ASSESSING THE LIKELIHOOD OF RARE MEDICAL EVENTS IN ASTRONAUTS

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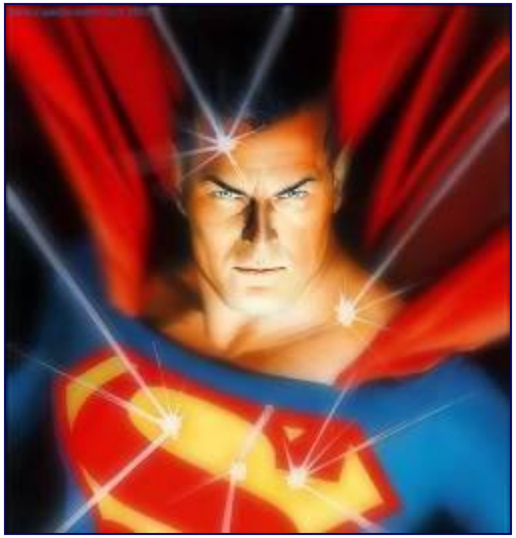
Sometimes we see our

NASA ASTRONAUTS

as

SUPERMAN

Not always like a SUPERPERSON



SUPERMAN can resist almost any type of injury or disease …
… outside of **Kryptonite and magic!**

ASTRONAUTS can have:

Muscle and bone loss
Cardiovascular adaptations
Compromised immune systems
Impaired healing
Headaches & stuffy noses
Tummy problems
…and *food tastes different*

ISS and Shuttle Crew: June 10, 2008

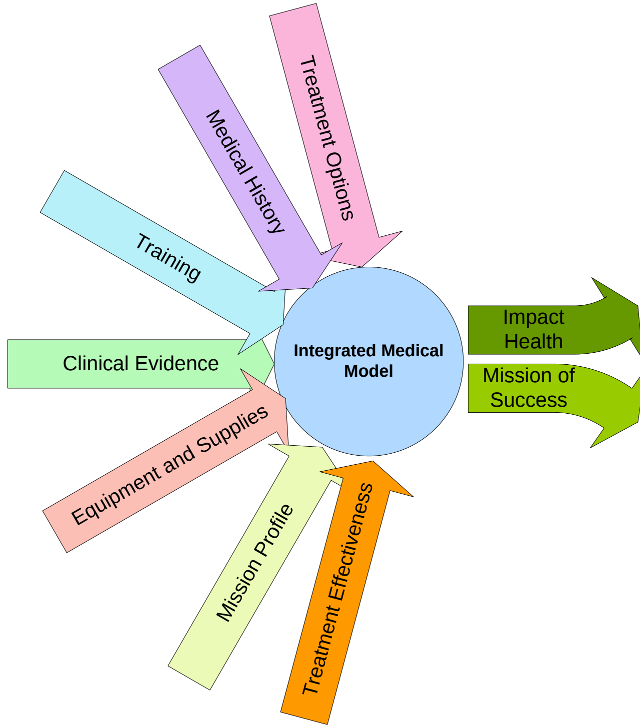
Designing a Space Mission: Astronaut Health Considerations

- Understanding the risks
  - Likelihood of health concern
  - Likelihood it can be treated successfully
    - The Trinity
      - Mass, Volume, Power
  - Mission impact after presentation of health issue
- How do these likelihoods compare to more "Engineering Risks"
  - Launch vehicle failure
  - Re-entry vehicle failure
  - In mission risks: micro meteorites or life support failure

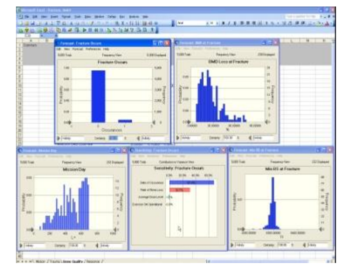
Integrated Medical Model (IMM)

Potential Medical Condition

Evaluate with IMM



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



- 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

Mission Simulation

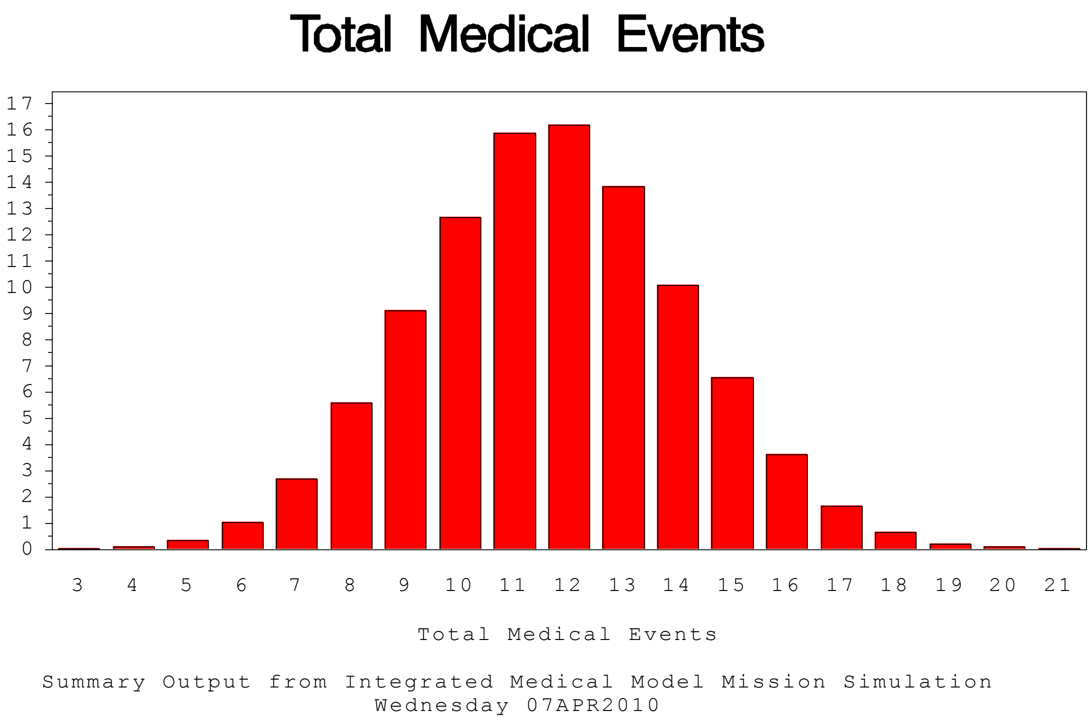
1. For each condition and/or crewmember, randomly select an incidence rate based on input data
2. Based on this incidence rate, randomly select the number of occurrences
3. For each occurrence, randomly select the scenario (best or worst case).
4. Based on the scenario, calculate resource utilization and determine if sufficient resources exist to treat each condition.
5. Based on the scenario and treatment status, randomly select the functional impairment and endstate (EVAC, LOCL)

Key Model Assumptions

1	83 medical conditions
2	No Timeline. All events occur at the beginning of the flight. Conservative estimate of CHI.
3	Treatment order is based on incidence and crewmember ID.
4	All medical conditions are independent (except ARS).
5	Assumes another skilled crew member to give care with100% correct diagnosis, 100% effective medications and equipment and uninterrupted communications.
6	ISS Health Maintenance System (HMS). No IMAKS, no Russian resources.

Example Mission

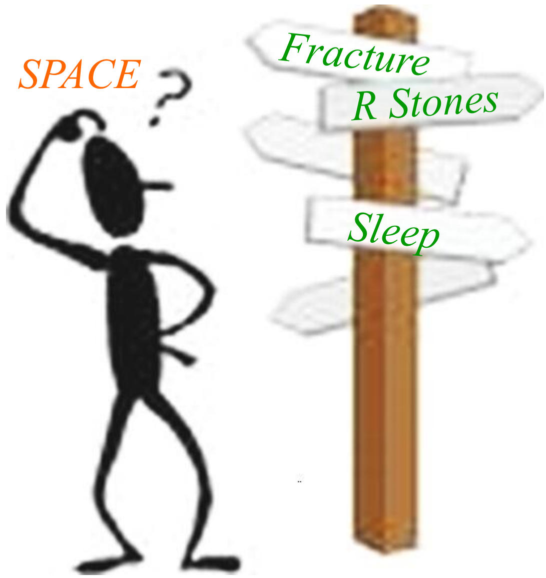
- What medical events, outcomes and resource utilization would we expect on a three-day, four-crew ISS transfer mission?



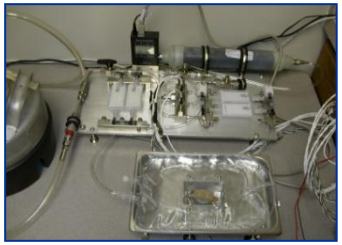
Top 10 occurring medical events:
SPACE MOTION SICKNESS (SA)
BACK PAIN (SA)
NASAL CONGESTION (SA)
EARLY INSOMNIA (SA)
HEADACHE (SA)
CONSTIPATION (SA)
SKIN RASH
SKIN ABRASION/LACERATION
EYE ABRASION
URINARY RETENTION (SA)

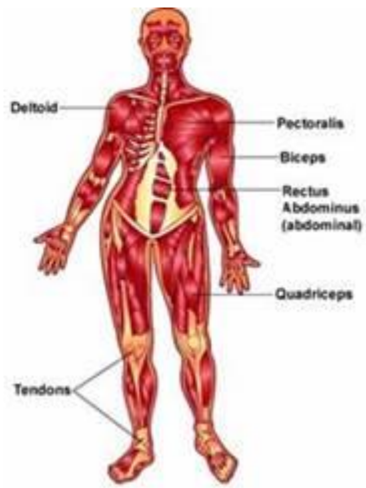
IMM and External Modeling

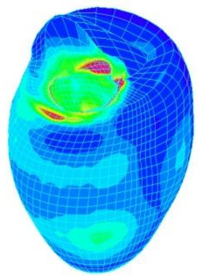
- Forecasting rare medical concerns confounded by space travel
  - Insufficient data (few or no occurrences)
  - No clear correlation to terrestrial analog
- Examples
  - Traumatic injury
    - Skeletal fracture
  - Renal stone
  - Sleep medication use
- Hypothesis
  - Much like an engineering problem, higher fidelity models can provide guidance in assessing medical incidence risk
- Requires
  - Acceptable level of model maturity
  - Proper integration of model and observed data



GRC Core Capabilities Applied to IMM







- Advanced capabilities in physiological modeling
  - Devising computational approaches to estimate the changes induced by space flight
  - Stochastic and deterministic modeling expertise in human physiology
- Cross-disciplinary capabilities
  - Development of flight hardware for preventive and acute medical treatment
- History of successfully partnering with regional expertise
  - Direct collaborations with research and clinical experts to enhance understanding and technology development
- *Results in allowing IMM to expand to the next level of complexity*
  - *Improved and unique perspective on the physiological parameters*
  - *Improved basis of decisions and forecasts from first principle and root cause information*

