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

Ten Simple Rules of Credible Practice of Modeling and Simulation: *Application to Bone Remodeling and Heart Valve Modeling*

Presented by Lealem Mulugeta and Andrew Drach
On Behalf of the Committee

ROSA Worldwide Webinar Series:
Impact of Modeling & Simulation in Drug Development
May 17, 2018

Objectives

- Introduction to The Committee on Credible Practice of Modeling & Simulation in Healthcare
- Overview of the current draft of the Ten Simple Rules of Credible Practice
- Example Applications
  - Bone Remodeling Model (L. Mulugeta)
  - Heart Valve Model (A. Drach)

The Challenge

Am I applying credible practice?

Common practice guidelines <u>do not exist</u> to ensure that appropriate credibility processes are followed

Adapted from http://beaver1003.com

About the Committee

Credible Practice of M&S in Healthcare

To establish credible practice guidelines, consistent terminology and a model certification process, as well as to demonstrate workflows and identify new areas of research for reliable development and application of M&S in healthcare practice and research

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IMAG & Multiscale Modeling (MSM) Consortium

NIH FDA nsf NASA USDA MITACS IARPA

Overview of Committee's Charges

- **Guidelines & Procedures**
  - Credible practice in computational medicine
  - Leveraging readily available techniques
  - Define novel translational workflows to enhance credibility practice
- **Demonstrate Workflows**
  - Conduct studies to develop novel credibility assessment procedures
  - Disseminating examples of credibility assessment
- **Consistent Terminology**
  - Unify the use of M&S vocabulary across all stakeholders
- **Promote Good Practice**
  - Bridge synergistic activities within the M&S communities
  - conduct outreach activities.
- **Target End Products**
  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

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TEN SIMPLE RULES (TSR) OF CREDIBLE PRACTICE

Primary deliverable: *"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

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Two Main Approaches for TSR

1. Surveyed the Committee
   - Publication in progress
2. Surveyed the Global Community
   - A forum discussion thread has been initiated: https://simtk.org/forums/viewtopic.php?f=848&t=5616&sid=fdcab3f040d5c52b8667a0b0812d2e2b
   - The raw data is also available at: https://simtk.org/websvn/wsvn/cpms/dat/Survey/Complete%20Survey%20Results_Clean_04242015.xlsx
   - Publication in Progress

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Draft: The Ten Simple Rules of Credible Practice

Rule	Description
R1: Define context clearly	Develop and document the subject, purpose, and intended use(s) of the model or simulation.
R2: Use appropriate data	Employ relevant and traceable information in the development or operation of a model or simulation.
R3: Evaluate within context	Verification, validation, uncertainty quantification, and sensitivity analysis of the model or simulation are accomplished with respect to the reality of interest and intended use(s) of the model or simulation.
R4: List limitations explicitly	Restrictions, constraints, or qualifications for or on the use of the model or simulation are available for consideration by the users or customers of a model or simulation.
R5: Use version control	Implement a system to trace the time history of M&S activities including delineation of contributors' efforts.
R6: Document adequately	Maintain up-to-date informative records of all M&S activities, including simulation code, model mark-up, scope and intended use of M&S activities, as well as users' and developers' guides.
R7: Disseminate broadly	Publish all components of M&S activities, including simulation software, models, simulation scenarios and results.
R8: Get independent reviews	Have the M&S activity reviewed by nonpartisan third-party users and developers.
R9: Test competing implementations	Use contrasting M&S execution strategies to check the conclusions of the different execution strategies against each other.
R10: Conform to standards	Adopt and promote generally applicable and discipline specific operating procedures, guidelines, and regulations accepted as best practices.

Alignment between Committee survey and the Global Community survey

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APPLICATION OF THE TEN SIMPLE RULES TO COMPUTATIONAL MODEL OF BONE REMODELING

Presented by Lealem Mulugeta

Summary of

J. Pennline and L. Mulugeta (2014), "A Computational Model for Simulating Spaceflight Induced Bone Remodeling", *44th International Conference on Environmental Systems*, ICES2014-083.

Purpose of this presentation

- Demonstrate:
  - The **deliberate** processes (NASA-STD-7009) we used to demonstrate the credibility of a computational model of bone remodeling intended for NASA's spaceflight bone physiology research efforts [1-4]
  - How the processes align/translate with *the Ten Simple Rules of Credible Practice of M&S in Healthcare*

- The purpose of this presentation is NOT to discuss modeling techniques or science

- For more information about M&S methodologies, please refer to the following publication, and additional references

J. Pennline and L. Mulugeta (2014), "A Computational Model for Simulating Spaceflight Induced Bone Remodeling", *44th International Conference on Environmental Systems*, ICES2014-083.

