Development of Bone Remodeling Model for Spaceflight Bone Physiology Analysis

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Introduction

- Current spaceflight exercise countermeasures do not eliminate bone loss
  - Astronauts lose bone mass at a rate of 1-2% a month (Lang et al. 2004, Buckey 2006, LeBlanc et al. 2007)
- This may lead to early onset osteoporosis and place the astronauts at greater risk of fracture later in their lives
- NASA seeks to improve understanding of the mechanisms of bone remodeling and demineralization in µg in order to appropriately quantify long term risks to astronauts and improve countermeasures
- NASA's Digital Astronaut Project (DAP) is working with NASA's bone discipline to develop a validated computational model to augment research efforts aimed at achieving this goal
- Initial site of applicability – Femoral Neck
  - Hip fracture can be debilitating to overall performance and health of astronauts
  - Available data in the literature for physiologically based model development (cortical remodeling unit dimensions, ash density, elastic modulus)

Definition of Bone Remodeling and Cells

Bone remodeling: The physiological mechanism for maintenance, renewal, and repair of bone in the adult skeleton accomplished through the replacement of bone in units by the coupled action of bone cells on the same bone surface.

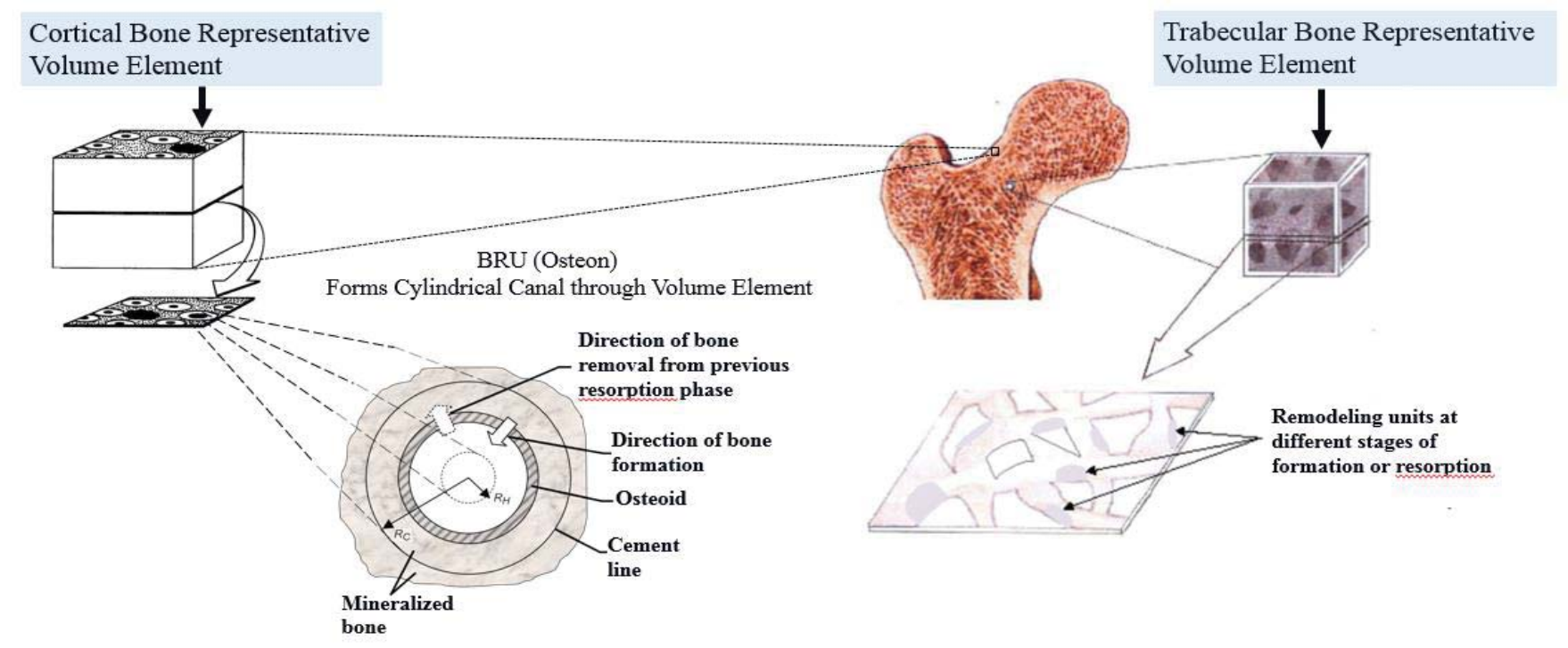
Cell Types

***Osteoclasts*:** the bone resorbing cells that remove or resorb old or damaged bone

***Osteoblasts*:** the bone forming cells that form an initial collagen matrix and then mineralize the collagen

***Osteocytes*:** cells within bone, derived from osteoblasts, that are understood to be the sensor cells that form a signaling network.

Structural and Remodeling Units



Cortical Osteon: Single Haversian system shaped like a cylinder running almost parallel to longitudinal axis

Trabecular Hemi-Osteon: Shaped like an osteon split open, unrolled lying parallel to the plane of a plate. In 2-D shaped like thin crescents forming the trabecular surface.