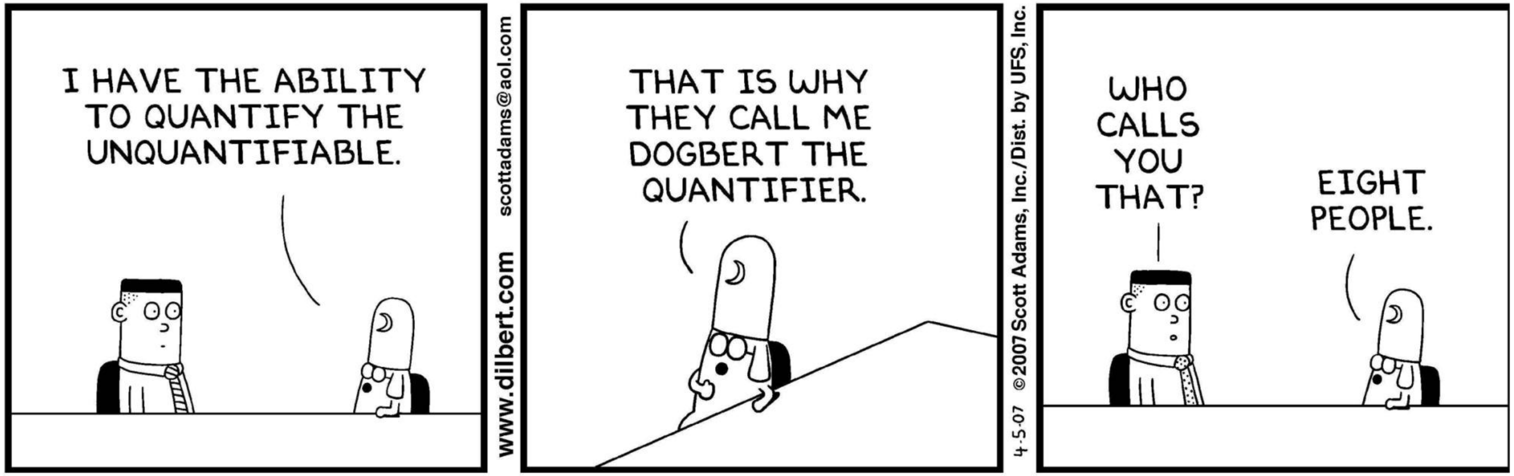
"There are no new ideas. There are only new ways of making them felt." Audre Lorde

- Process for Model Development
  - Formulate the problem
  - Collect information / data
  - Construct and validate conceptual model
  - Program the simulation
  - Validate the programmed simulation
  - Design and analyze simulation experiments
  - Document simulation results

Sargent, 1999

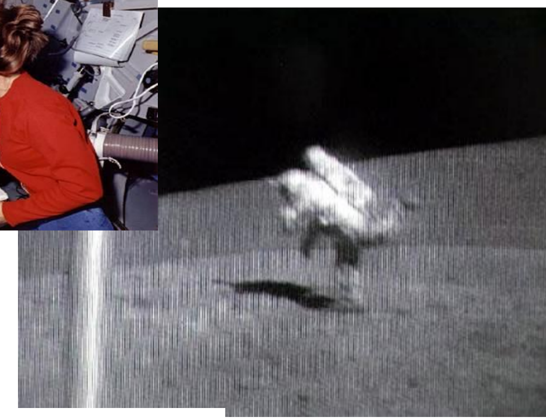
Formulate the Problem

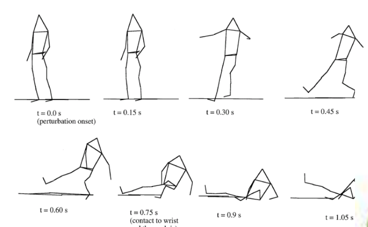
- Appropriate Risk Statements
  - Lead to appropriate questions
- Context for the Risk
  - IMM scenarios provides limits on the scope of the model
- Contributing factors to address
  - Expert community concerns guide initial content of the model
- Should be formulated so output can be quantified

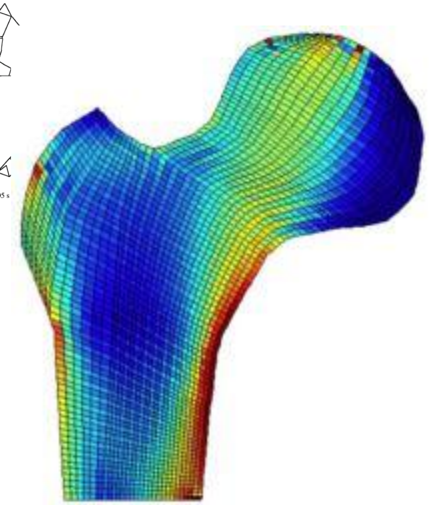


Sources of Model Data

- Observed Data
  - Open literature
  - In flight observations
  - Ground studies
- Expert Opinion
  - SME and med ops guidance
  - Clinical guidance
- Deterministic Model
  - Simple engineering models
  - Complex physiology models
- Limitations
  - Small n - “Attributable” data

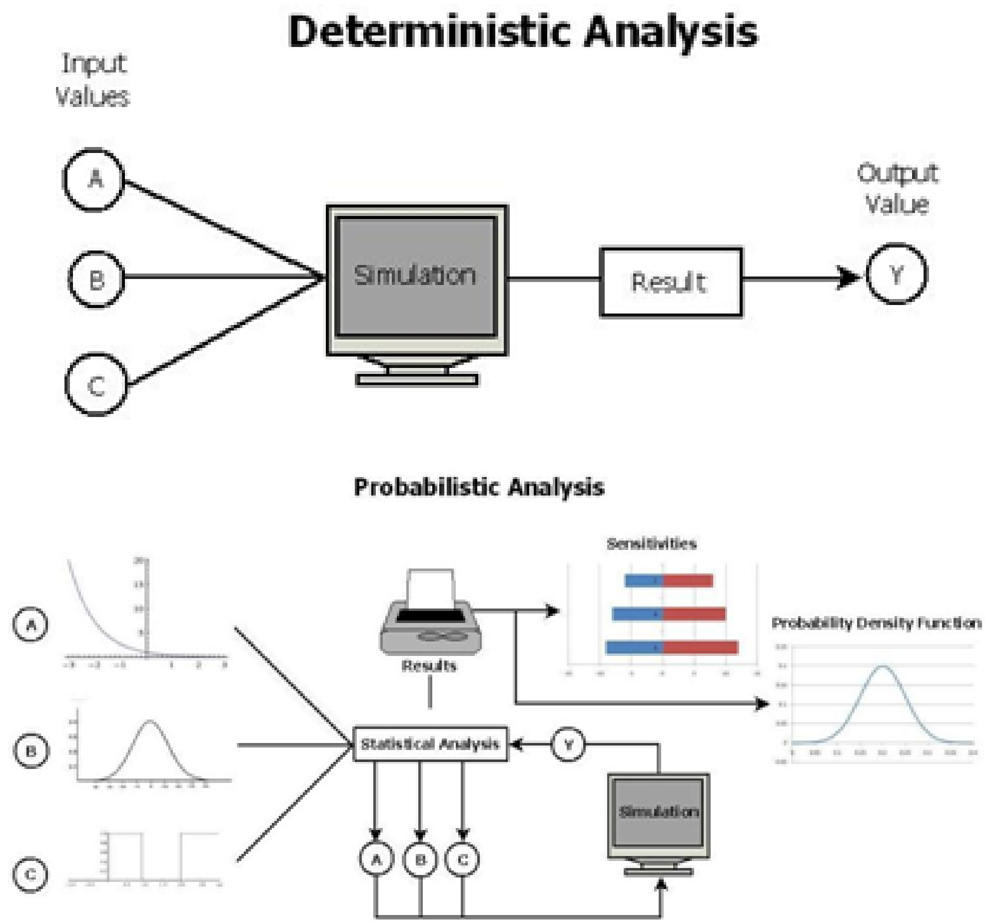






Building a Model Using Deterministic Tools

- Modified Probabilistic Approach
  - Physics + physiological + probabilistic simulations
    - Simulation PRA and deterministic modeling sensitivity analysis
  - Account for interacting contributions
    - Acts as integrator for contributing conditions
    - Supplementing areas with little incidence data
    - Supplementing areas using research data
- Not married to single modeling system
  - Cross platform versions of Crystal ball, C, Matlab, Fortran, WinBUGS, R, SAS

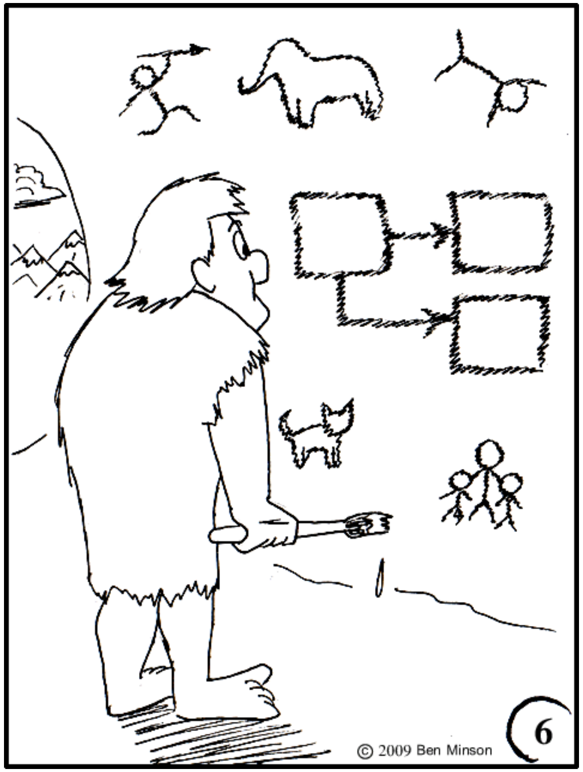


Provided By N&R Engineering

Implementation of IMM Modules

- Implementation requires that modules
  - Undergo subject matter review
    - Conceptual model, input data, validation process reviewed SME
  - Undergo integration team review
    - Credibility MUST be at least that of the rest of the IMM
  - New IMM model undergoes V&V and credibility assessment
- All evidence meticulously documented
  - "We can lick gravity, but sometimes the paperwork is overwhelming." ~Wernher von Braun
- Always report known model limitations
  - Knowing what a model can't do is often as important as knowing what a model can do.

