National Aeronautics and Space Administration

Glenn Research Center
Human Research Program

Probabilistic Risk Assessment for Bone Fracture - Bone Fracture Risk Module (BFxRM)

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Agenda

- Historical fracture likelihood assessment [DXA,FRAX]
- Limitations on the reliance of BMD
- Concept and application of the NASA Bone Fracture Risk Model (BFxRM)
- Discussion on expanding capabilities to fracture risk modeling

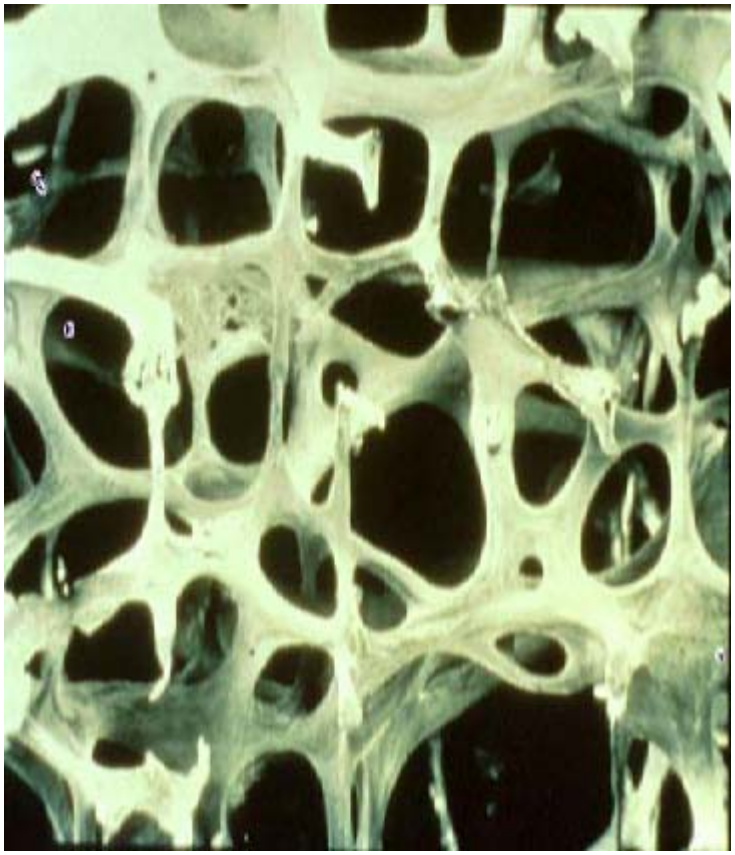
Why Develop a Risk Tool

- History of fracture probability calculation
  - Typically aimed at clinical/treatment planning

- Original development of DXA / T-score system
  - **Postmenopausal Caucasian women, elderly**
  - **To assess risk for fragility fracture**
  - **High prevalence of disease osteoporosis**
  - **Highest risk for those ≤ - 2.5 s.d. from population mean [T-score]**
  - **Reference population may not be analogous to the astronaut corps**
    - **young healthy, physically fit, work in unique environment, engage in unique activity**

T-score ≤ -2.5

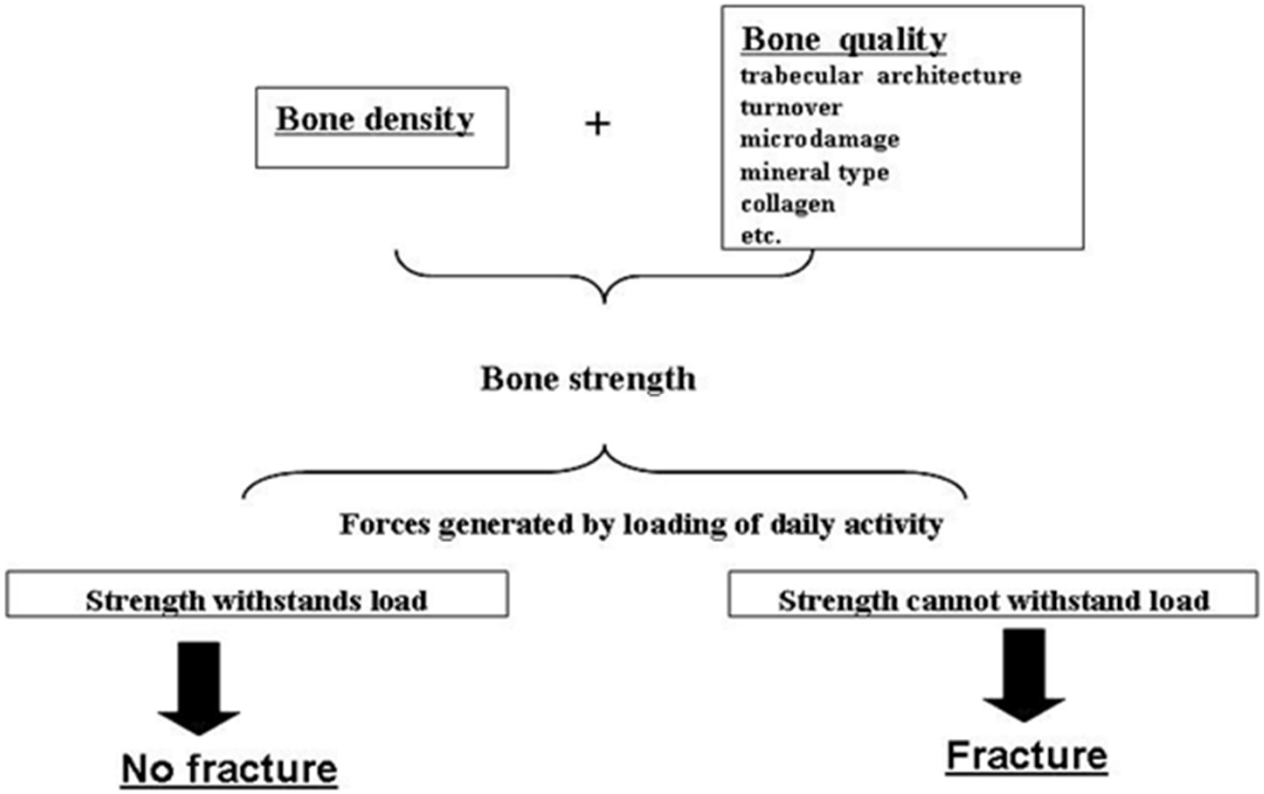
- **Became surrogate marker of a disease and architectural change, strength loss**