Bone Remodeling Unit: The collection of cells that accomplish the erosion of one cavity and its refilling to form one new structural unit

Model Description (1/2)
Physical Domain

- Population of BRUs distributed over a Volume Element or Section of Bone.
- BRUs are all at different phases of the remodeling cycle
- Variables in the model represent ensemble averages.
- Size is chosen so that BRUs are all under the same external stimuli.

TA = Total Area; BA = Bone Area; TV = Total Volume; BV = Bone Volume

BVF = Bone Volume Fraction = $\frac{BV}{TV} = \frac{BA}{TA}$

BVF Rate of Change = Rate of Formation – Rate of Resorption ≈ 0 (Balance Healthy State)

BVF

Mineralized Volume Fraction (MVF) M + Osteoid Volume Fraction (OVF) O

Model Description (2/2)
Mathematical System

Variables	Driving Process	Dependencies
Bone Volume Fractions Rates of Change $\dot{M}$ Mineralized V F $\dot{O}$ Osteoid V F	**Removal and Replacement of Bone Packets (Remodeling Units)**	Activation Density Bone Remodeling Units BRU Area Resorbed BRU Area Formed Active Resorbing Cell Population Active Forming Cell Population
Cell population Rates of Change $\dot{B}$ Active Osteoblasts $\dot{C}$ Active Osteoclasts $\dot{B}_r$ Responding Osteoblasts	**RANK-RANKL-OPG Pathway**	Transforming Growth Factor $TGF\ beta$ Parathyroid Hormone PTH $RANKL$ Osteoprotegerin OPG Hormone PGE_2 Nitric Oxide NO

Normal maintenance and balanced process of bone formation and bone resorption influenced by endocrine regulation, by local biochemical mediators, and by skeletal loading.

Key Intermediaries in Skeletal Loading Hormone like compound PGE_2 and NO

- Shown to be released by osteocytes & osteoblasts by **pulsatile fluid flow** and mechanical strain.
- Pulsatile fluid flow considered to be **cyclic strain induced**.

PGE_2
- May promote differentiation of osteoblast precursors. Stimulates proliferation of osteoblasts.
- Mediates Osteocyte signaling