A Guiding Principle For Conceptual Model

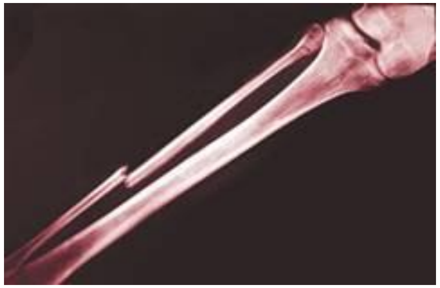


Keep

It

"Bone-Head" Simple

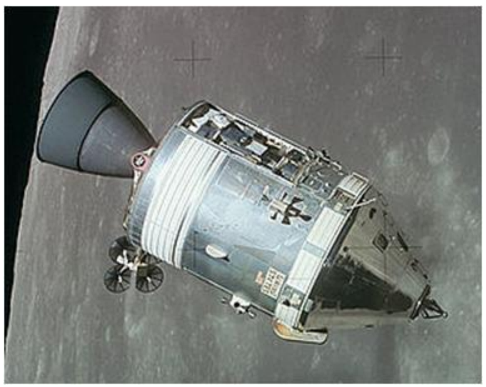
AND Straightforward As Possible

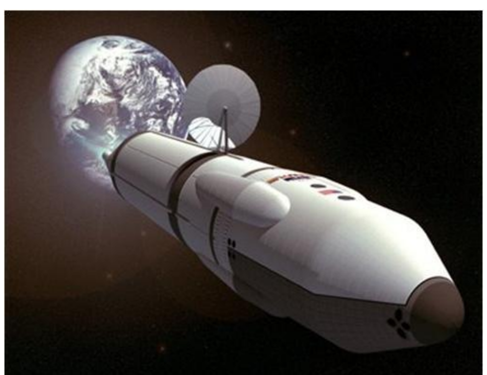


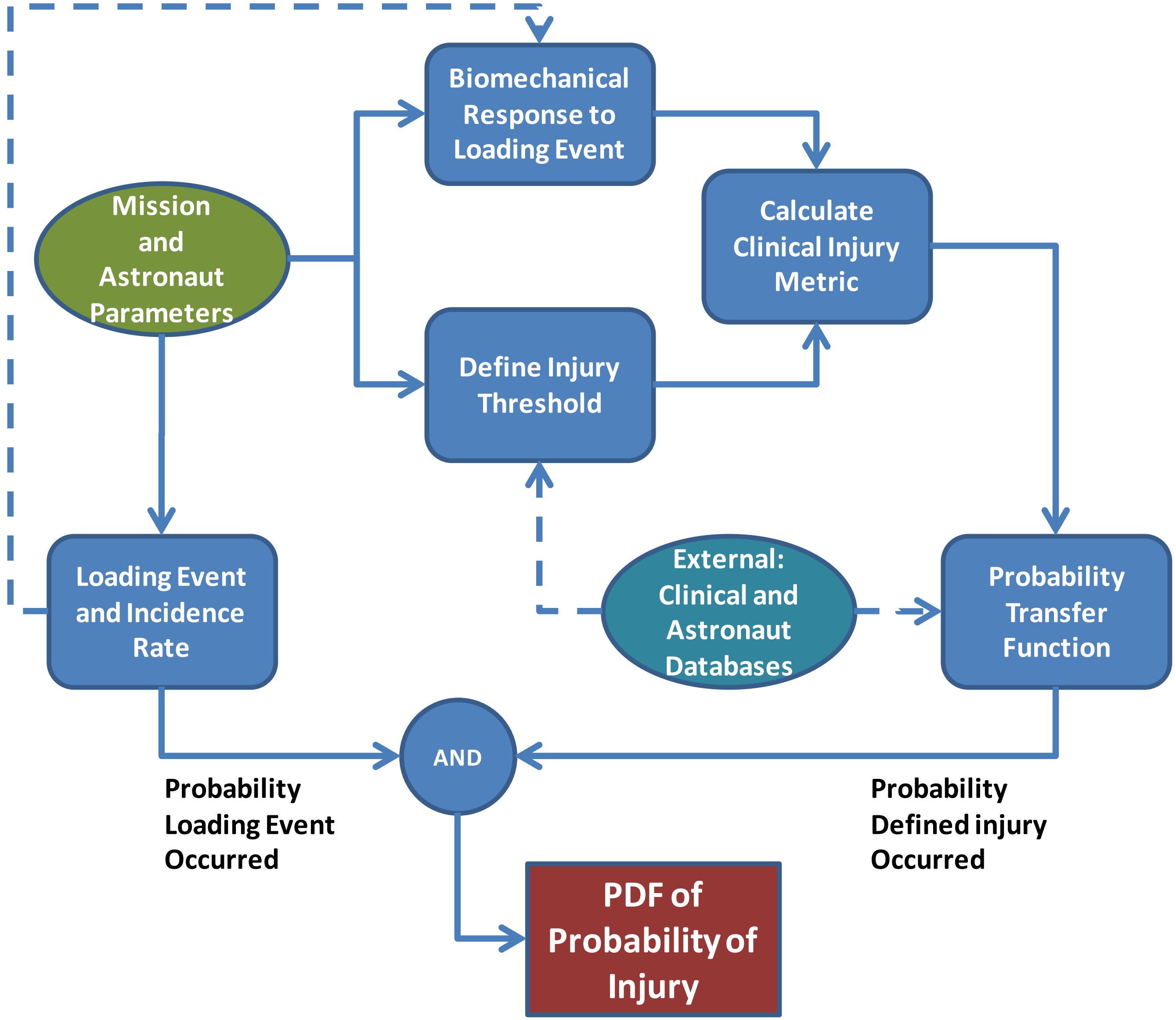
Lead By Example If You Expect Success

LIKELIHOOD OF IN-MISSION INJURY

Conceptual Approach to Injury Modeling

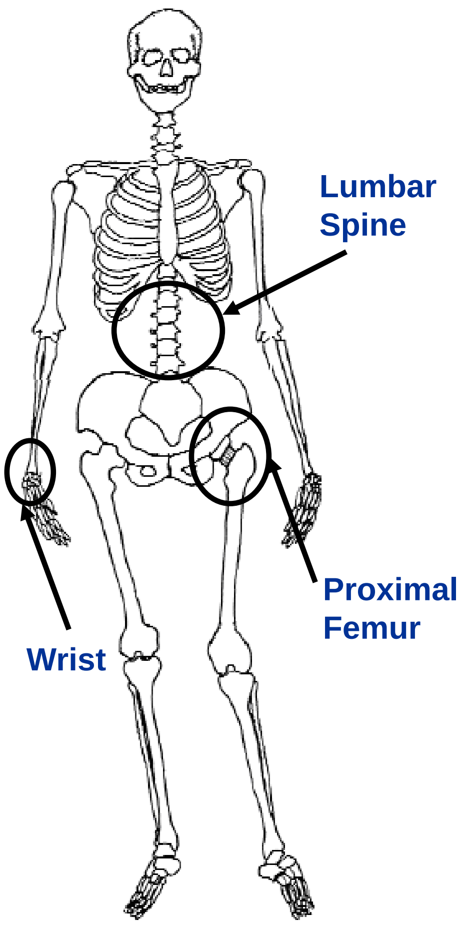






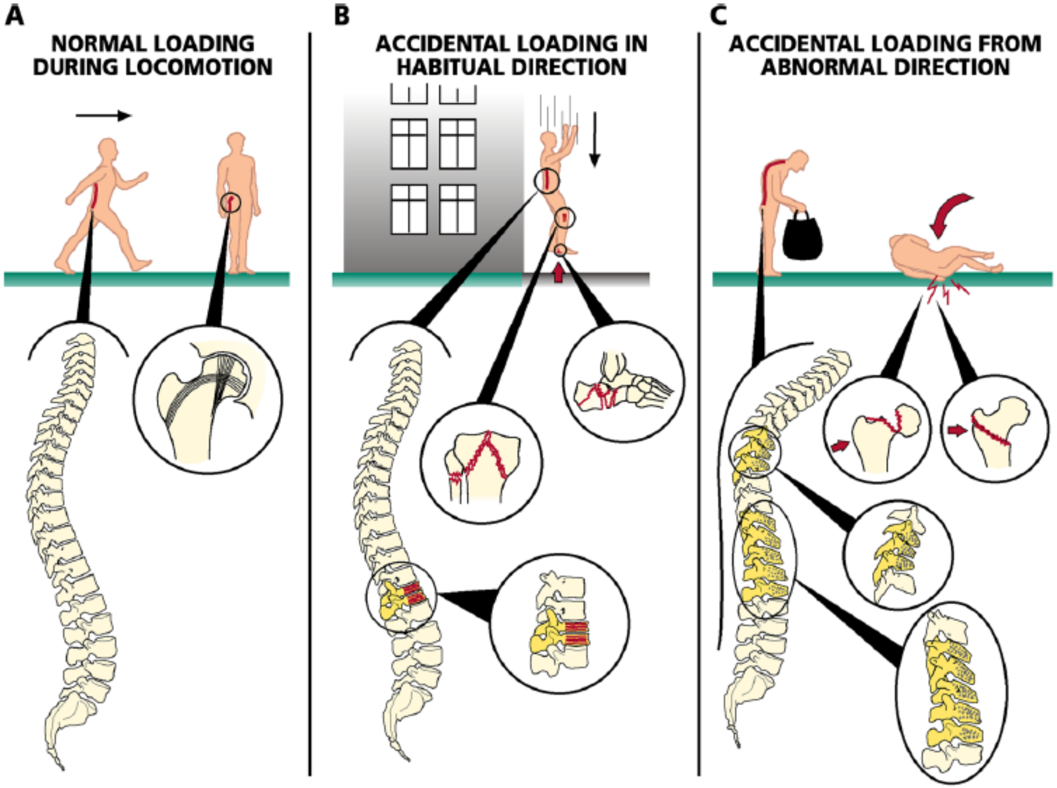
Formulate the Problem: In Flight Fracture Risk

- Real and Present Concern: Skeletal Fracture
  - Weakened bones
  - Off-nominal loading states
- Lack of In Flight Injuries
  - Even at areas of high bone loss
    - Spine and proximal femur
- Fracture risk
  - Some non-fracture in-flight injuries
  - Load level and rate uncertain
- What is the fracture risk in space and on planetary activities?



Formulating the problem context.