BMD Limitations in Predicting Bone Strength

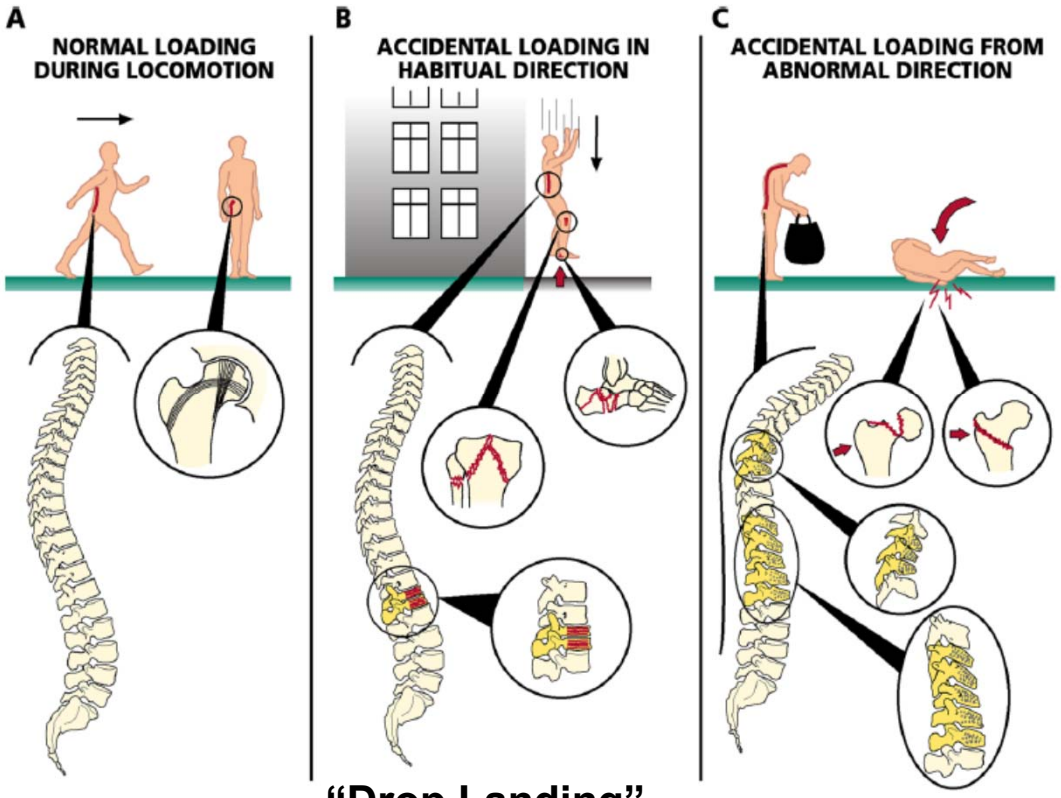
- **Discordance between DXA and bone strength or [resistance to fracture] , other factors of importance**

- **“quality” and loading**



The Loading Environment

Micro-g Translation

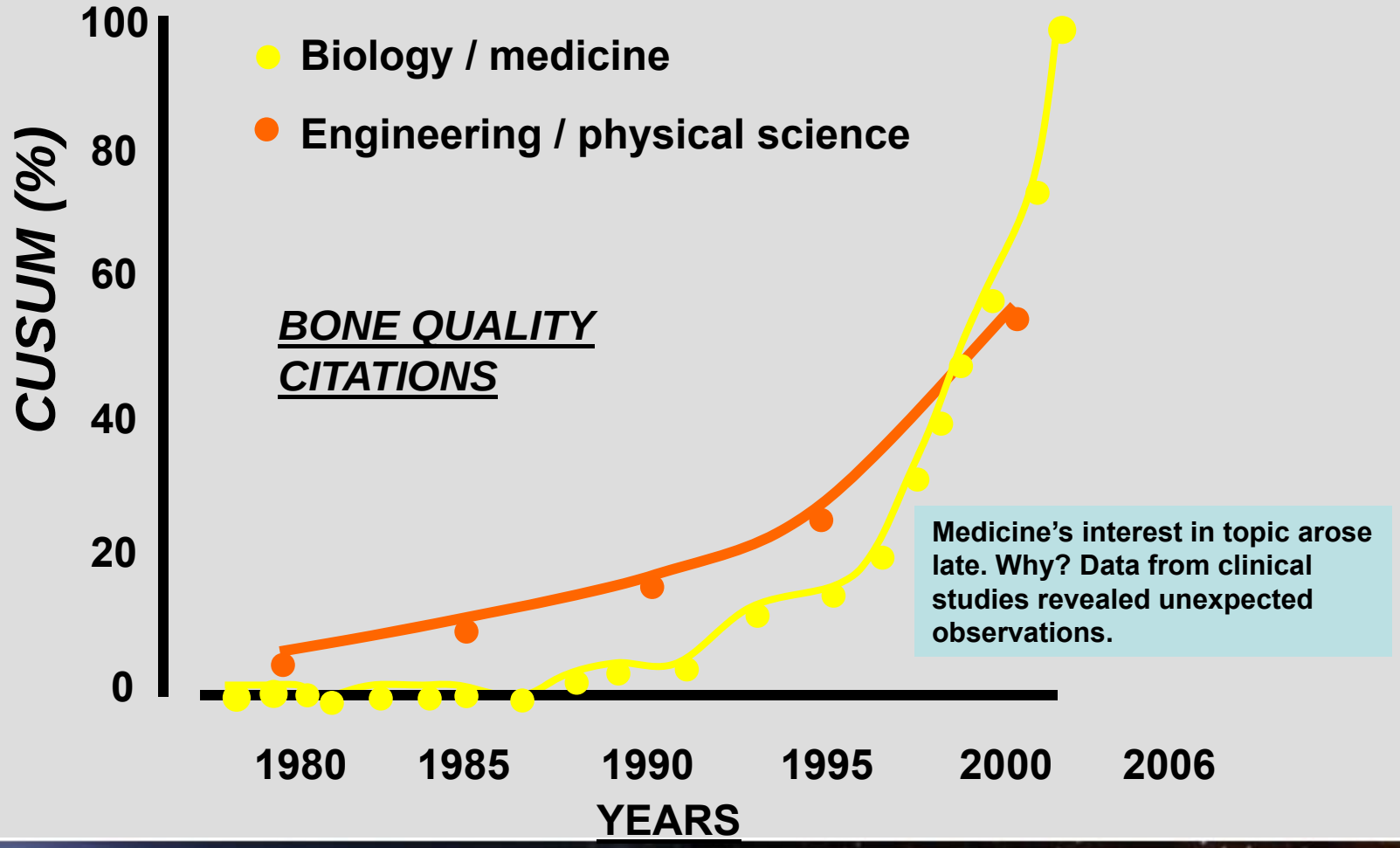


Stance
Walking
Ladder/Stair
Ascent/Decent

"Drop Landing"

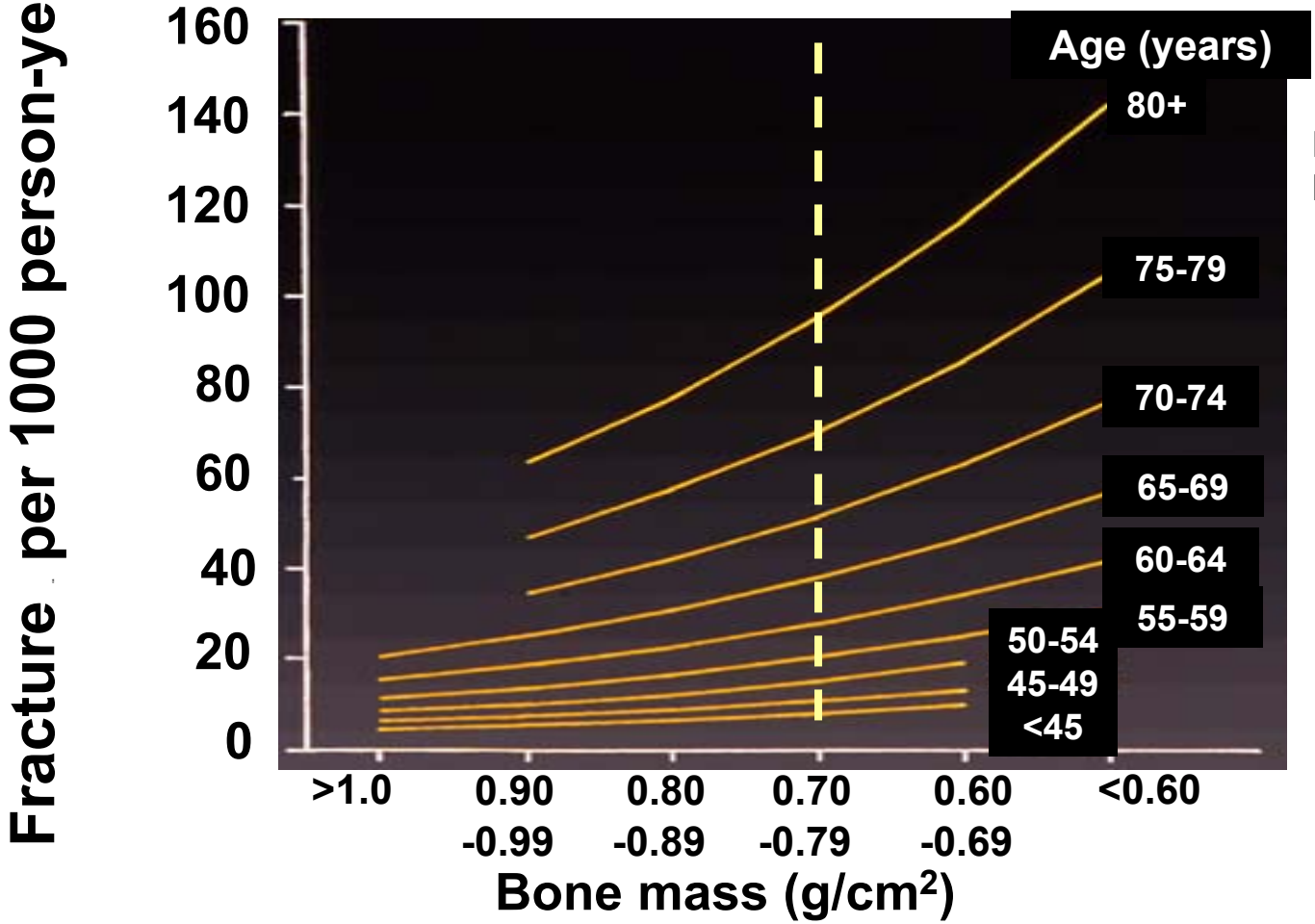
Lateral/Posterolateral
Fall Impacting the Hip
Or
Abnormal Lifting