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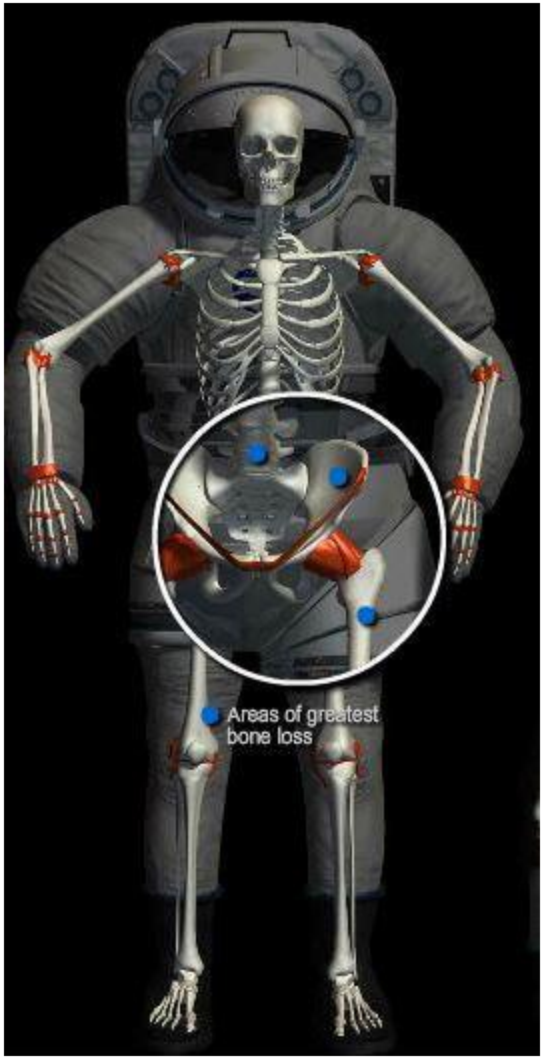
Problem Statement



- Astronauts experience bone demineralization at a rate of 1% to 2% a month in microgravity (“weightlessness”)
- These losses are most pronounced at load bearing lower extremities (e.g. proximal femur)
- Existing exercise countermeasures do not completely eliminate bone loss in long duration, 4 to 6 months, spaceflight
- Health risks to astronauts:
  - *Early onset osteoporosis*
  - *Fracture later in their lives*

Objective

- Understand bone remodeling and demineralization mechanisms in microgravity in order to:
  - Appropriately quantify long term bone health risks (osteoporosis & bone fracture), and
  - Establish appropriate countermeasures

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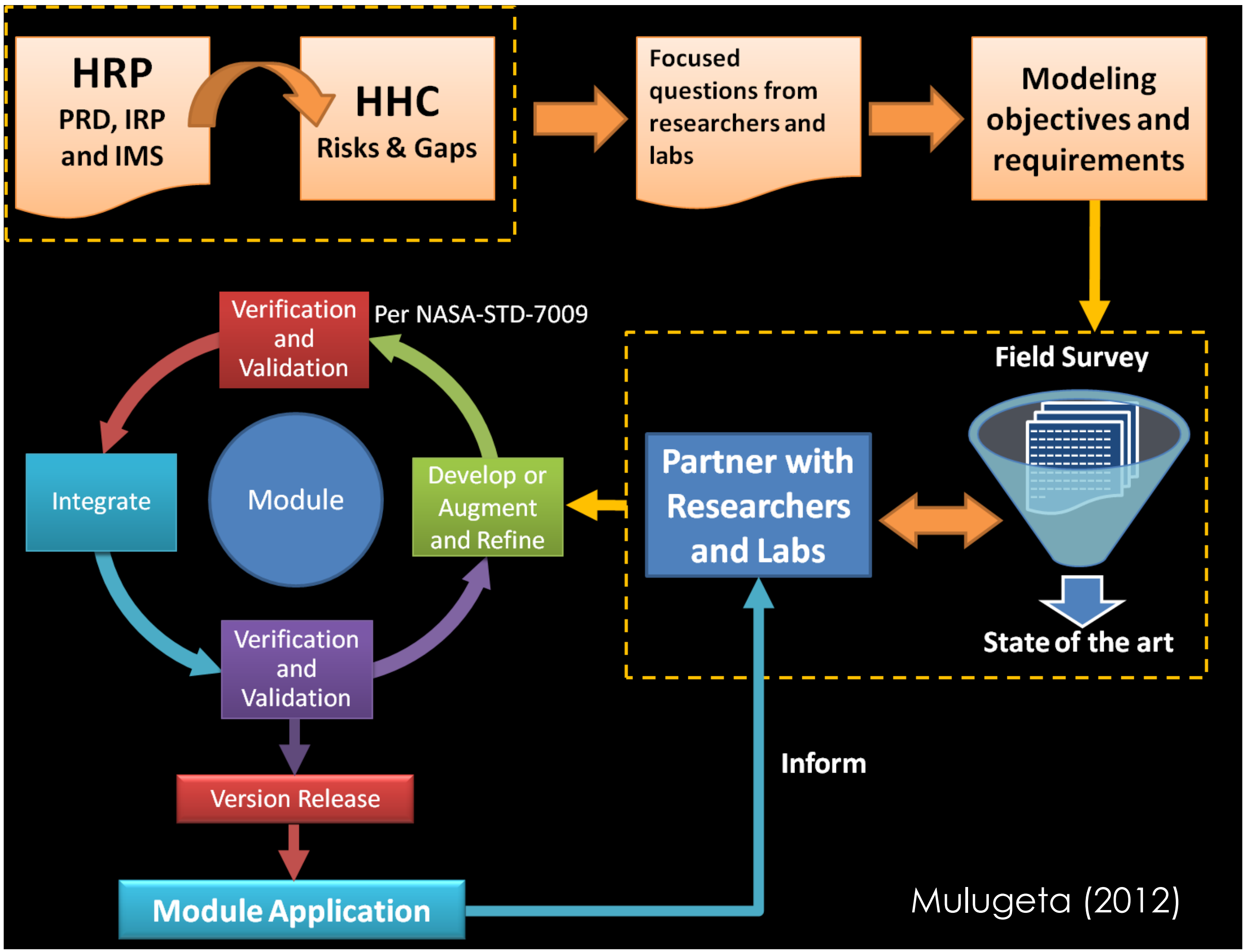
Proposed Tool: Computational M&S