Micro-g Translation

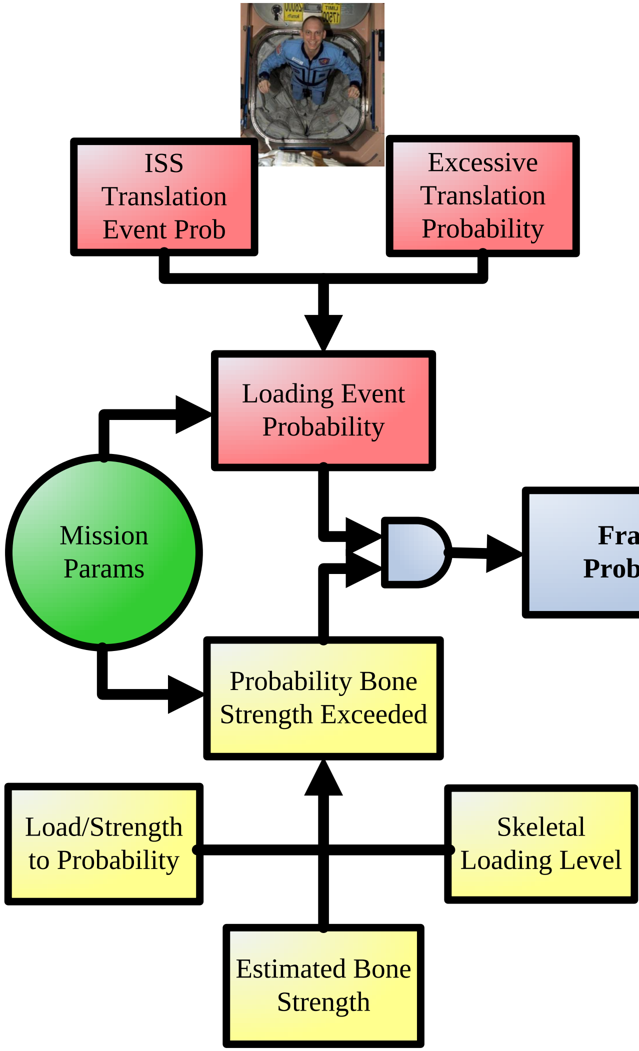


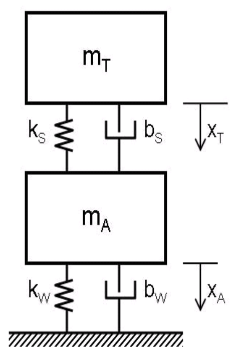
Stance
Walking
Ladder/Stair Ascent/Decent

"Drop Landing"

Lateral/Posterolateral Fall Impacting the Hip
Or
Abnormal Lifting

Collect Information and Design Model

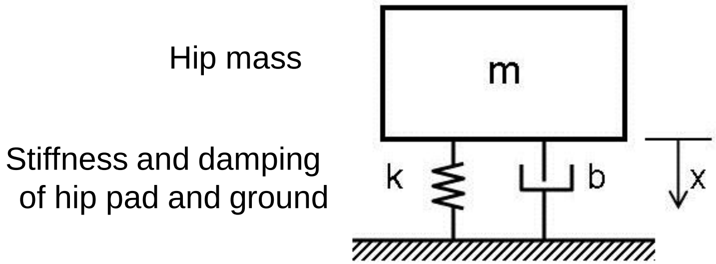




- Estimate the probability of loading event occurrence during each mission day
- Estimate the skeletal strength distribution at the wrist
- Skeletal loading
  - Mass-spring-damper, biomechanical model of the wrist, arm and shoulder
  - Identify distributions of all parameters
- Transfer function that translates FRI to a probability of fracture
  - FRI = Loading/ Skeletal strength
- Monte Carlo simulation to integrate model and data components
  - Output is a PDF of the probability of fracture per mission

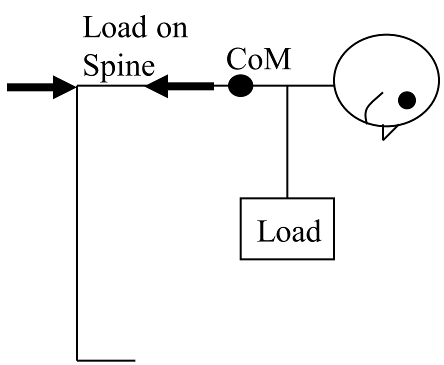
Library of biomechanical loading models

Femoral Neck – Fall to the side



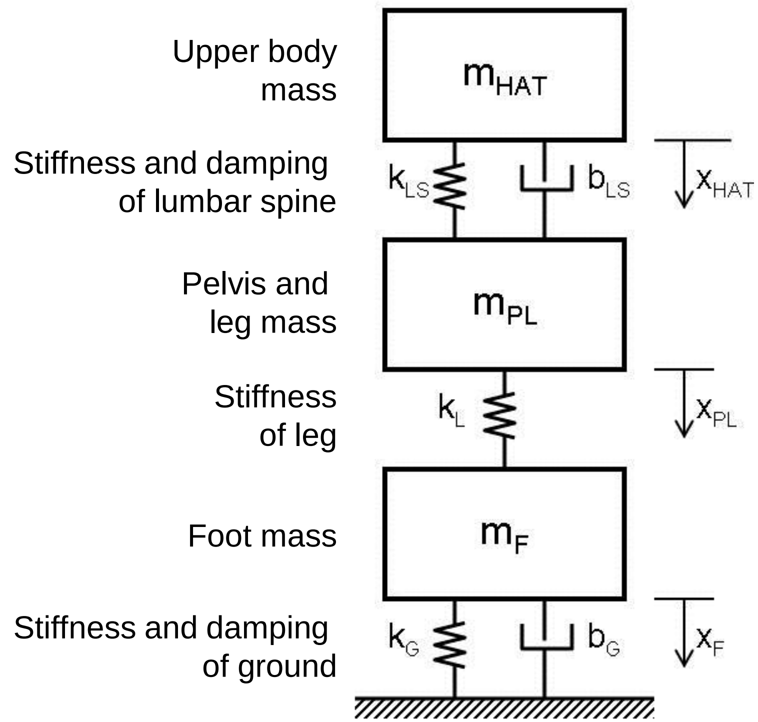
S. N. Robinovitch, W. C. Hayes, and T. A. McMahon, "Prediction of femoral impact forces in falls on the hip," J. Biomech. Eng, vol. 113, no. 4, pp. 366-374, Nov.1991.

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.

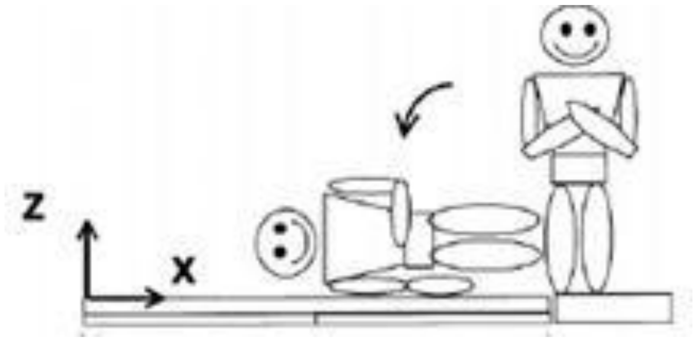
Lumbar Spine – Fall, landing on two feet

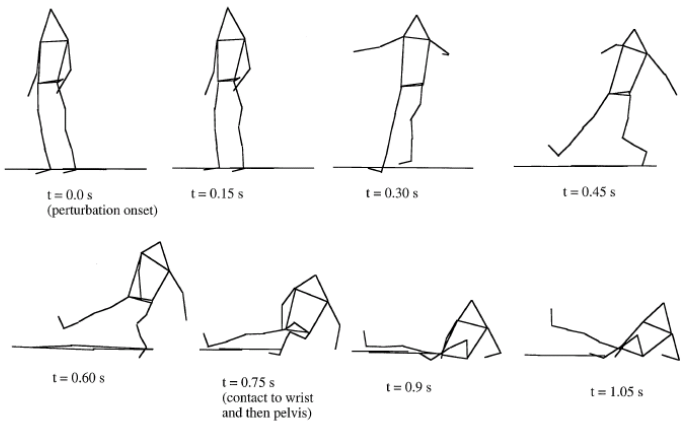


K. J. Chi and D. Schmitt, "Mechanical energy and effective foot mass during impact loading of walking and running," J. Biomech., vol. 38, no. 7, pp. 1387-1395, July2005.

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**

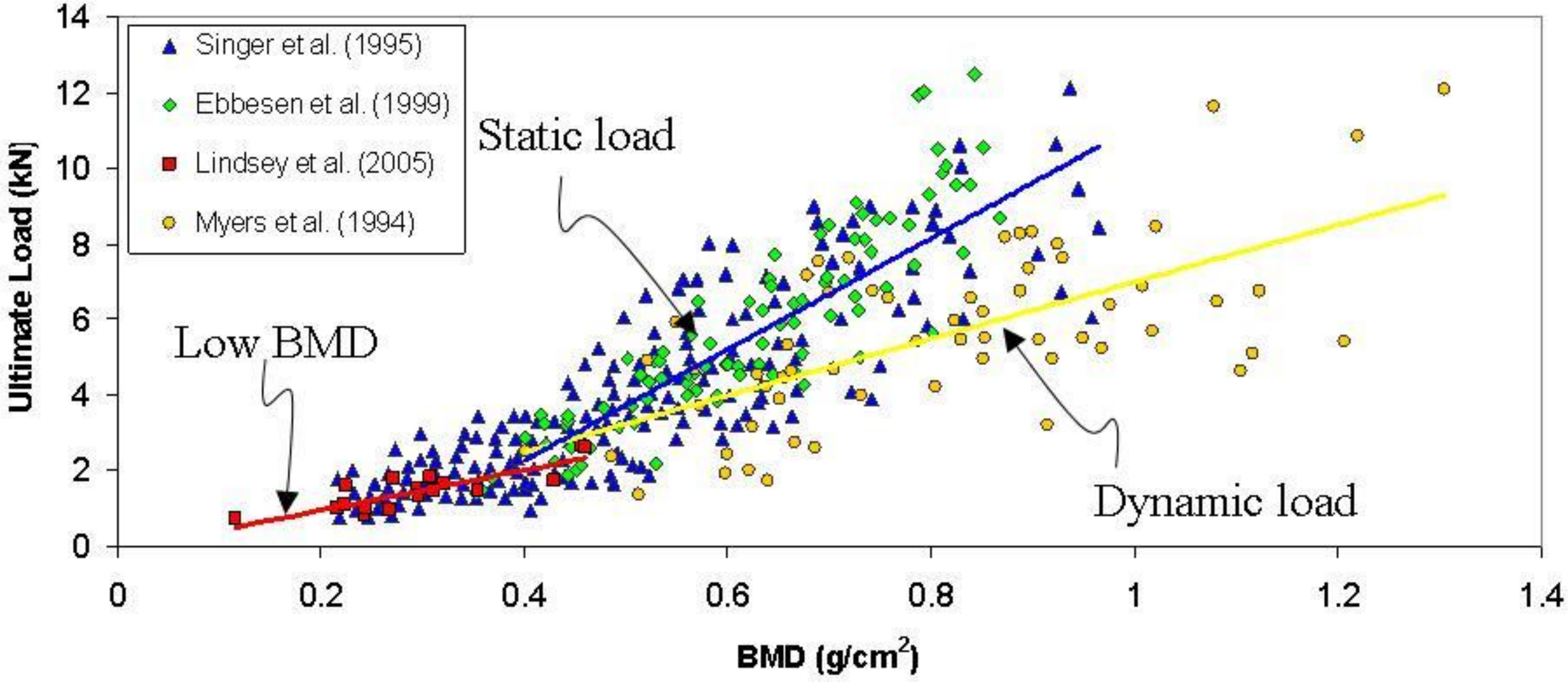
LeBanc et al, 2000

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.