NO
- Stimulates production of OPG
- Inhibits production of RANKL

Prostaglandin – acts as a chemical messenger

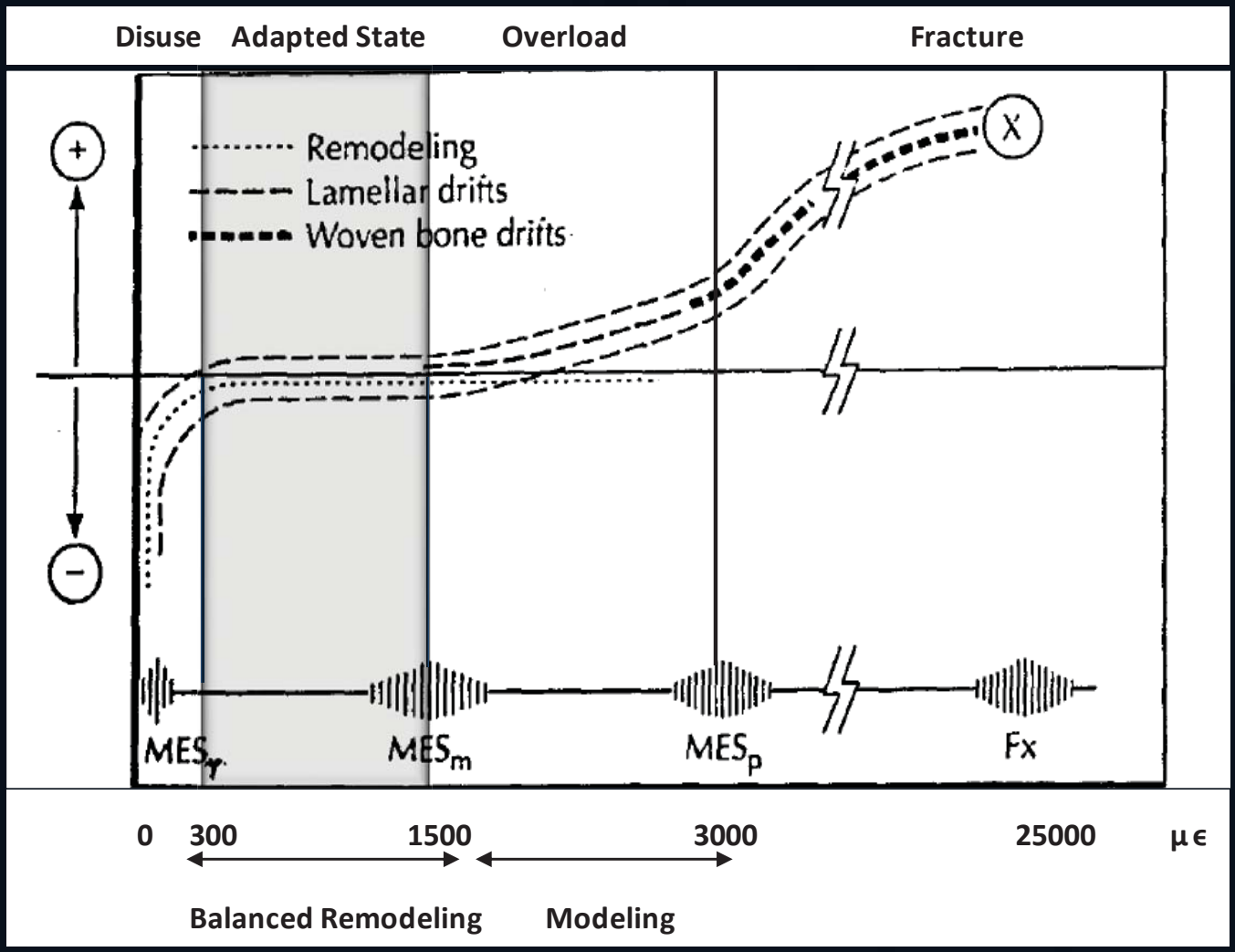
Nitric oxide - cellular signaling molecule

Concentrations are obtained via mass balance relations set to steady state
Cell Populations are affected by receptor-occupancy ratios (ROR)

Cell proliferation (ant proliferation) is directly (indirectly) proportional to ROR.