Bone Quality – Biology and Engineering



Bone Quality – Age Dependence

Similar BMD in young and old does not carry the same fracture risk (i.e., age and bone quality)



Hui et al., J Clin Invest, 1988

Clinical Observation about DXA and Strength

- **Vertebral fracture reduction with various anti-resorption therapies is very similar across drug classes but the increases in BMD are different.**

- **Significant reduction of vertebral fractures occurs within the first year of anti-resorption therapy in pivotal clinical studies but BMD does not increase much at all.**

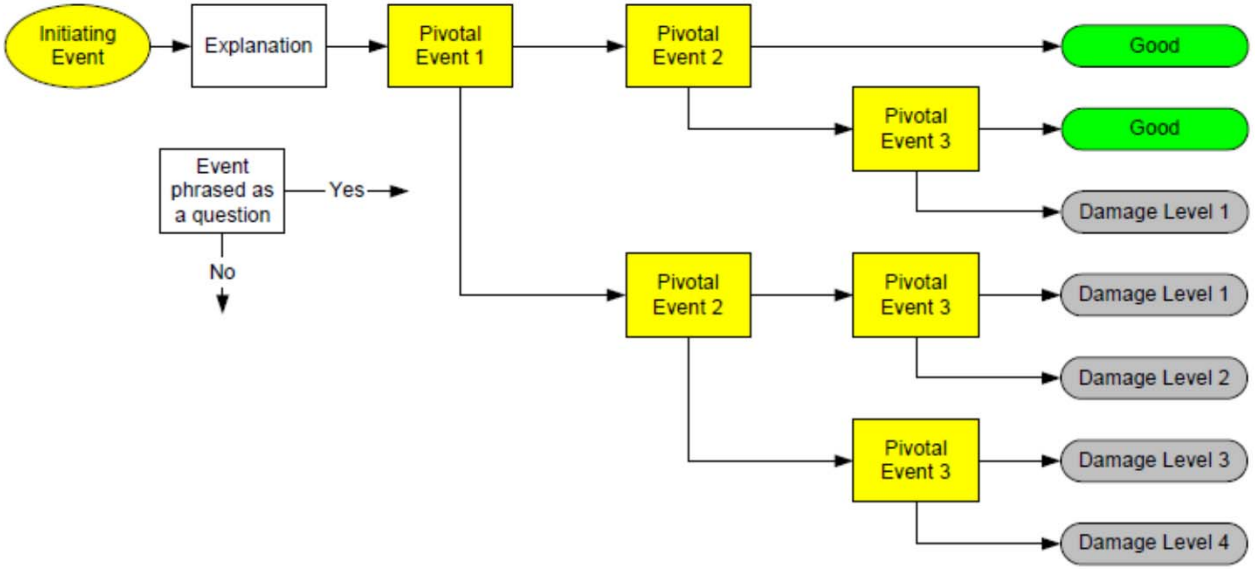
- **Fracture risk with glucocorticoid [steroids] drugs maybe high even with normal BMD.**

- **Increased BMD does not always coincide with increased strength**
  (e.g., sodium fluoride, osteopetrosis, diabetes mellitus).

What about the FRAX model?

- **WHO FRAX model is being promoted for use in helping to understand fracture risk in clinical evaluation of patients.**
  - An amalgamation of bone density data with dichotomous clinical risk factors
  - Can it be used for Astronauts?
- **Concerns exist that FRAX**
  - Includes variables and conditions that are not generally a concern of the astronaut corps.
  - Age ranges only slightly overlap the age range of the astronaut corps.
  - Assumes a different loading environment – limited analogy
  - Likelihoods are specified in terms of generalized 10-year risk level which makes application of the assessment questionable for in mission likelihood estimates.
- **Although good clinical tool, FRAX is likely not applicable to the astronaut corps.**
  - What are other potential alternatives