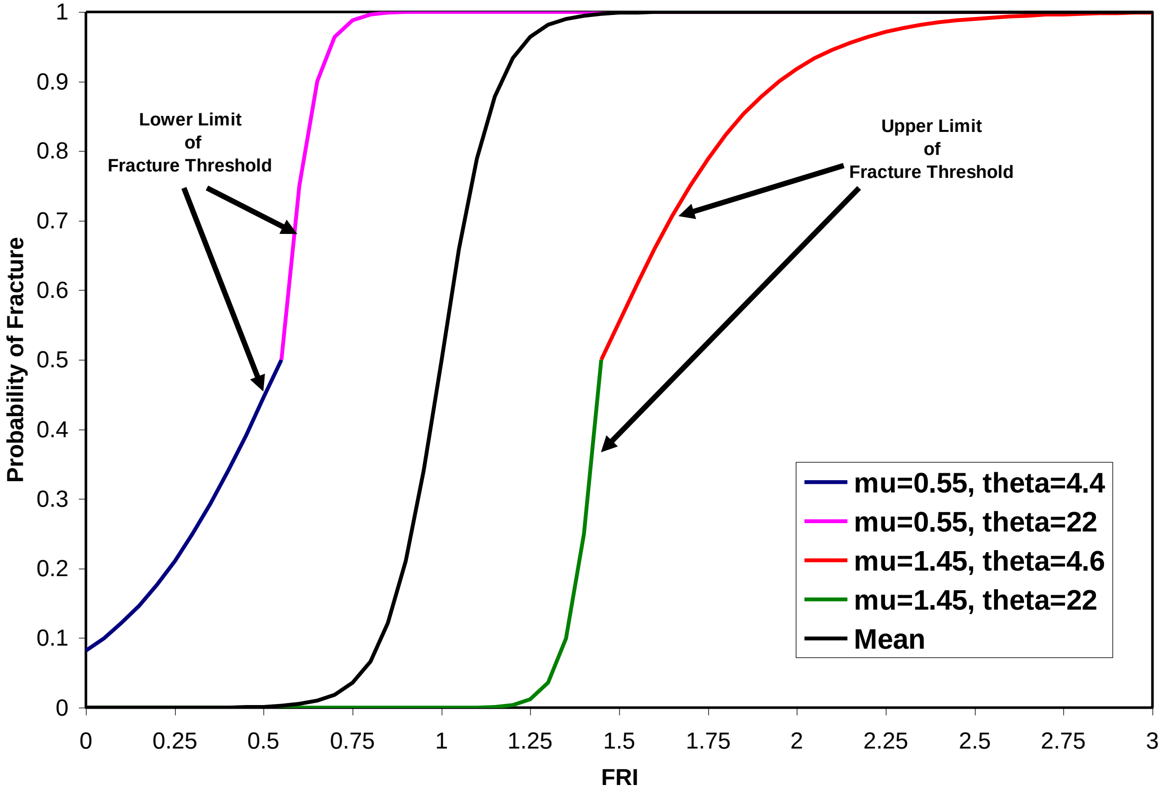
E. N. Ebbesen, J. S. Thomsen, H. Beck-Nielsen, H. J. Nepper-Rasmussen, and L. Mosekilde, "Lumbar vertebral body compressive strength evaluated by dual-energy X-ray absorptiometry, quantitative computed tomography, and ashing," Bone, vol. 25, no. 6, pp. 713-724, Dec.1999.

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.

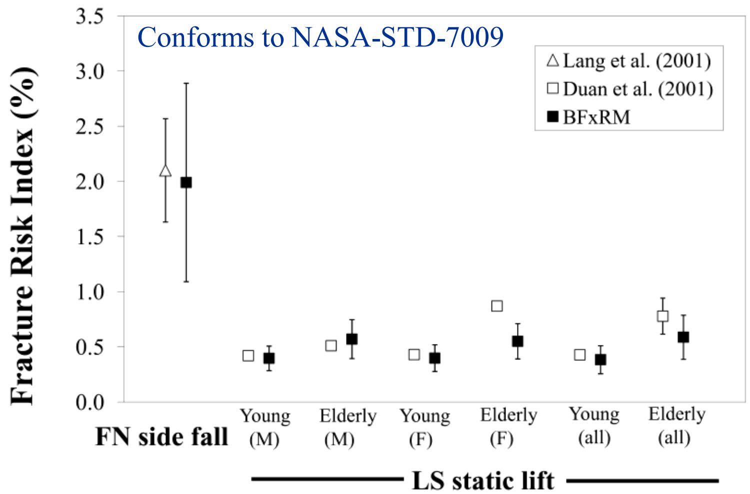
Estimating Probability of Fracture

- 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



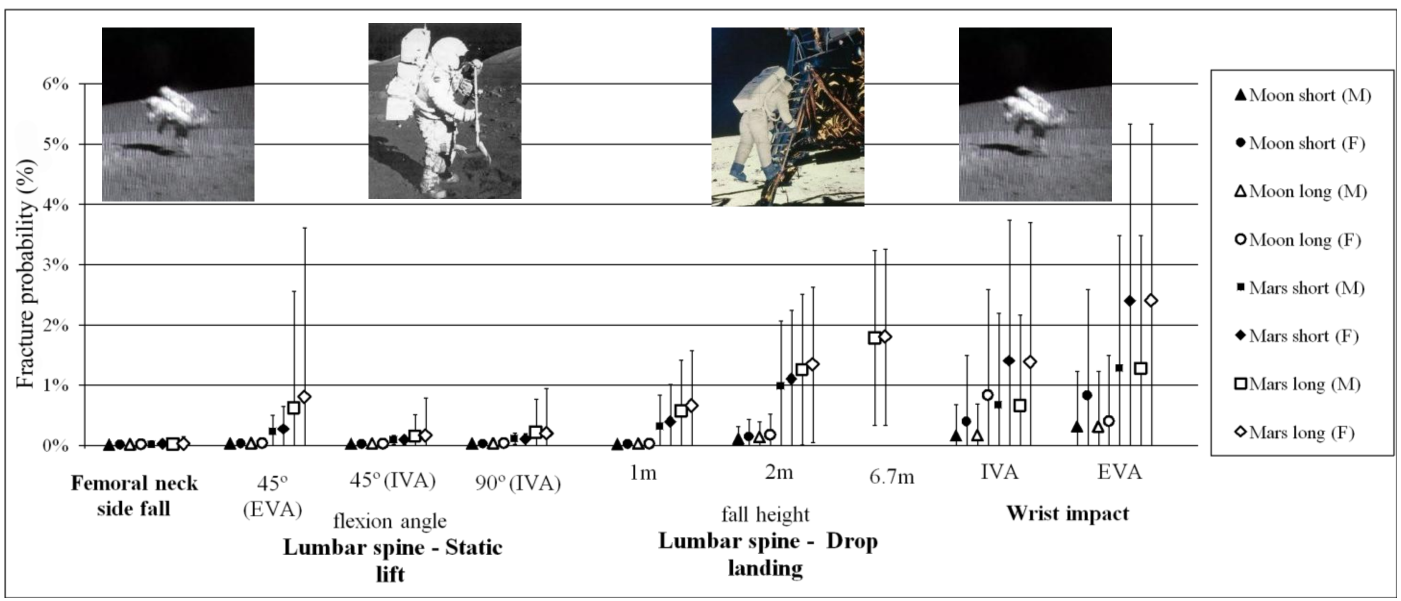
$$P(FRI) = \frac{1}{\left(1 + \exp\left(-1 * \left(FRI - \mu\right) * \theta\right)\right)}$$

Model Validation and Predictive Results



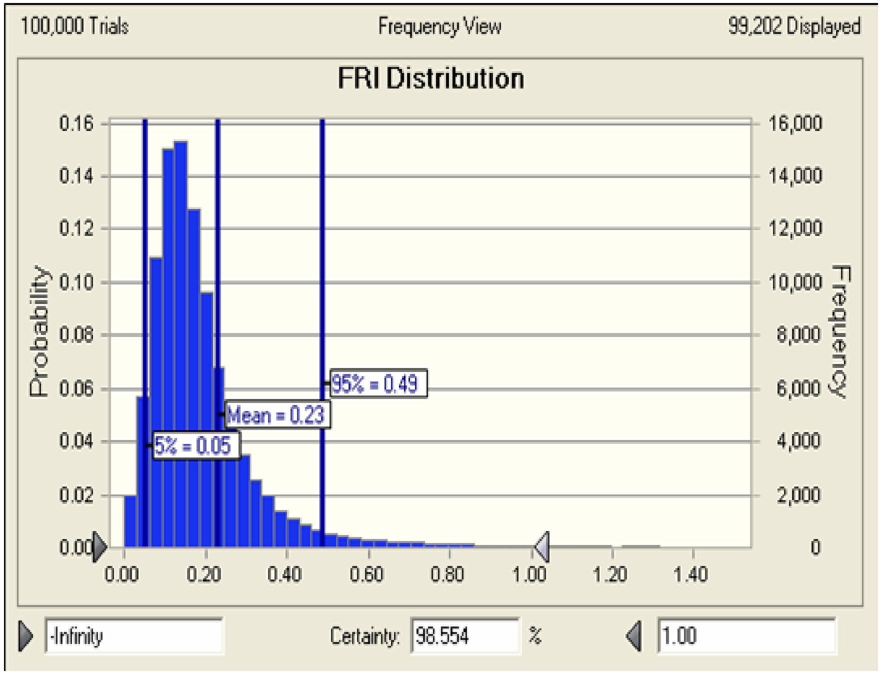
- Although femoral neck fracture is of high concern
  - Least likely location of fracture
- Wrist most likely fracture location