Mechanostat Theory

Frost 2003 update



NOTE: The DAP Model does not consider fracture

Influence of Skeletal Loading Modeling Approach

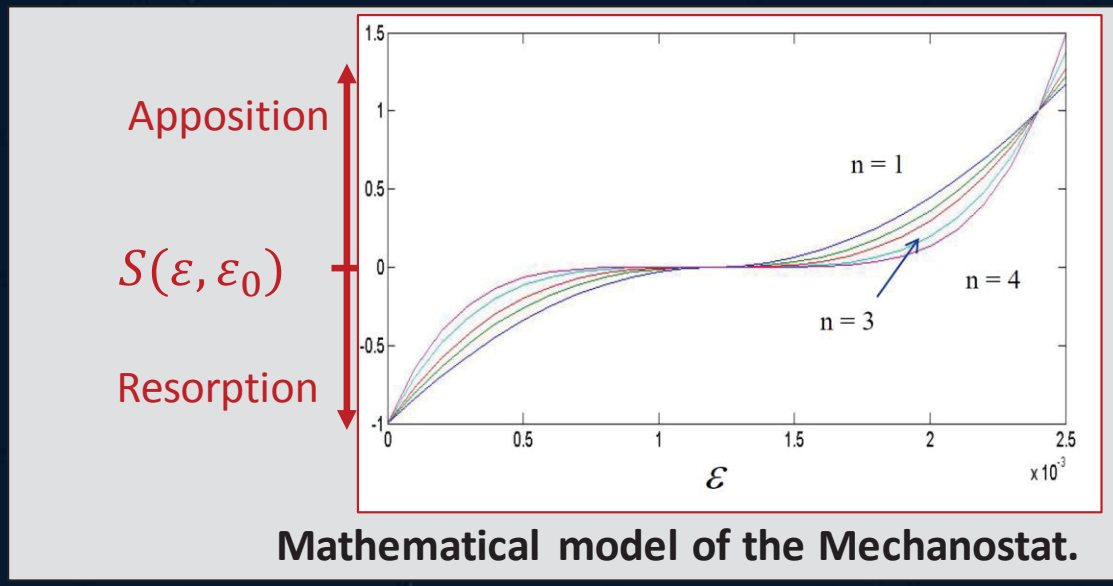
The model gages the level of NO and PGE_2 expression according to the level of bone apposition or bone resorption suggested by the daily strain ε in Frost's Mechanostat Theory:

Sensing strength or sensing level (SL) defined in relation to bone strain

$$SL = f_s(\epsilon) = [S(\varepsilon, \varepsilon_0) + 1]$$

Complete Unloading $\varepsilon = 0$ SL = 0
Remodeling Balance $\varepsilon = \varepsilon_0$ SL = 1

NO and PGE_2 synthesis are defined to be proportional to SL



Mathematical model of the Mechanostat.