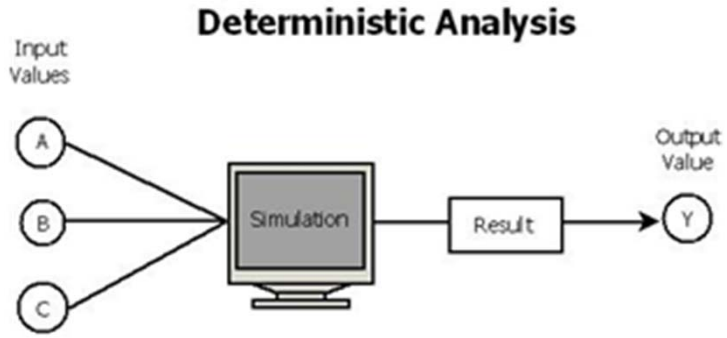
PRA - Event System Diagrams and IMM

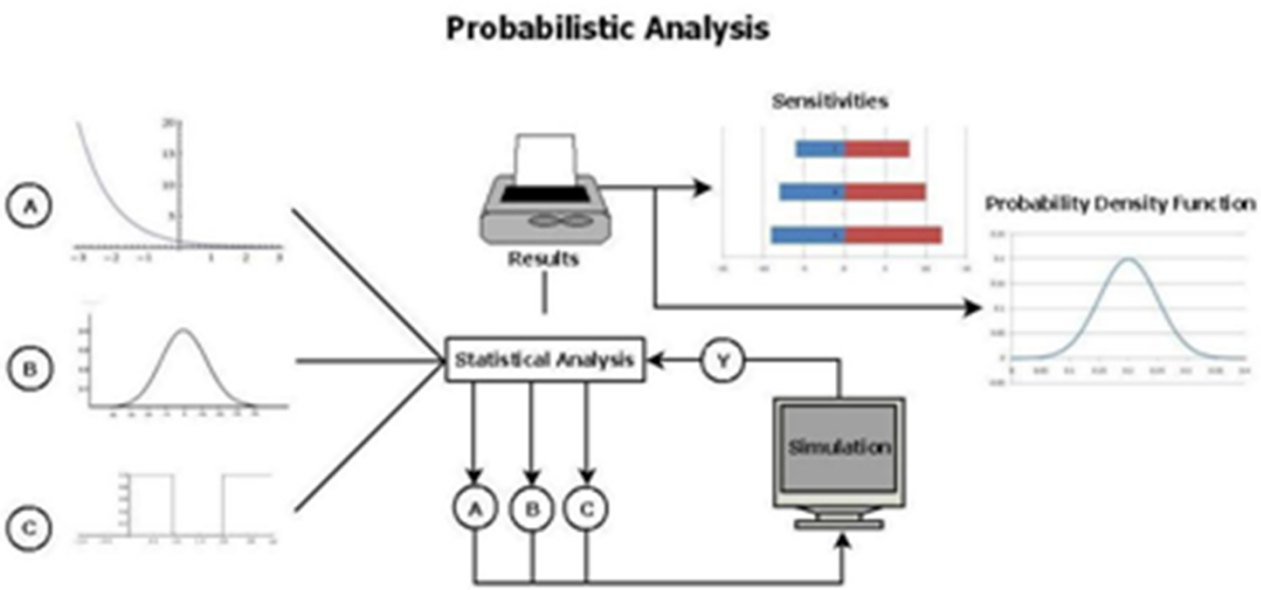


- Integrated Medical Model PRA application:
  - Probability and consequences of medical risks.
  - Integrate best evidence in a quantifiable assessment of risk.
  - Identify medical resources necessary to optimize health and mission success considering 83 medical conditions.

Building a Model Using Simulation PRA

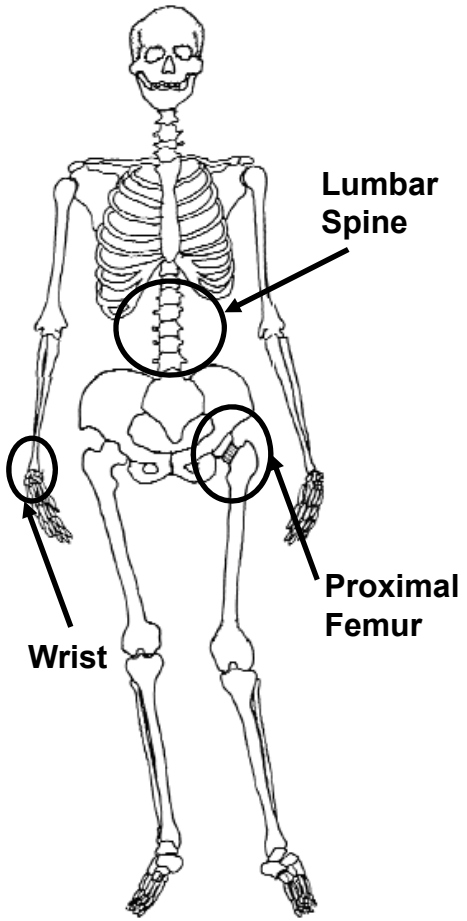
- **Simulation Probabilistic Risk Assessment (PRA)**
  - Physical models + physiological data + probabilistic simulations
  - Integration through Monte Carlo Simulation
  - Account for interacting contributions
  - Acts as integrator for contributing conditions





Bone Fracture Risk Model (BFxRM) for Assessing In Flight Fracture Risk

- **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?



Bone Fracture Risk Module Concept

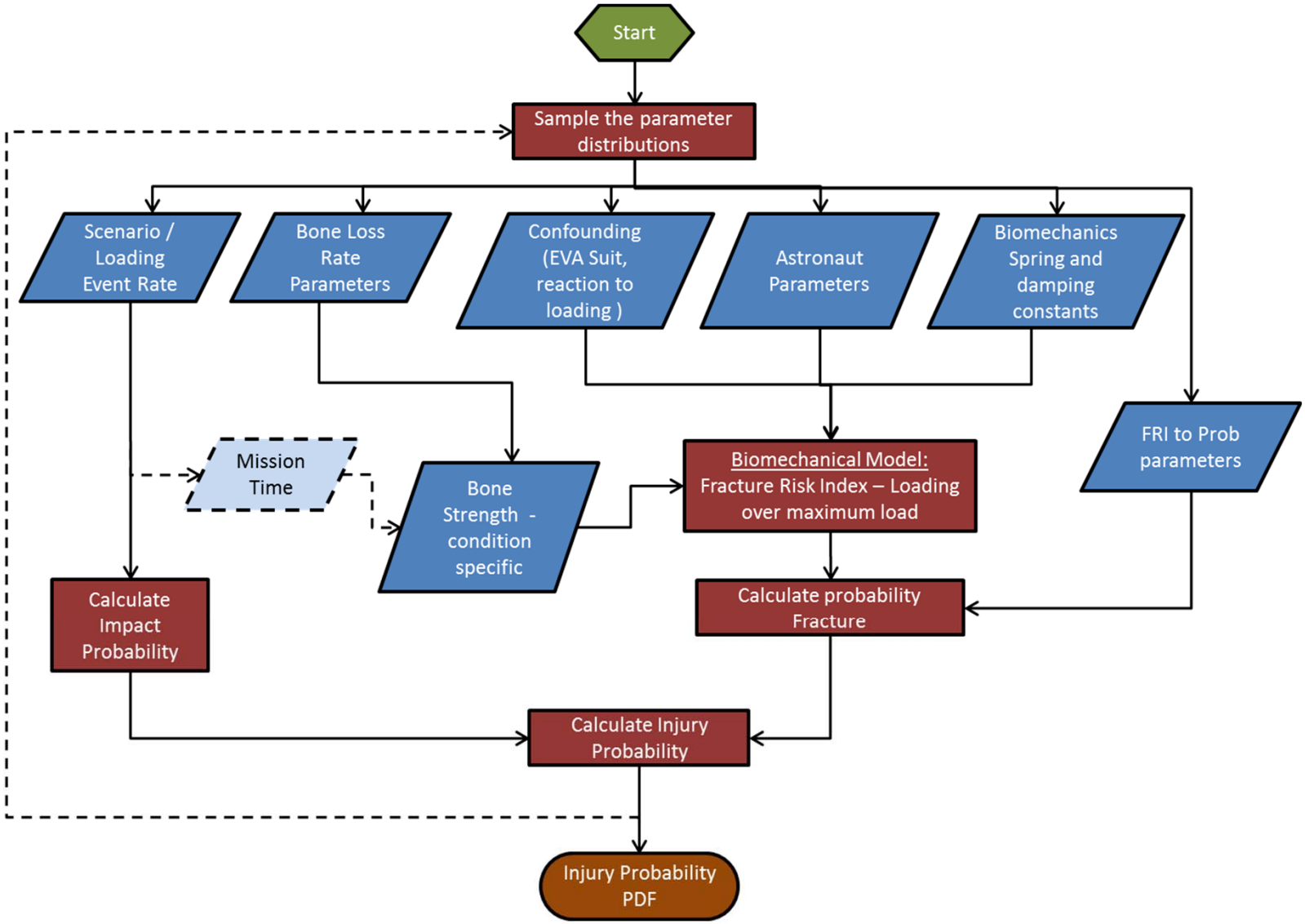
GOAL

- Capture the state of knowledge of the likelihood of fracture
  - Incorporating mission related factors, environmental influences, and best available clinical and biomedical knowledge
  - Represent this in such a way as to communicate the state of knowledge to risk assessment efforts while acceptably representing the state of uncertainty of that knowledge.
  - Aligns to NASA PRA engineering analysis