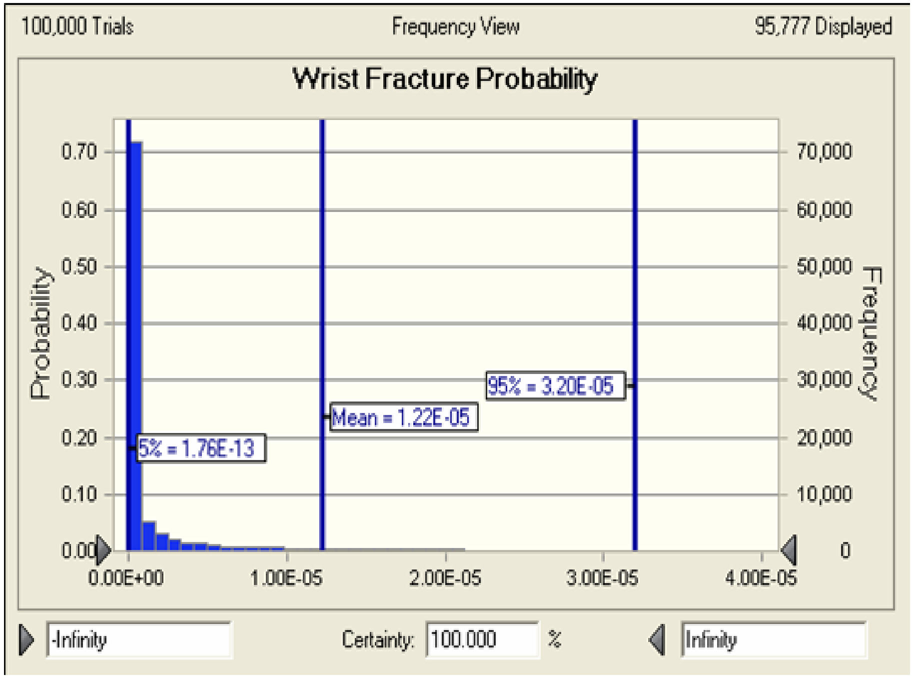
Highest sensitivities: EMU properties



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

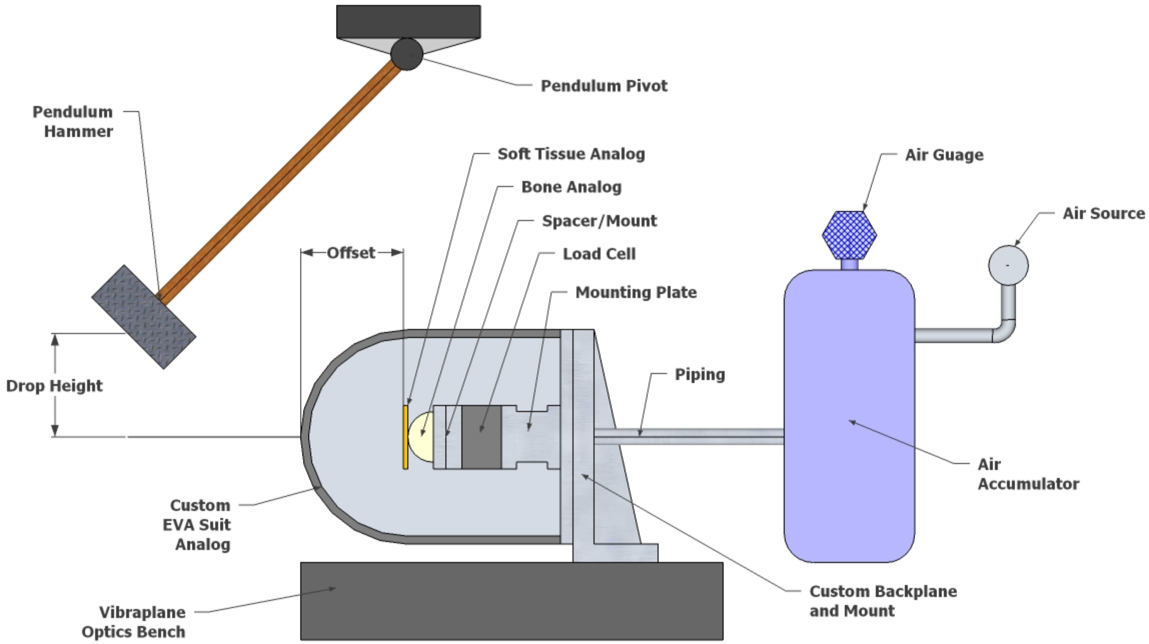
ISS: Wrist Fracture Probability Estimates

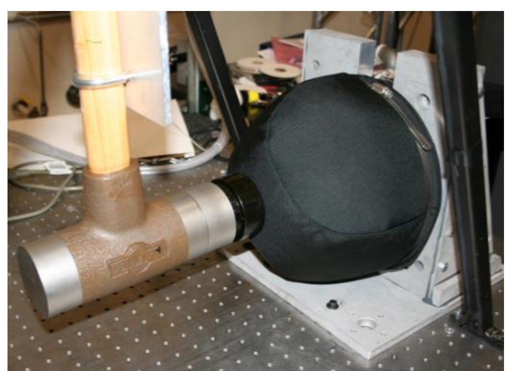




Probability of wrist fracture is relatively low, but not insignificant
Qualitatively agrees with the Med-Ops Physician assessments

SILAS (Suit Impact Load Attenuation Study)



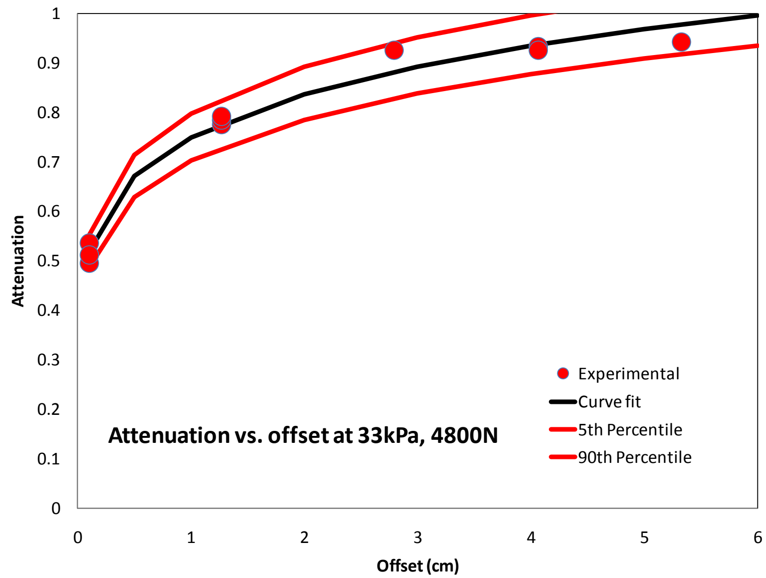


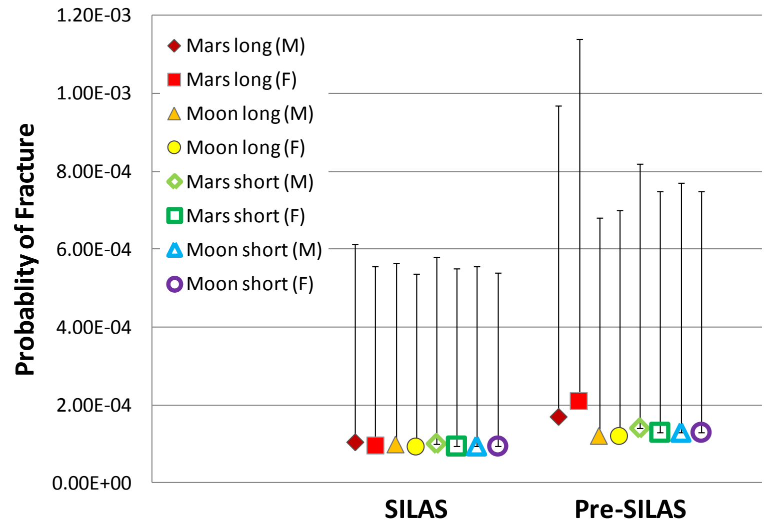
- Characterize load attenuation of the EMU suit
  - Fall or other impact scenario
  - Improve the predictive capabilities of the IMM-BFxRM
- Pressurized bladder configuration
  - COTS equivalent material layup
  - Repositionable load cell/impact site
  - Simulates impact to hip area
- Impact Loads
  - 3700 N, 5493 N and 7293 N
- Offsets of Impact site
  - 0, 0.25, 1.2, 1.5, 2.8, 4.1 and 5.3 cm
- Pressures
  - 27 to 33 kPa (4.0 to 4.8 psig)

SILAS Results

- Attenuation characteristics dependent on
  - Distance between hip and suit
  - Magnitude of the loading condition.
- Similar performance above 27 kPa (for range of offsets)
- Relatively constant for offsets >3cm (per load level)
- Implementation in the Bone Fracture Risk Model (BFxRM)
  - Improved fidelity and predictive capability
    - Reduced epistemic uncertainty
  - Reduced the mean probability of fracture
  - Decreased the 90th percentile by about 20%

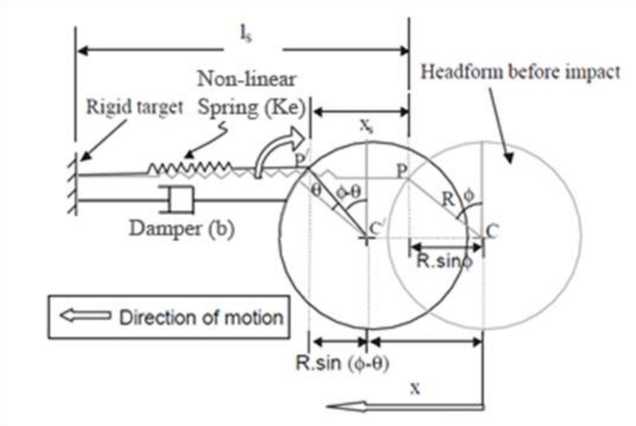
Sulkowski et al. An Extravehicular Suit Impact Load Attenuation Study to Improve Astronaut Bone Fracture Prediction, Aviation, Space, and Environmental Medicine, Vol 82, No. 4, April 2011 , pp. 455-462(8)



