uncertainty Characterization**	**Results Robustness**	**M&S History**	**M&S Process / Product Management**
4	All data known & traceable to RWS with acceptable accuracy, precision, & uncertainty.	Reliable practices applied to verify the end-to-end model; all model errors satisfy requirements.	All M&S outputs agree with data from the RWS over the full range of operation in its real operating environment.	All input data known & traceable to RWS with acceptable accuracy, precision, & uncertainty.	Statistical analysis of the output uncertainty after propagation of all known sources of uncertainty.	Sensitivities known for most parameters; most key sensitivities identified.	Nearly identical model and use.	Controlled processes are applied; measurements used for process improvement.
3	All data known & traced to sufficient referent. Significant data has acceptable accuracy, precision, & uncertainty.	Formal practices applied to verify the end-to-end model; all important errors satisfy requirements.	All key M&S outputs agree with data from the RWS operating in a representative environment.	All input data known & traced to sufficient referent. Significant input data has acceptable accuracy, precision, & uncertainty.	Uncertainty of results are provided quantitatively through propagation of all known uncertainty.	Sensitivities known for many parameters including many of the key sensitivities.	At most minor changes in model and at most minor differences in model use.	Controlled processes are applied; process compliance is measured.
2	Some data known & formally traceable with estimated uncertainties.	Documented practices applied to verify all model features; most important errors satisfy requirements.	Key M&S outputs agree with data from a sufficiently similar referent system.	Some input data known & formally traceable with estimated uncertainties.	Most sources of uncertainty identified, expressed quantitatively, and correctly classified. Propagation of the uncertainties is assessed.	Sensitivities known for a few parameters. Few or no key sensitivities identified.	At most moderate changes in model and at most moderate differences in model use.	Formal processes are applied.
1	Some data known and informally traceable.	Informal practices applied to verify some features of the model and assess errors.	Conceptual model addresses problem statement and agrees with available referents.	Some input data known and informally traceable.	Sources of uncertainty identified and qualitatively assessed.	Qualitative estimates only for sensitivities in M&S.	New model or major changes in model, or major differences in model use; but, model/changes/uses documented.	Informal processes are applied.
0	Insufficient evidence.	Insufficient evidence.	Insufficient evidence.	Insufficient evidence.	Insufficient evidence.	Insufficient evidence.	Insufficient evidence.	Insufficient evidence.

Important Definitions

Credible: Dependable, with a desired certainty level to guide research or support decision-making within a prescribed application domain and intended use; establishing reproducibility and accountability.

Practice: Any activity involving the development, solution, interpretation and application of computational representations of biological, environmental and man-made systems and their interaction thereof.

Modeling: Virtual, in silico, representation of system(s) of interest in a usable form in order to provide descriptive and predictive metrics for timely and systematic exploration of said system(s).

Simulation: Computational solution of models that quantify descriptive and predictive metrics of system(s) of interest, including related post-processing efforts to calculate these metrics from raw analysis results.

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.