NASA's Digital Astronaut Project (DAP) worked with NASA's bone specialists to apply computational modeling to elucidate changes in weight-bearing skeletal sites that are most susceptible to bone loss in microgravity, and thus at higher risk for fracture



R1: Define context clearly (1/3)

The DAP computational model of bone remodeling was developed:

1) Primarily as a research tool, and not as a clinical tool
2) To augment bone research and exercise countermeasure development

It was intended to provide additional data to:

1) Gain insight on the mechanisms of bone demineralization due to exposure to microgravity,
2) Gain insight on the volumetric changes at the various bone sites in response to in-flight and post-flight exercise countermeasures, and
3) Be used with finite element methods to gain insight on how bone strength may change during and after flight

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R1: Define context clearly (2/3)

It was not developed to predict bone fracture

The initial model reported by Pennline and Mulugeta (2014a) focused on the femoral neck since this bone site:

1) Is a dynamic load bearing sight,
2) Is highly susceptible to microgravity induced demineralization, and
3) Presents potentially debilitating fracture risk

Future work will include other key load bearing bone sites: greater trochanter, lower lumbar vertebrae, proximal femur and calcaneus.

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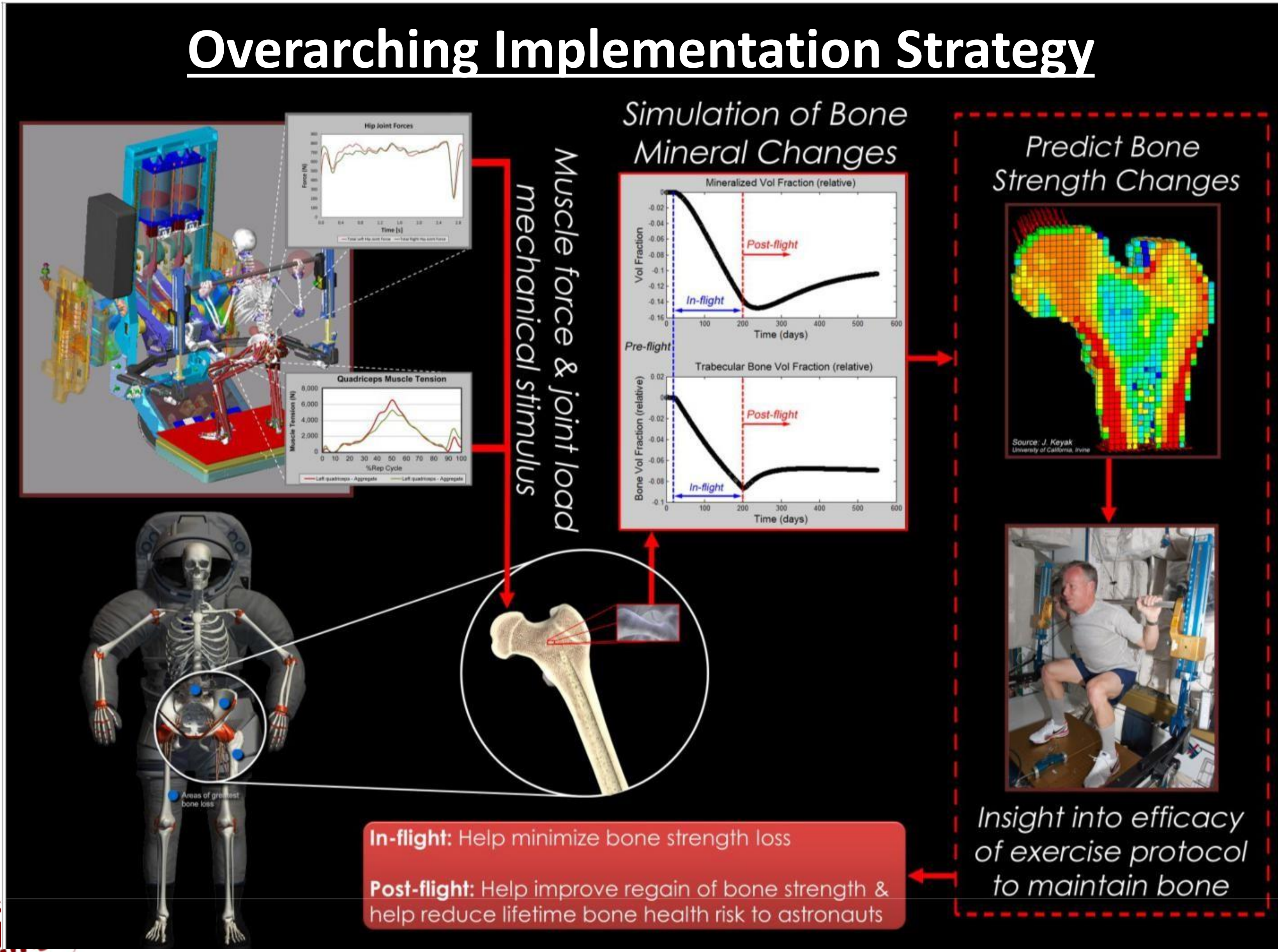
R1: Define context clearly (3/3)