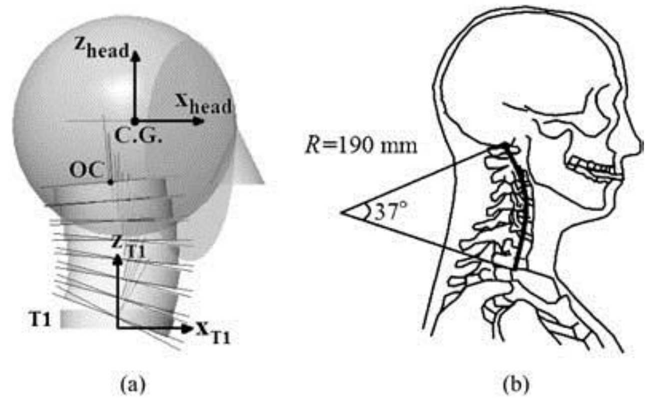


Additional Injuries of Interest

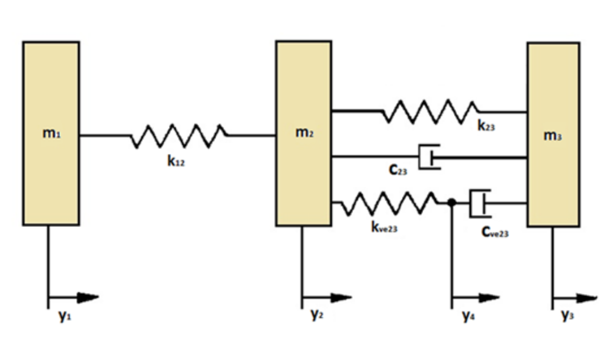
- Head Injury



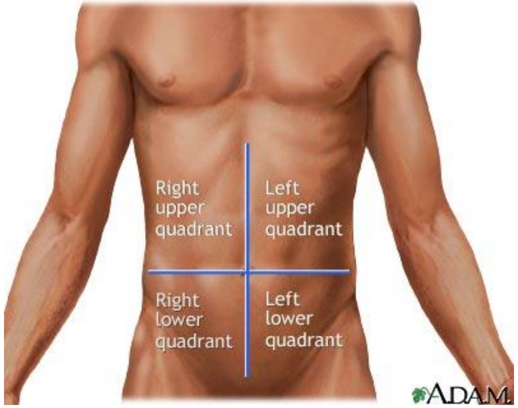
- Cervical Spine Injury



- Chest Injury

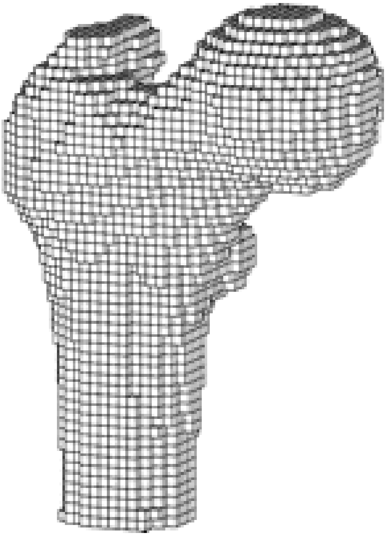


- Abdominal Injury



Benefits and Limitations

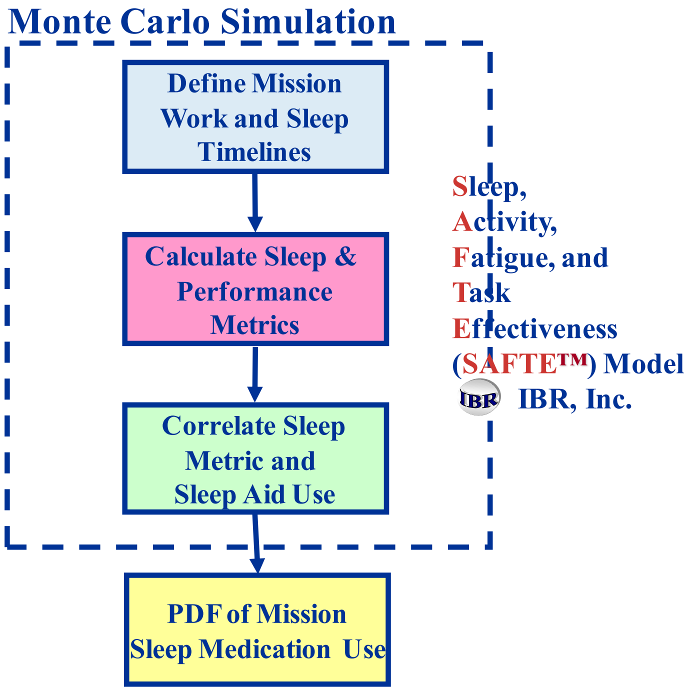
- Benefits
  - Captures the understanding of most critical factors in an equivalent "engineering" format
  - Allows for assessment of the most sensitive factors
  - New data easily implemented to improve decision making impact
- Limitations
  - Lacks specificity needed for astronaut specific risk assessment
  - Better if simpler models are used in the assessment
    - Requires decision on the level complexity of model



Lead By Example If You Expect Success

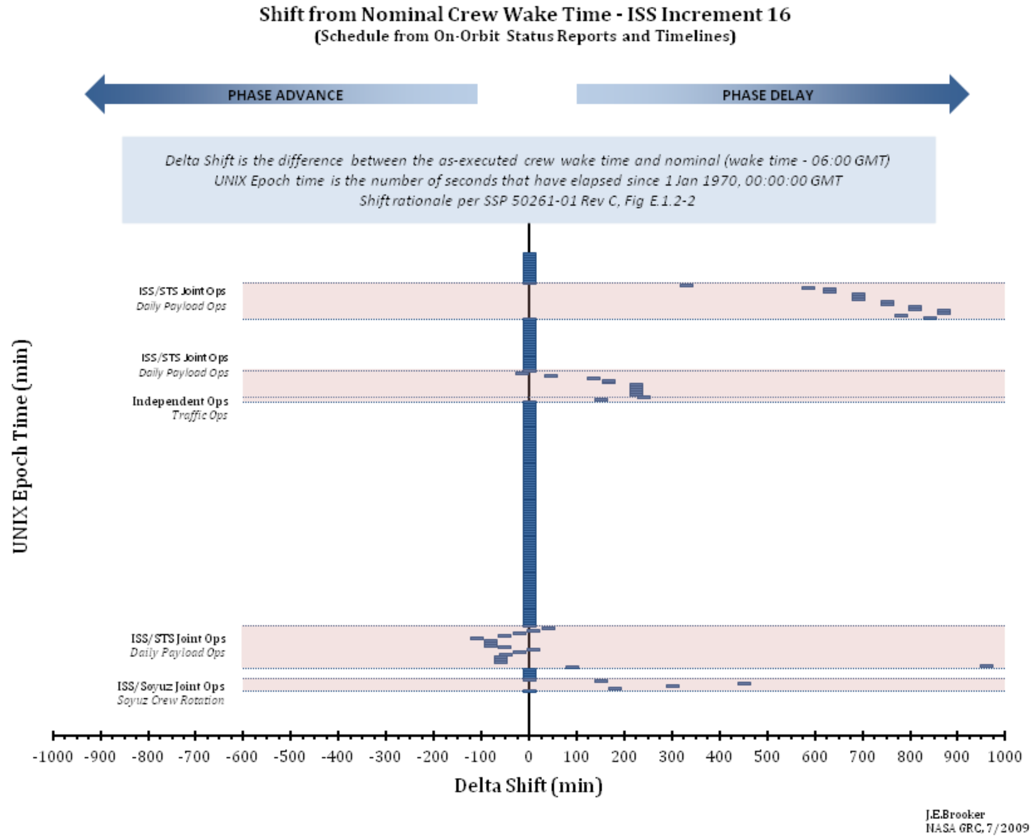
OTHER USEFUL APPLICATIONS

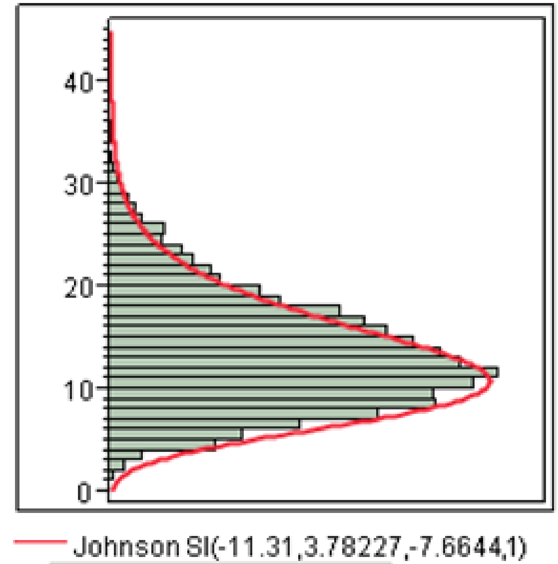
Space Flight and Sleep



- Space flight induces reductions in sleep quality and quantity
  - Strict sleep opportunities
  - ***Medications*** or sleep aids
    - 6 crew, 2 pills a night, 0.5 years = 2K doses
- What approach would allow the assessment of the rates of medical intervention resulting from low sleep quality and duration?
  - Derive realistic daily schedule
  - Utilize validated modeling of sleep and performance
  - Calculate sleep intensity from the output
  - Execute a bootstrap decision for sleep medication utilization

Sleep Disruption- Medical Intervention Forecasting (SDMIF) Tool





Quantiles

100.0%	maximum	44
99.5%		29
97.5%		25
90.0%		20
75.0%	quartile	16
50.0%	median	12
25.0%	quartile	9
10.0%		6
2.5%		4
0.5%		3
0.0%	minimum	1

Formational Analysis of Renal Stones in Space

≠

Pain

Misery

Agony

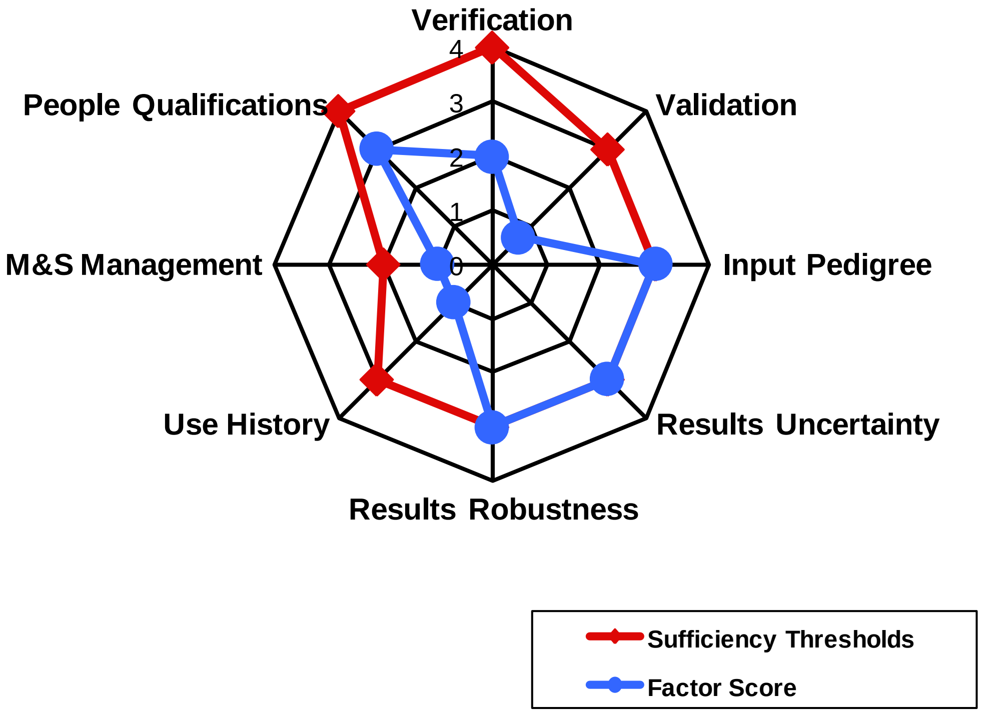
- IMM Risk
  - Given that astronauts could experience stone promoting urine chemistry, potentially exacerbated by hypogravity exposure, there is the possibility that astronauts will develop clinically significant renal stones in flight.
- Goal
  - Pilot study to develop a probabilistic model of the urinary system sufficient to estimate the risk of stone formation in astronauts.
  - Utilize model to estimate the effect of water intake on the probability of renal stones