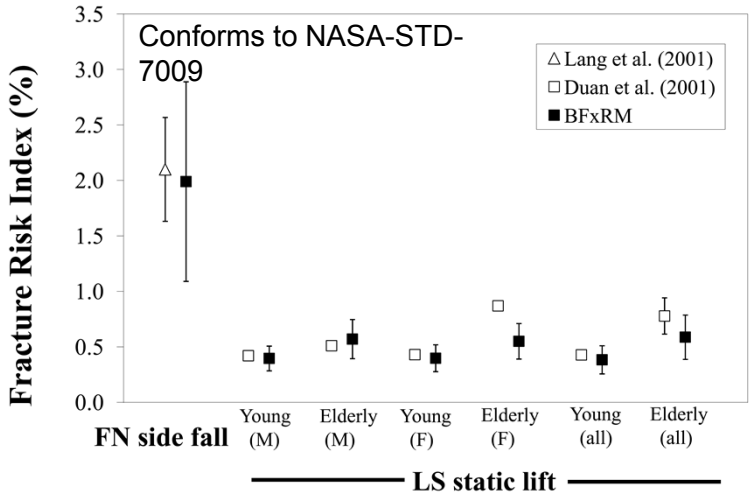
CONCEPT

- Estimate the probability of loading event during mission
- Estimate the skeletal strength at the time of loading (pre-, in- or post-mission)
- Estimate the skeletal loading with regard to the type of load and astronaut parameters
- From well established studies, develop a “transfer function” that translates Fracture Risk Index (FRI) to a probability of fracture
- Monte Carlo simulation to integrate model and data components
- Develop a probability density function (PDF)of the representative probability of fracture per mission

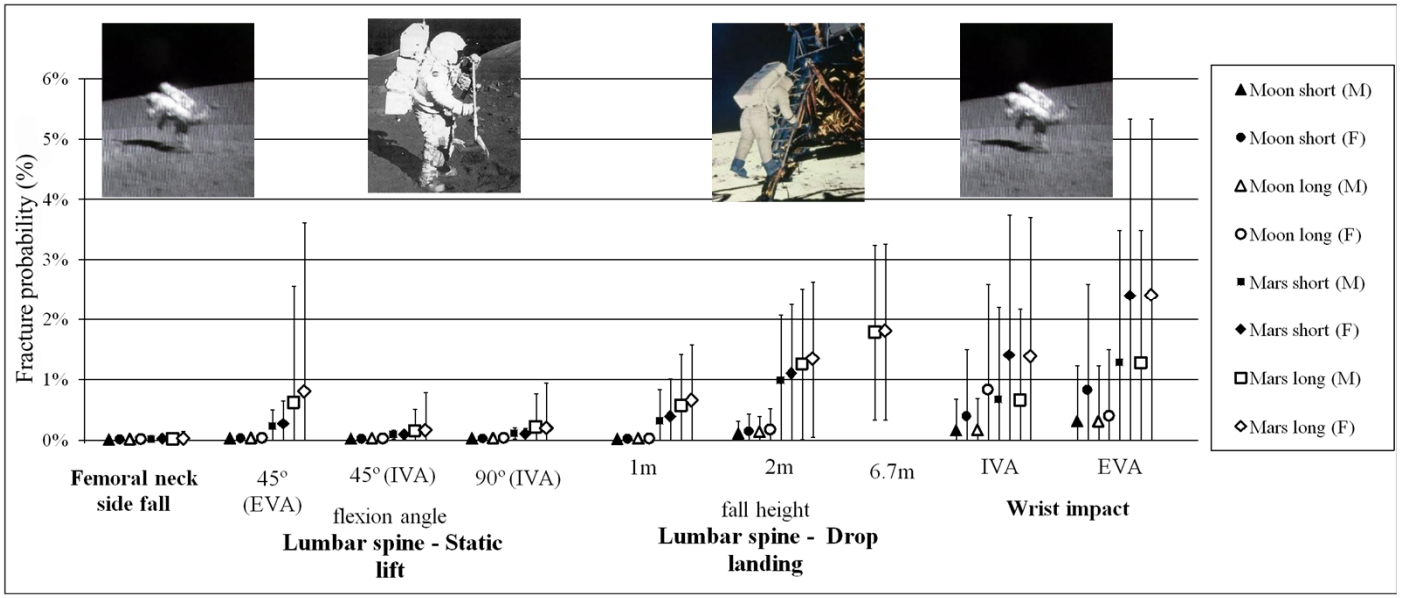
Bone Fracture Risk Modeling Process



Model Validation and Predictive Results



- Validation : Compared to two published data sets
- Applied to 4 design reference missions
  - Wrist most likely fracture location
  - Highest sensitivities: Space suit properties
- Succeeds
  - Representing state of knowledge
  - Quantitates BMD as bone quality metric



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

BFxRM - Applications

- **In flight**
  - Same logic used for wrist fracture due to translation activities on ISS
  - Used to predict ISS evacuation rate in IMM
- **Post-Flight**
  - Increased likelihood of fracture
    - Includes post-flight BMD recovery
    - Specific loading scenarios
      - Elevated, unprotected falls
      - Translational impacts – Bicycle
- **Support of Injury Criteria Definition**
  - Supplied input for fitness for duty standards review
  - Injury loading thresholds – off-nominal Orion landing
- **Countermeasures induce changes to inflight injury likelihood resulting from**
  - Improved exercise with ARED and T2
  - Use of Bisphosphonates

Suggested Discussion Questions

- **Is there further utility in the BFxRM approach**
  - Assessing ongoing astronaut fracture risk
    - Inflight (mission activity)
    - Post-flight (daily activity on return to earth)

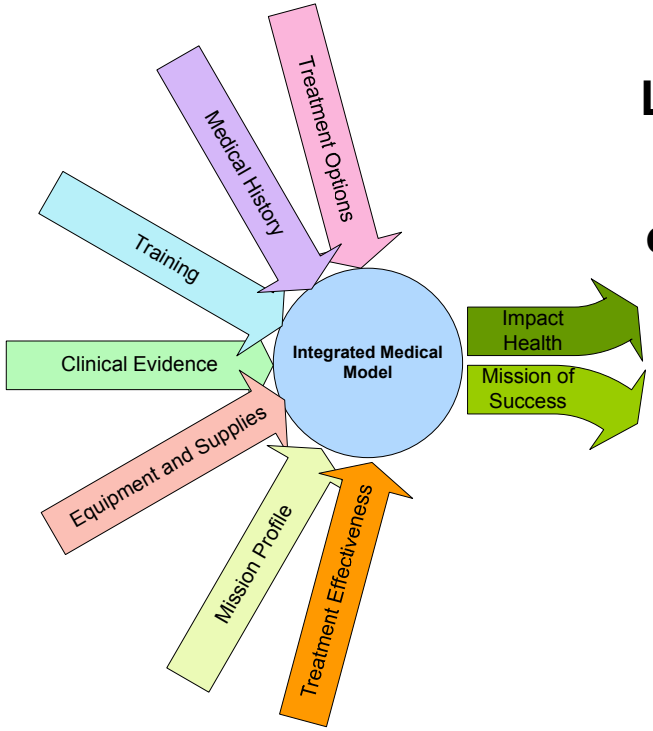
- **What additional capabilities (variables) should be implemented to improve the clinical assessment potential of this approach?**
  - Currently rely on idealized loading scenarios and DXA for maximum bone loading for the loading scenario.
  - How would integration with FEM or other combination of “quality parameters” increase the predictive capability and acceptance of the simulation? What quality of data is available in these areas?

- **What type of Verification, Validation and Credibility assessment would make this approach clinically acceptable for decision support?**
  - NASA STD 7009 is being used as the basis for FDA and NIH-IMAG model credibility assessment approaches

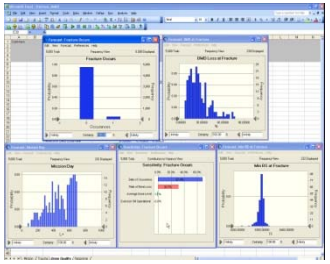
EXTRAS

Integrated Medical Model (IMM)

Potential Medical Condition



Likelihood of occurrence, probable severity of occurrence, and optimization of treatment and resources.