Pennline and Mulugeta (2014a)

R2: Use appropriate data (1/2)

- Since bone parameter values are still under active research by the scientific community, we used average values from the scientific literature – see Pennline and Mulugeta (2014a) for details
- **Examples**
  - ***Resorption depth (depth of remodeling unit):*** *0.05 mm for trabecular hemi-osteon, and 0.0955 mm and 0.0271mm for cortical bone*
  - ***Activation frequency:*** *0.001/day*
  - ***TGF-beta 1:*** *200 µg/kg*

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R2: Use appropriate data (2/2)

- Since most of the bone mineral density(BMD) data available was DEXA aBMD, we created a regression equation that maps aBMD with QCT vBMD
- The regression was developed using total femur DEXA and QCT data from the flight study reported in Lang et al. (2004) – raw data was provided by NASA's Life Science Data Archives
- This regression "sub-model" helped expand the data set we were able to draw on to validate the computational mode, as well as run investigative simulations

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R3: Evaluate within context (1/3) – Criteria & Definitions

Validation?

- does not mean the absolute substantiation of the model's capability to predict bone adaptation
- refers to the degree which the model is able to reproduce the observed behavior under consideration (e.g. BMD or BVF changes) in comparison to an appropriate referent.

Validation Criteria:

1. Bone Volume Fraction (BVF) - Base Equation
2. Volumetric BMD (vBMD) – Quantitative Computed Tomography (QCT)
   1. Trabecular
   2. Cortical
3. Areal BMD (aBMD) - Dual-Energy X-ray Absorptiometry (DEXA)

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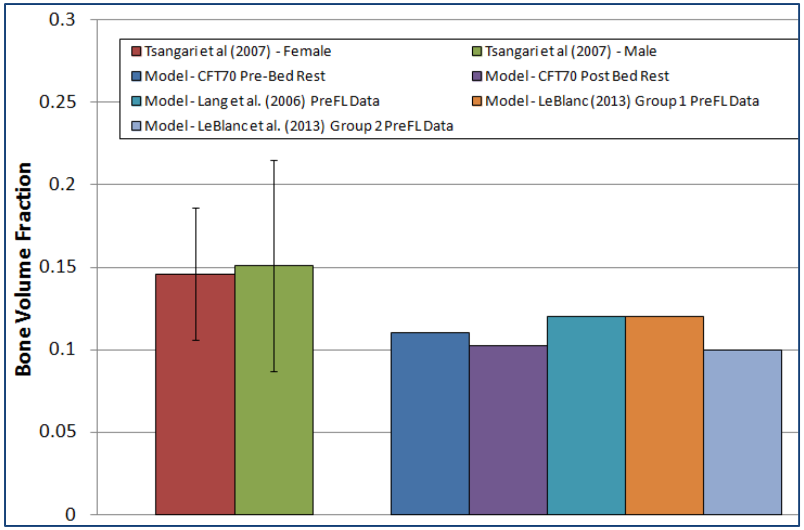
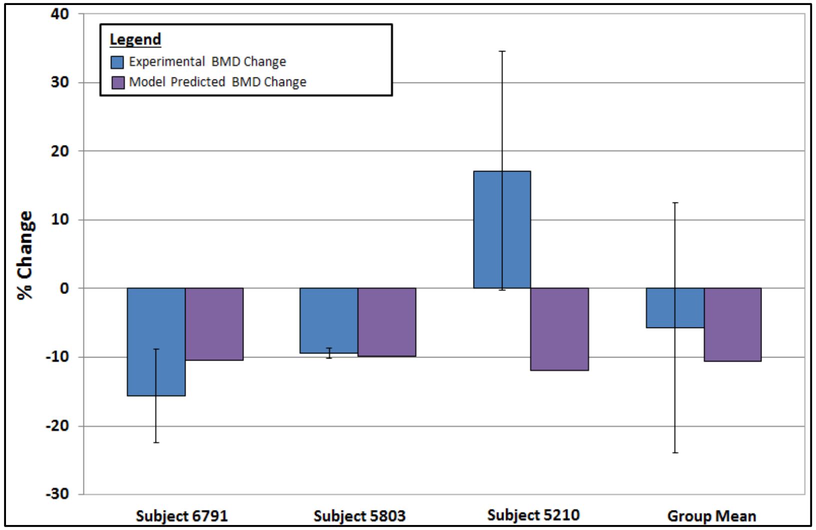
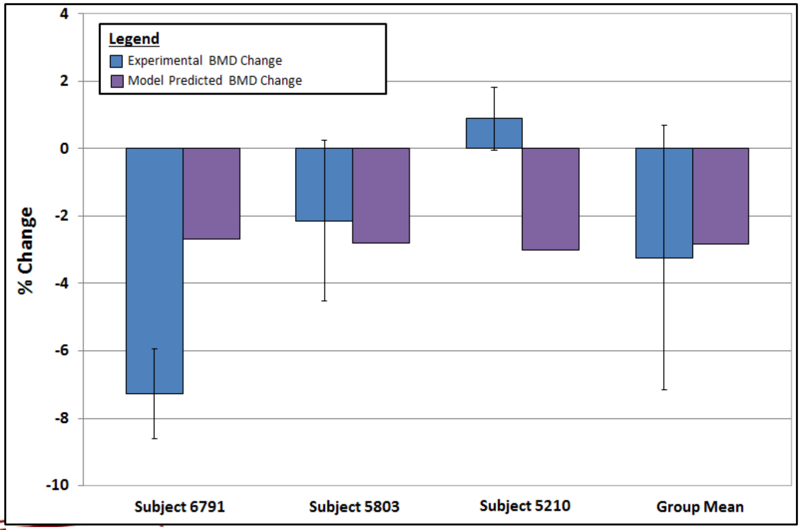
R3: Evaluate within context (2/3) – Prelim. Validation