ASSESSING CREDIBILITY

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
  - Validation
- M&S Operations
  - Input Pedigree
  - Results Uncertainty
  - Results Robustness
- Supporting Evidence
  - Use History
  - M&S Management
  - People Qualifications



V&V follows standard best practices

Verification and Validation

- Limited space flight data most likely used in the development of the model
- Verification exercises
  - Fixed and Extreme value testing of all PDFs
  - Estimates of numerical error
- Validation of individual components
  - Validate conceptual structure by SME review
    - Schedulers verify mission schedule component
    - Medical Ops validate the diagnosis component
- Validation of Module Performance
  - Face validation as V&V tool
    - Turing or Schruben tests with operational and flight medical experts
  - Direct comparison to observed incidence
    - Historical testing – Select data used for validation
    - Prospective validation – Future missions observations

Model Data, Robustness and Uncertainty

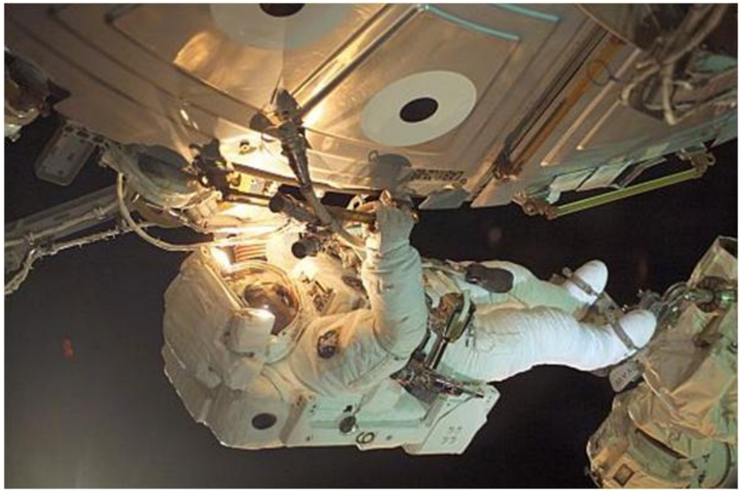
- Model Data
  - Desired: Assure data are appropriate for the intended model use
  - Achieved: Highest quality of the data correlated to the scenario
- Model Robustness
  - Desired: Percentage of the contribution of an independent variable to the variation of the outcome
  - Achieved : Rank order correlation sensitivity analysis
- Model Uncertainty
  - Desired: Magnitude and confidence of estimate
  - Achieved: Quantified based on non-deterministic analysis

Use History, Management and Qualifications

- Use History
  - Desired: Model use extended to address similar questions
  - Achieved:
    - Similar outputs to other tools in limited scenarios
    - When Model is used to inform real world decisions
- Management: Continuous Improvement
  - Desired and Achieved: Document all activity, management processes and decisions affecting code development, input changes, and V&V efforts.
- Qualifications
  - Desired: Staff can interpret and use the results
  - Achieved: Development staff maintains expertise levels required to develop, maintain, update and operate the model environment.

Let's Review

- IMM utilizes external modules to supplement observed data
- External modules
  - Utilize PRA concepts in high fidelity probabilistic models
    - Flexible well vetted modeling practices
    - Address confounding contributions
  - Produces "best estimate likelihood" of space specific, unobserved hazards
- Models related to medical events used to inform Space Flight Operations and Planning
  - Must exhibit a high level of *Credibility* for the intended use
  - Must have their *Credibility* assessed over multiple factors



"The most important questions of life are indeed, for the most part, really only problems of probability." ~Pierre Simon Laplace

QUESTIONS

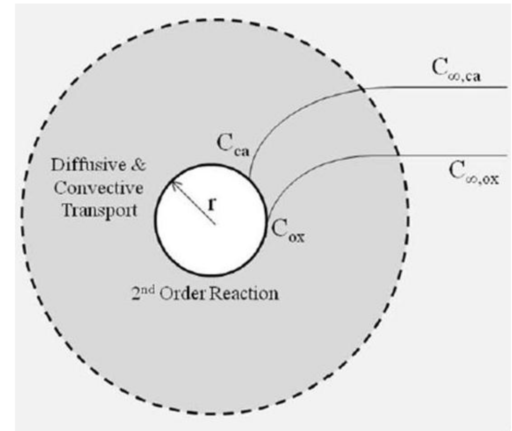
NASA-GRC Approach

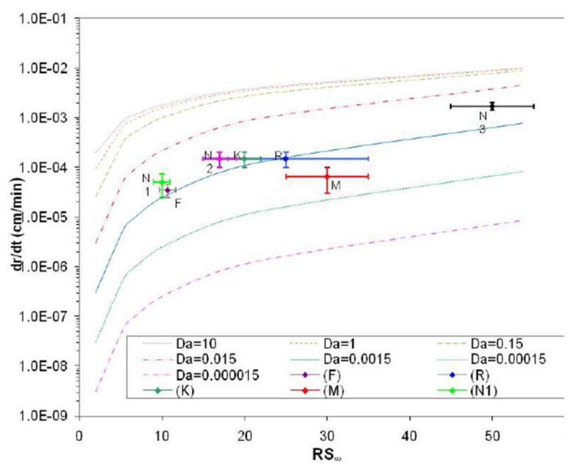
- Specific Team Components
  - Clinical/physiological expertise
  - Computational modeling
  - Biomedical engineer
  - Statistician
  - Students and external collaborators
  - Project manager
- Early and continuous buy-in from customer
  - Good communications
  - Frequent reviews
- Critical pieces to consider early
  - Access to data
  - Access to SME

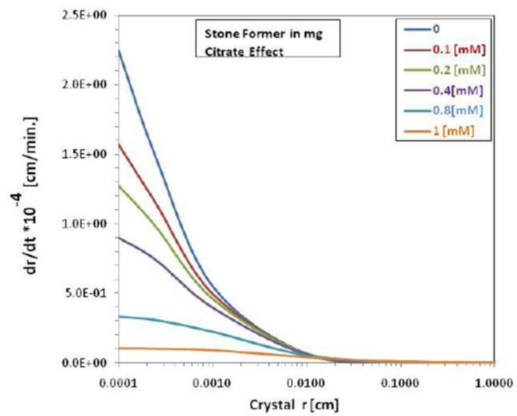
Renal Stone

- Complex Simulation PRA model of renal stone growth
  - Accounting for dietary and environment conditions
- First stage of growth model completed
  - Balances transport and surface reactions
  - Extended to include inhibitors
- Validation agreement with referent data is excellent

Pain

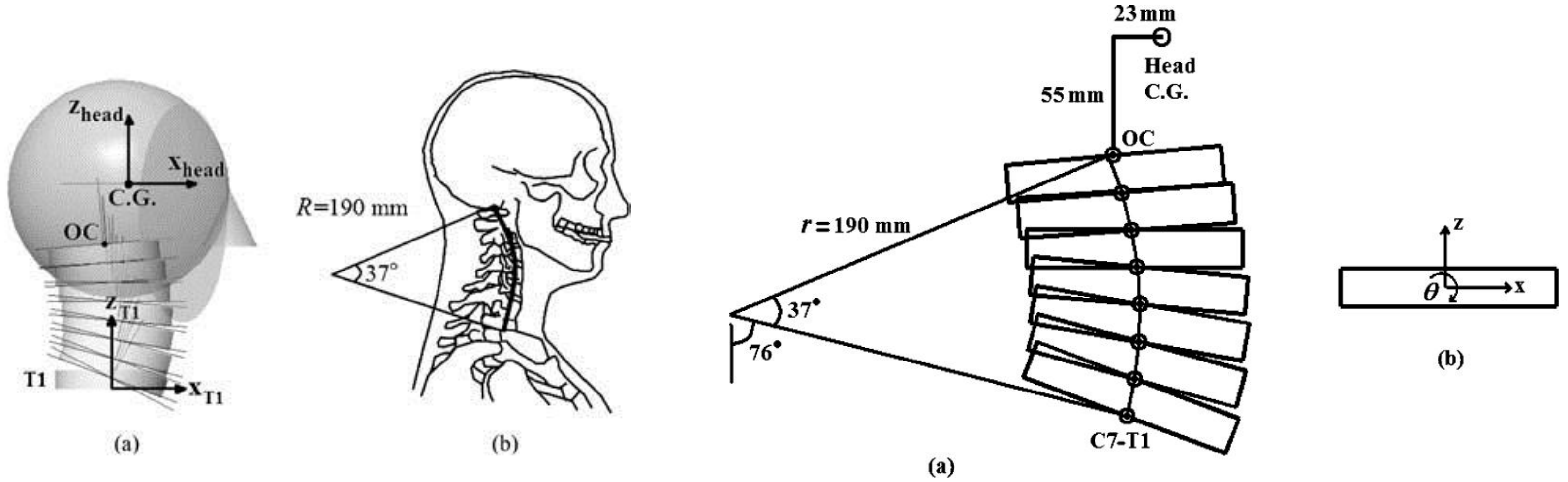






Neck Injury Model

- Proposal in the works – Draft March 31, 2011



(a) Multibody, lumped parameter cervical spine model in its initial configuration.
(b) Arc approximating the head and neck in the normal driving posture.
(c) Model configuration employing relative orientation vectors and angles.
(d) Neck segment frame axis showing degrees of freedom
[Himmetoglu, et al. 2007].