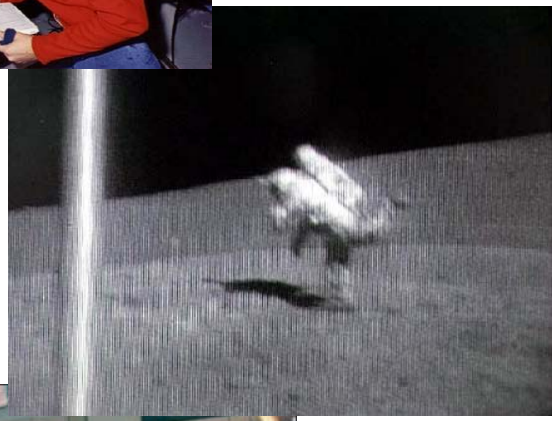


Evaluate with IMM

- **Probability and consequences of medical risks.**
- **Integrate best evidence in a quantifiable assessment of risk.**
- **Identify medical resources necessary to optimize health and mission success considering 83 medical conditions.**

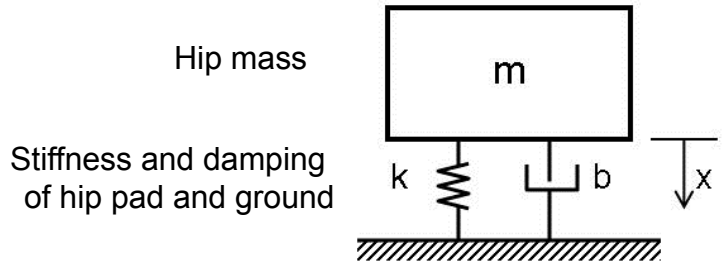
Sources of Model Data

- **Limitations**
  - Small n - “Attributable” data
- **Observed Data**
  - Open literature
  - In flight observations
  - Ground studies
- **Expert Opinion**



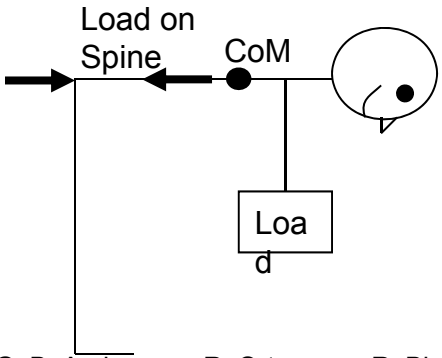
Library of biomechanical loading models

Femoral Neck – Fall to the side



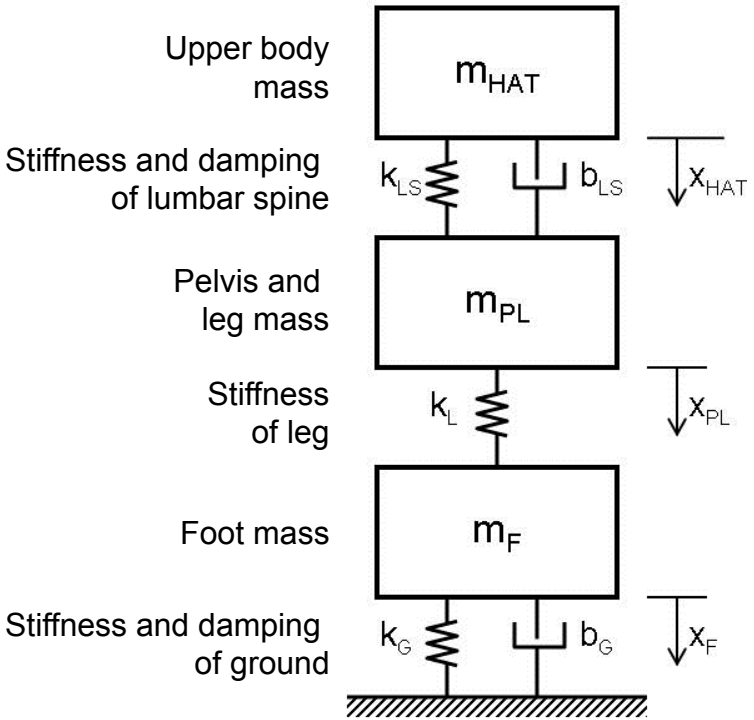
S. N. Robinovitch, W. C. Hayes, and T. A. McMahon, "Prediction of femoral impact forces in falls on the hip," J. Biomech. Eng, vol. 113, no. 4, pp. 366-374, Nov.1991.

Lumbar Spine – Trunk flexed, holding a load



A. Schultz, G. B. Andersson, R. Ortengren, R. Bjork, and M. Nordin, "Analysis and quantitative myoelectric measurements of loads on the lumbar spine when holding weights in standing postures," Spine, vol. 7, no. 4, pp. 390-397, July1982.

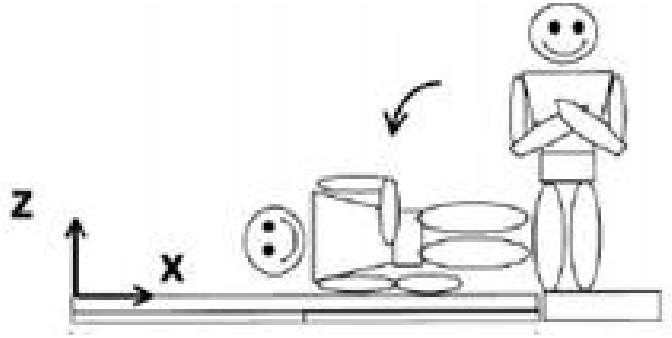
Lumbar Spine – Fall, landing on two feet

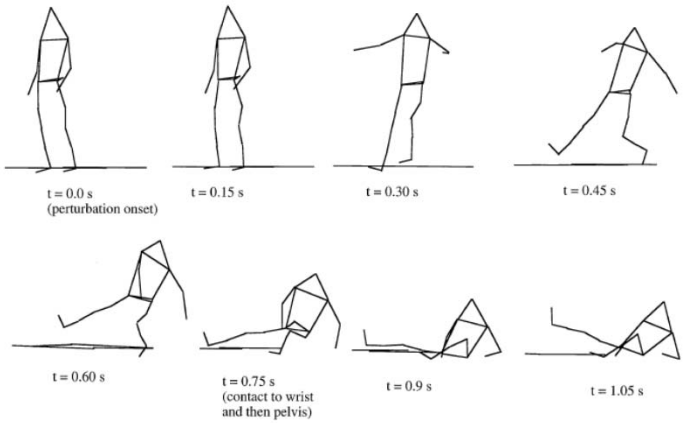


K. J. Chi and D. Schmitt, "Mechanical energy and effective foot mass during impact loading of walking and running," J. Biomech., vol. 38, no. 7, pp. 1387-1395, July2005.