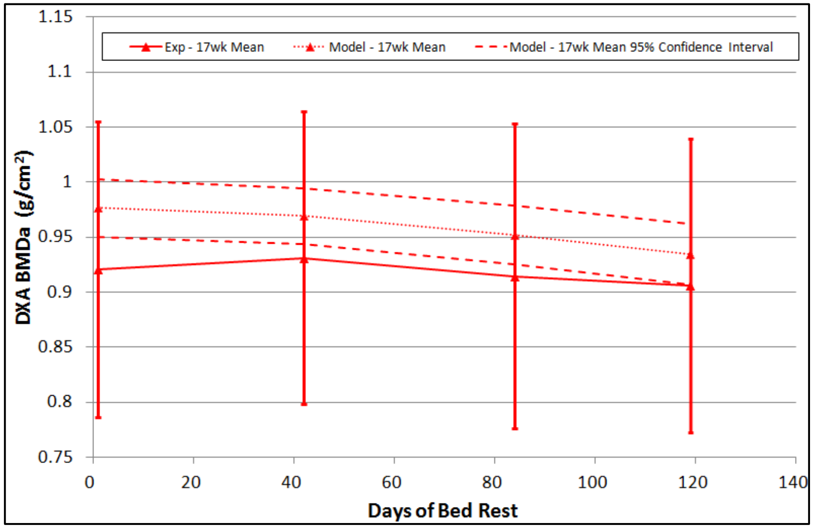
Group mean BVF prediction.



70-day bed rest trabecular bone loss (4 subj.)

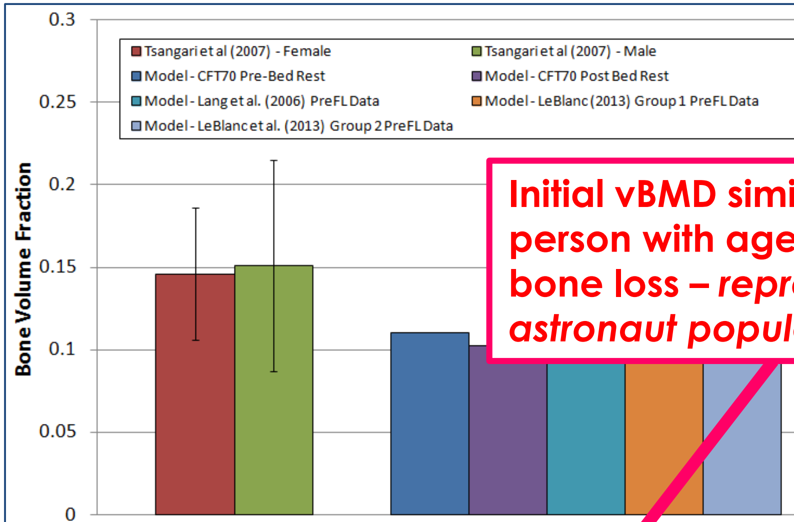


70-day bed rest cortical bone loss (4 subj.)



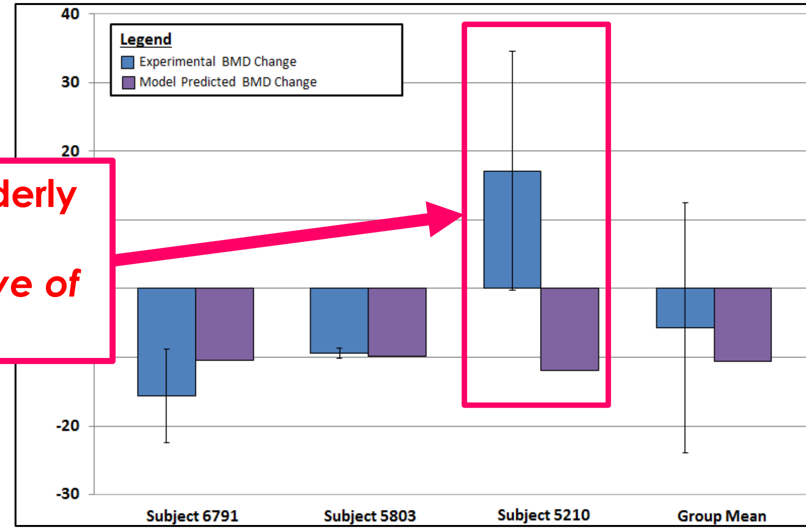
Time course mean aBMD change for 18 subjects during 17 weeks of bed rest [8].