Context: Active Response

- **Active Response**
  - Taking action to arrest fall impact
    - Re-orienting during fall
    - Reaching out to break fall with arm
  - Active response successfully occurs 72% of the time: Hsiao and Robinovitch, 1998
    - Successful if occurs in time frame to attenuate the load to the hip
    - Higher likelihood in reduced g
  - With a successful active response
    - Load Attenuation at hip is 12% +/-37% : Sabick et al (1999)
  - Wrist fracture becomes a concern





Level of Bone Loss on Day of Loading

- Accepted that bone loss occurs at an accelerated rate in microgravity
  - Especially at the femoral neck, trochanter and lumbar spine
  - Time course usually represented as linear
- Controversy as to the extent of loss
  - Consensus is that it does not go on indefinitely
  - Unclear what ultimate level is reached
- Assumption: Maximum limit corresponds to the maximum bone loss seen terrestrially
  - Combining observations of NHANES III and Cummings, JBMR 2004;19S1:S89
    - 60% ± 17% (max 69%)
    - **Review of Spinal Cord Injury Data indicates that this level of loss is high**

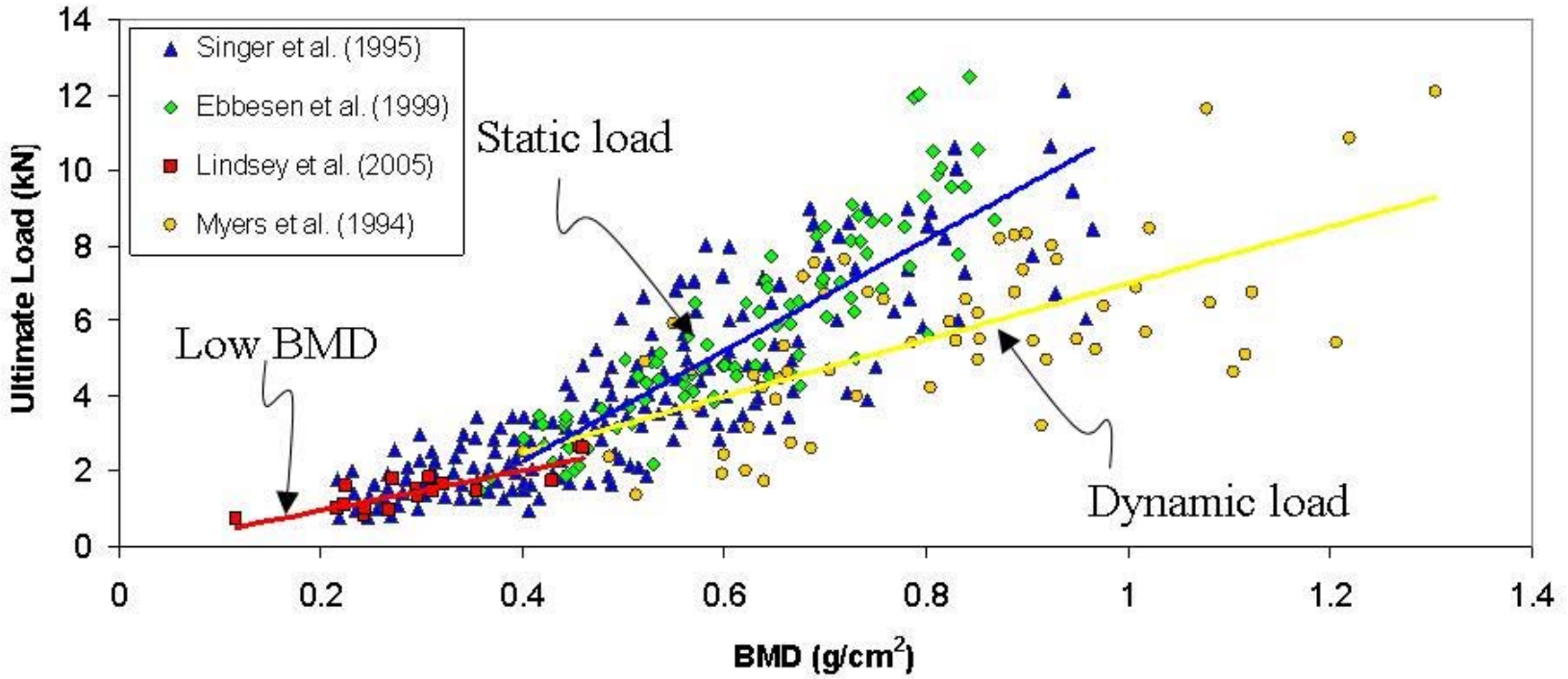
LeBanc et al, 2000

DXA BMD g/cm2	%/month
Lumbar Spine	-1.06±0.63
Femoral Neck	-1.15±0.84
Trochanter	-1.56±0.99
Pelvis	-1.35±0.54
Arm	-0.04±0.88
Leg	-0.34±0.33

LSAH Provided: Combined NASA-MIR and ISS-Expedition 1-12

	%/day	%/month	R^2
FN	-0.035	-1.059	0.824
LS	-0.024	-0.723	0.737
Troch	-0.040	-1.198	0.717
Pelvis	-0.042	-1.260	0.691

Relationship between BMD and Ultimate Load of bone for different loading conditions



K. Singer, S. Edmondston, R. Day, P. Breidahl, and R. Price, "Prediction of thoracic and lumbar vertebral body compressive strength - Correlations with Bone Mineral Density and vertebral region," Bone, vol. 17, no. 2, pp. 167-174, 1995.

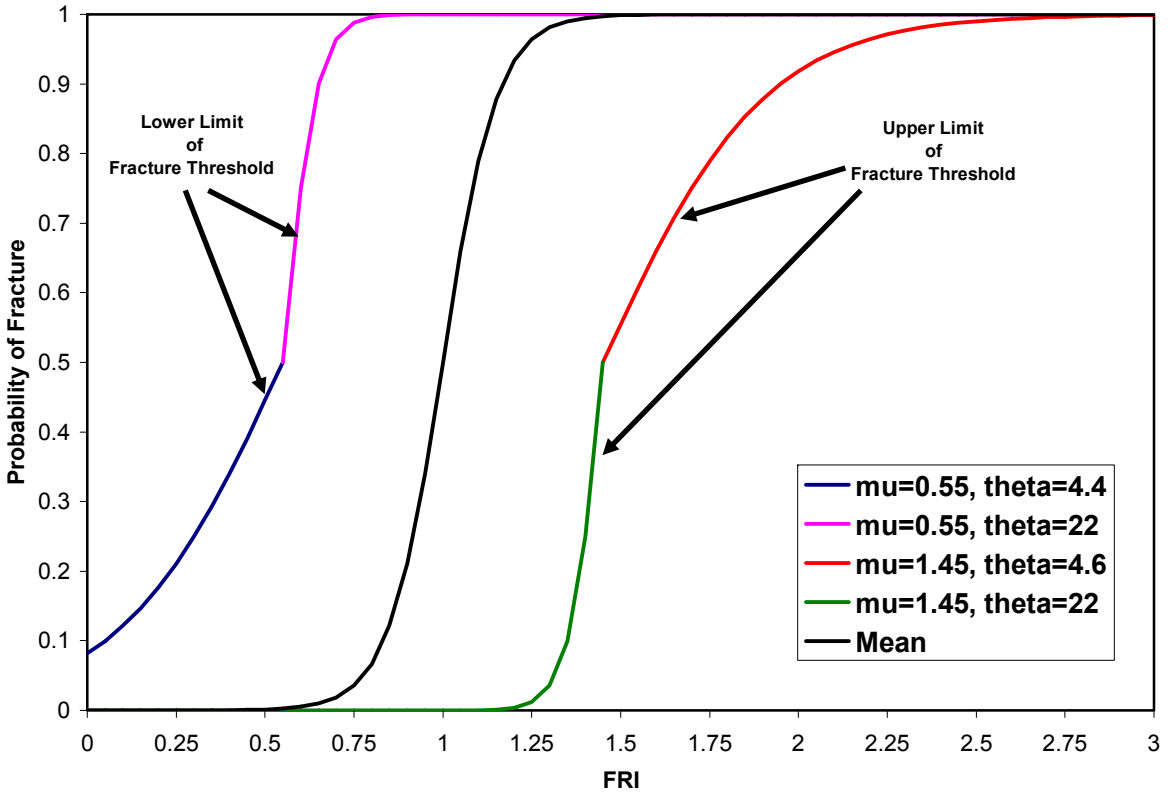
E. N. Ebbesen, J. S. Thomsen, H. Beck-Nielsen, H. J. Nepper-Rasmussen, and L. Mosekilde, "Lumbar vertebral body compressive strength evaluated by dual-energy X-ray absorptiometry, quantitative computed tomography, and ashing," Bone, vol. 25, no. 6, pp. 713-724, Dec.1999.

D. P. Lindsey, M. J. Kim, M. Hannibal, and T. F. Alamin, "The monotonic and fatigue properties of osteoporotic thoracic vertebral bodies," Spine, vol. 30, no. 6, pp. 645-649, Mar.2005.

B. S. Myers, K. B. Arbogast, B. Lobaugh, K. D. Harper, W. J. Richardson, and M. K. Drezner, "Improved assessment of lumbar vertebral body strength using supine lateral dual-energy x-ray absorptiometry," J. Bone Miner. Res., vol. 9, no. 5, pp. 687-693, May1994.

Estimating Probability of Fracture

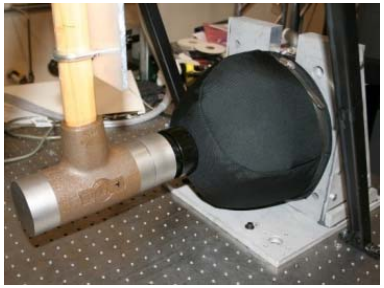
- **Follows from Davidson et al. 2006**
  - Logistic regression to relate FRI to Probability of Fracture
- **Define Threshold Based on Archival Literature**
  - 0.5 < P < 0.95
  - 1-σ < FRI=1< 1+σ

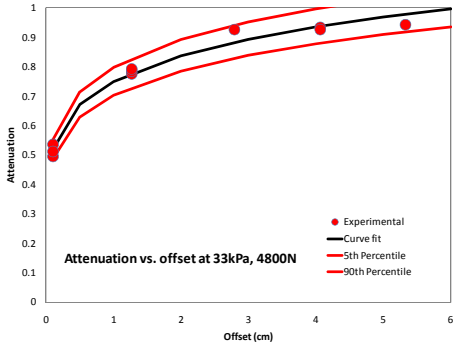


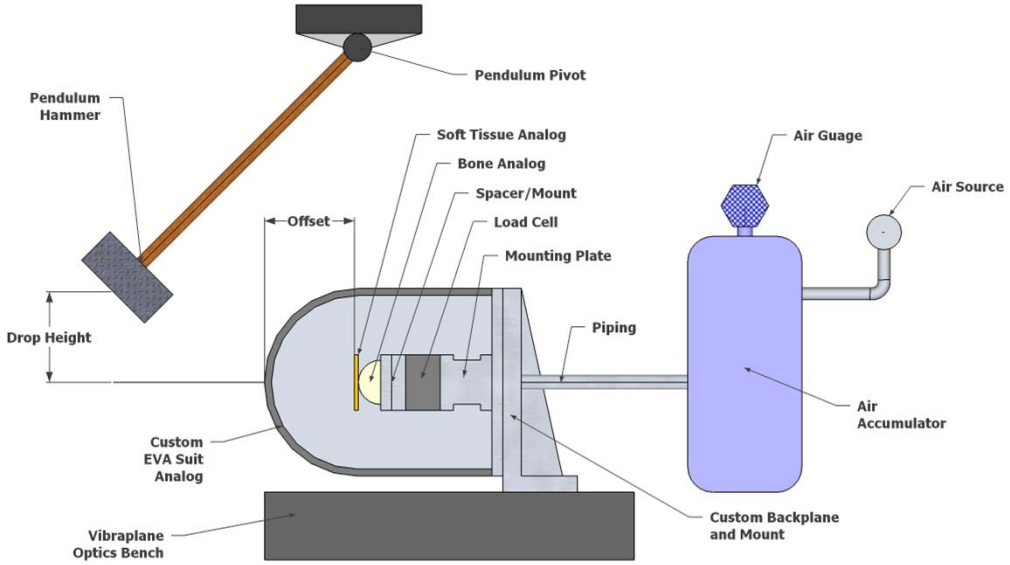
$$P(FRI) = \frac{1}{\left(1+\exp\left(-1*\left(FRI-\mu\right)*\theta\right)\right)}$$

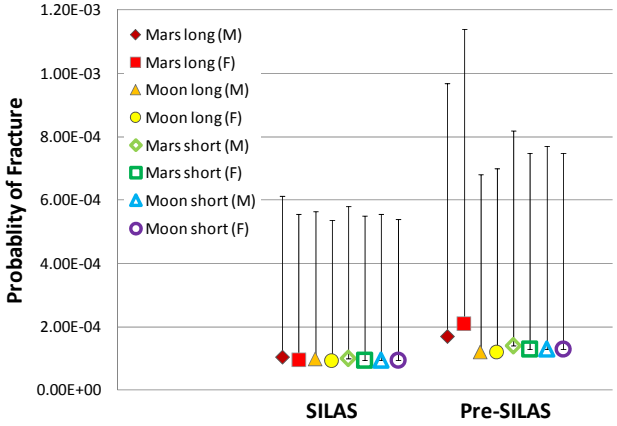
Experimental Reduction of Uncertainty

- **Analog estimates of Space suit injury protection – SILAS**
  - First quantifiable analog of pressurized suit impact load attenuation
- **Results**
  - Attenuation characteristics dependent on Distance between hip and suit and Magnitude of the loading condition
  - Implementation in the Bone Fracture Risk Model (BFxRM)
    - Reduced epistemic uncertainty, the mean probability of fracture, and the 90th percentile by about 20%





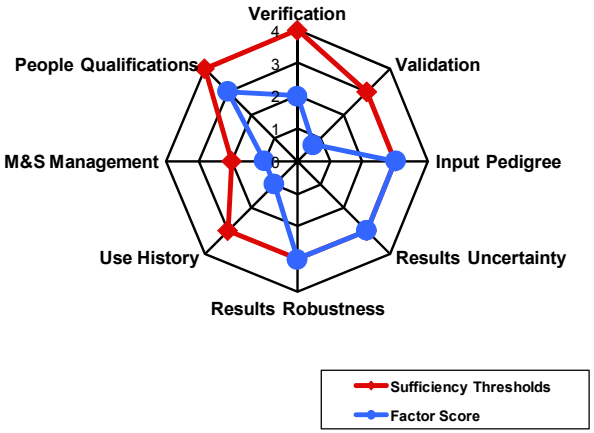




V&V - Its Really About Model *Credibility*!

Achieving a high level of belief or trust in the model

- **NASA-STD-7009**
  - Standard for Models and Simulations (M&S)
- **M&S Development**
  - Verification
    - Fixed and Extreme value testing to estimate numerical error
  - Validation
    - Face validation with medical experts/panels
    - Direct comparison historical, prospective and analog data
- **M&S Operations**
  - Input Pedigree
    - Highest quality of the data correlated to the scenario
  - Results Uncertainty
    - Quantified with non-deterministic analysis
  - Results Robustness
    - Quantified with rank order correlation
- **Supporting Evidence – Rigorously Documented**
  - Use History
  - M&S Management
  - People Qualifications



Note: HRP historically relies heavily SME and non-advocate review processes

Why Develop a Risk Tool (cont)?

- **Present medical tools inappropriate**

- **Original development of DXA / T-score system**

– **Postmenopausal Caucasian women, elderly**
– **To assess risk for fragility fracture**
– **Highest risk for those ≤ - 2.5 s.d. from population mean [T-score]**
– **Reference population used unlike astronaut corps young healthy, physically fit, work in unique environment, engage in unique activity**