R3: Evaluate within context (2/3) – Prelim. Validation

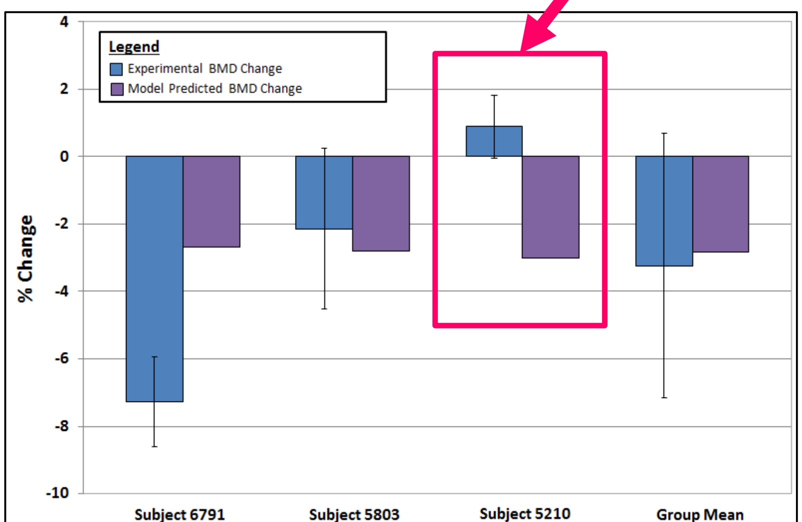


Group mean BVF prediction.

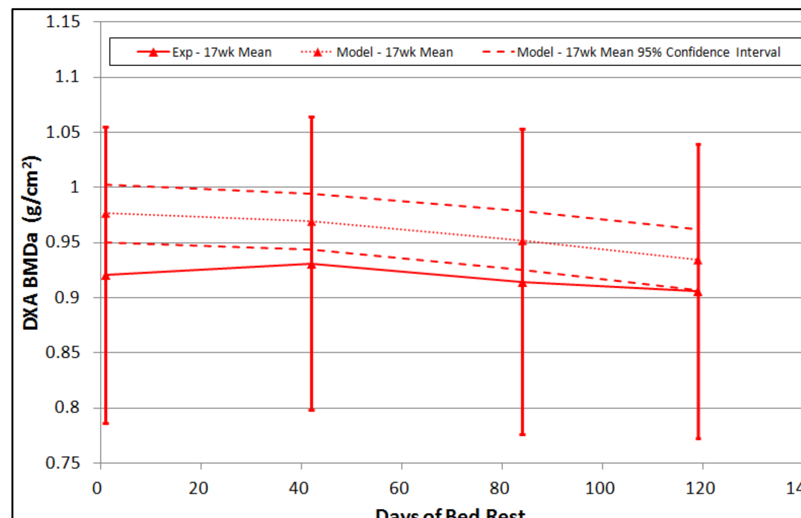
Initial vBMD similar to elderly person with age-related bone loss – *representative of astronaut population?*



70-day bed rest trabecular bone loss (4 subj.)



70-day bed rest cortical bone loss (4 subj.)



Time course mean aBMD change for 18 subjects during 17 weeks of bed rest [8].

R3: Evaluate within context (3/3)

- Validation results suggest that the model reported in Pennline and Mulugeta (2014):
  - Is most reliable for prediction of group mean BVF, vBMD and aBMD changes under bedrest conditions (spaceflight analog).
  - Has limited capability to predict subject specific trends in vBMD changes under bedrest conditions
- A good foundation was laid to establish a physiologically meaningful bone remodeling model to simulate site specific bone adaptation for spaceflight bone physiology research
- ***Future work:*** Rigorous verification, sensitivity and uncertainty analysis of the system of equations, parameters and variables

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R4: List limitations explicitly (1/2)

Limitations in the modeling approach:

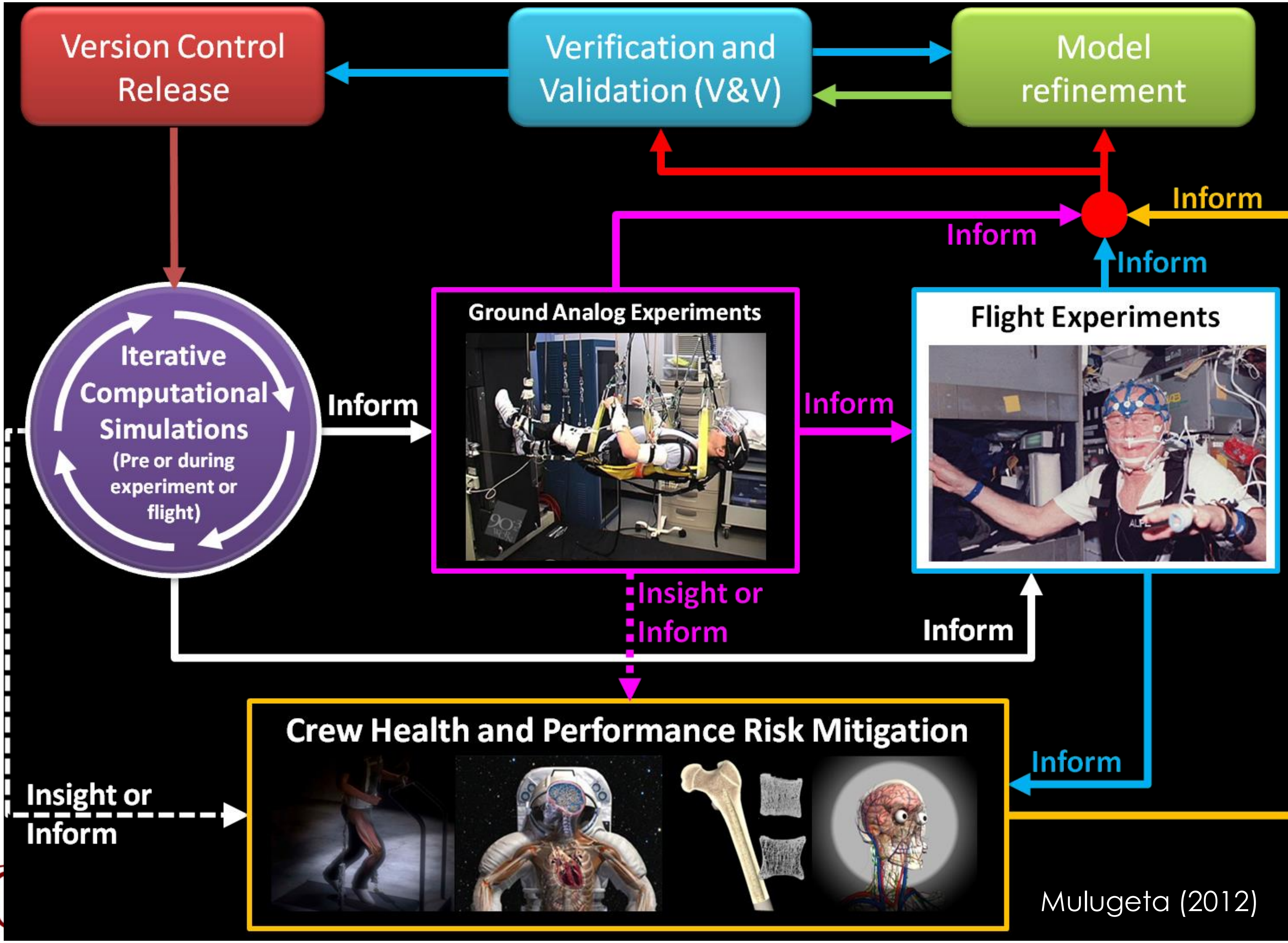
1. Remodeling formulation is limited to porosity, thus restricting it to density changes within the trabecular region and to intracortical density changes
2. It does not cover periosteal apposition or endocortical change.
3. Geometry changes in the bone site are not modeled.
4. Preliminary validation analysis of the computational predictions for deconditioning has only been done for up to 4 months in duration.
5. The validation data used is from bed rest control subjects as an analog to gravitational unloading due to exposure to microgravity
6. Age and gender differences are not yet factored in when initializing model variables
7. Limited capability to make subject specific predictions
8. The computational model is best suited for the mature adult between 25 and 55 years of age, or typical age of an astronaut.
9. The model does not include the effects of sclerostin, calcitonin, osteopontin, or Interleukins, some of which may play a role bone loss in microgravity and with disuse in 1g.

R4: List limitations explicitly (2/2)

Limitations imposed by the state of knowledge in bone science:

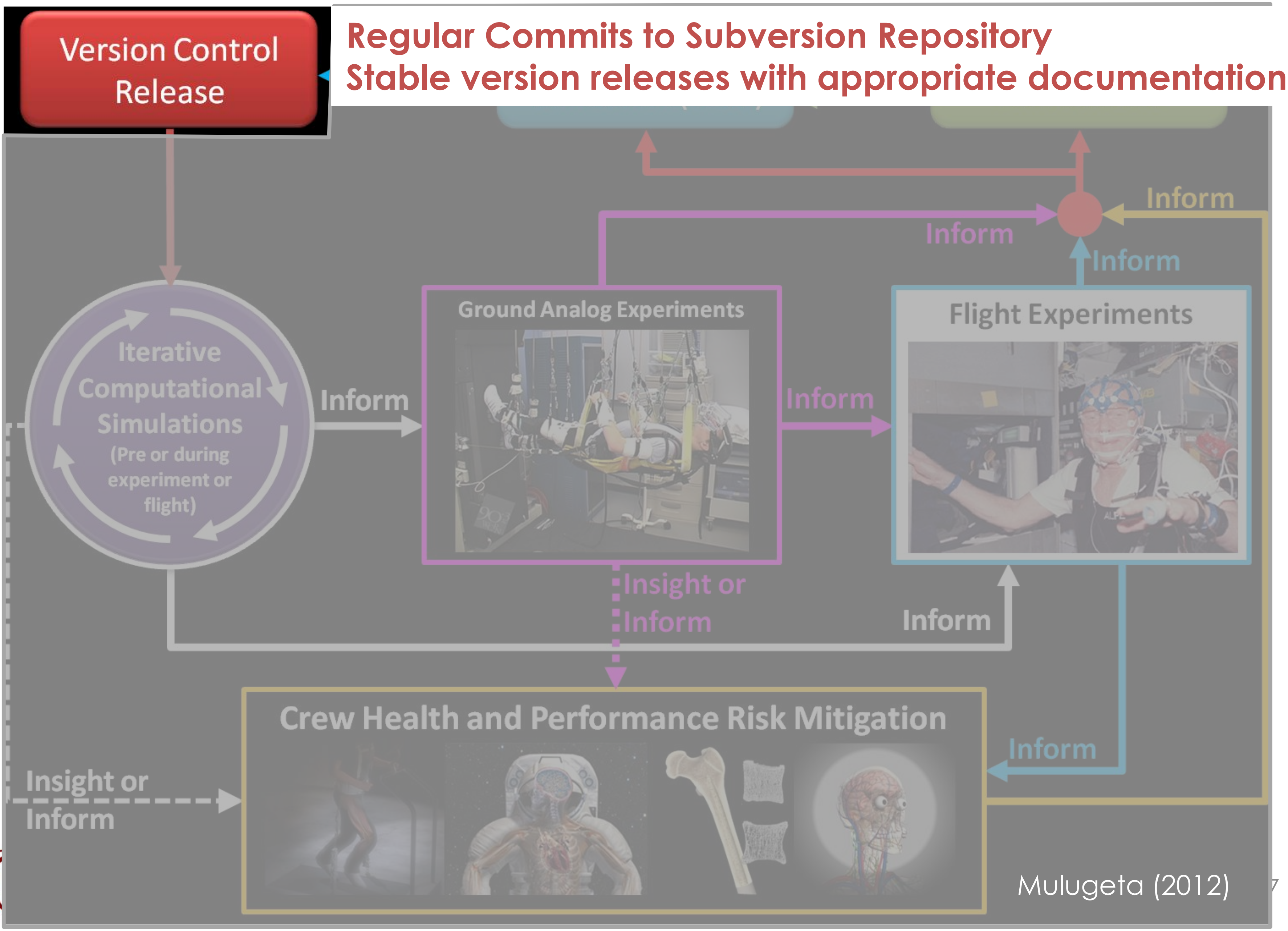
1. There is a degree of uncertainty and variation in remodeling unit geometry and dimensions reported in the literature
2. It is difficult to guarantee that the remodeling unit values used in the model agree for the particular skeletal site of interest
3. There is uncertainty in the way ash fraction is modeled, and the full potential range of values estimated from experimental studies is not completely understood.
4. Activation frequency and activation density are inherently difficult to appropriately model due to the lack of human values at skeletal sites other than the iliac crest or rib
5. There are several potential algebraic schemes for mapping initial data values to model state variables. They depend on several possible definitions of ash fraction and how the steady state version of their respective equations are used

R5: Use version control – Applied to all DAP Projects



R5: Use version control – Applied to all DAP Projects

Regular Commits to Subversion Repository
Stable version releases with appropriate documentation



Mulugeta (2012)

R6: Document adequately

- Code was documented sufficiently for modelers and scientists
- Graphical user interface was developed for intuitive use by end-users
- Every model delivery to stakeholders was accompanied with a report summarizing model features and credibility.
  - E.g. J. Pennline and L. Mulugeta, "The Digital Astronaut Project Computational Bone Remodeling Model (Beta Version) Bone Summit Summary Report", Bone Summit II Research and Clinical Advisory Panel Meeting, 1-5 Nov. 2013, Houston, TX, https://go.nasa.gov/2KvQi43.
- Presentations and briefings provided to stakeholder community at quarterly meetings, annual agency reports, and annual HRP Investigators' Workshop[7,8]
- Peer reviewed articles, conference presentations and technical memos were produced regularly (search Pennline and Mulugeta at https://ntrs.nasa.gov/)

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R7: Disseminate broadly

- The code was developed for use by NASA researchers, so it was not intended for release to the general public (at least not the beta model)

- However, peer reviewed articles and conference presentations are available for public consumption via the NASA Technical Report Server (search Pennline and Mulugeta at https://ntrs.nasa.gov/)

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R8: Get independent reviews

- In accordance to NASA-STD-7009, technical reviews were conducted to ensure critique from key stakeholders [4].
- In addition to obtaining feedback from the key stakeholders, NASA's Research and Clinical Advisory Panel (external subject matter experts) were provided a summary report [9]
- The Research and Clinical Advisory Panel used this report to provide feedback to the NASA Bone Discipline Lead regarding the potential utility and weakness of the DAP Bone Remodeling Model with respect to its context of use

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R9: Test competing implementations

- The foundational model was formed by comparing, contrasting, combine and modify previously developed set of biochemical, cellular dynamics, and mechanical stimulus equations in the literature [10,11]

- This is an ongoing process

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R10: Conform to standards

- The model and simulations were developed and applied in accordance to NASA's Standard for Models and Simulations (NASA-STD-7009) [2]

- All human subject data were used in accordance to HIPAA

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REFERENCES

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8. NASA, Human Research Program, 2013 Fiscal Year Annual Report, 2014, https://go.nasa.gov/2L5YKYM.
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