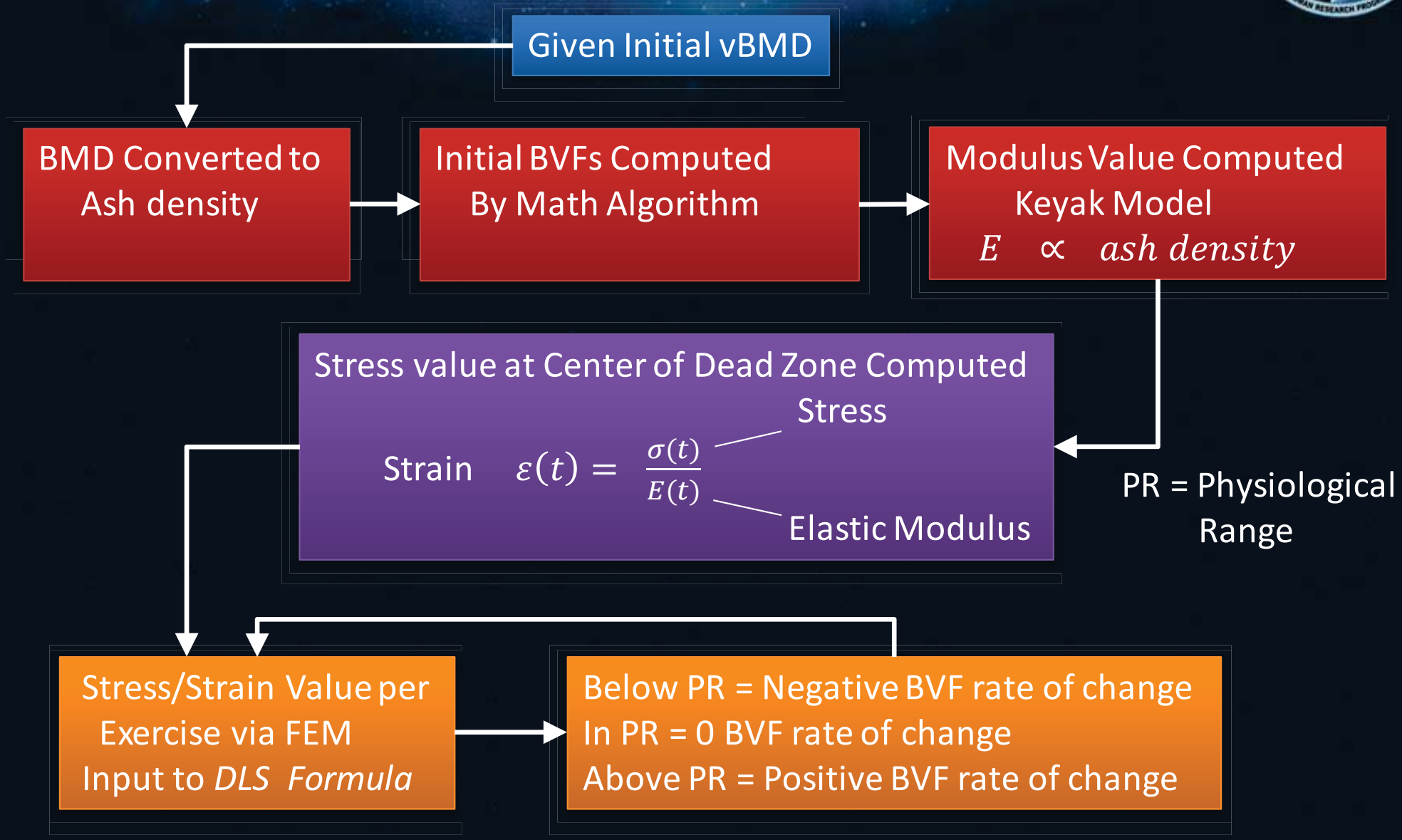
PGE Synthesis → $S_G = p_G$
NO Synthesis → $S_N = p_N$

Rate per cell

$$\times f_s(\varepsilon) \times Y_d \times BVF$$

Osteocytes density

Computational Implementation



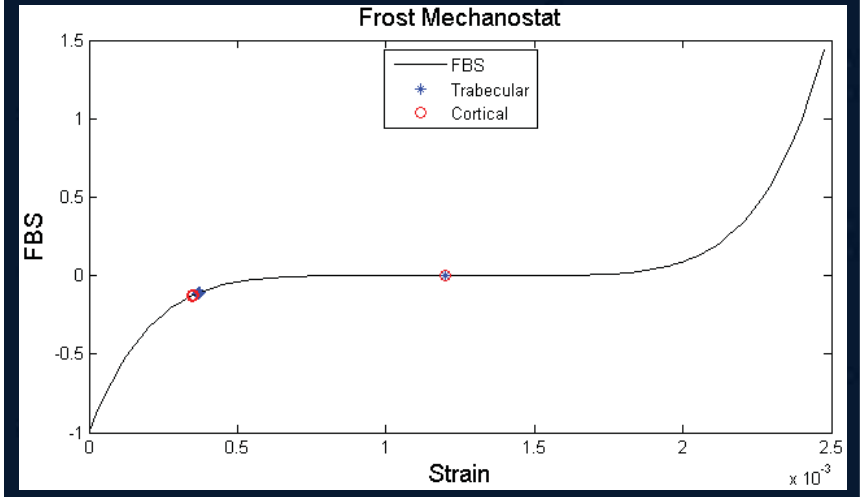
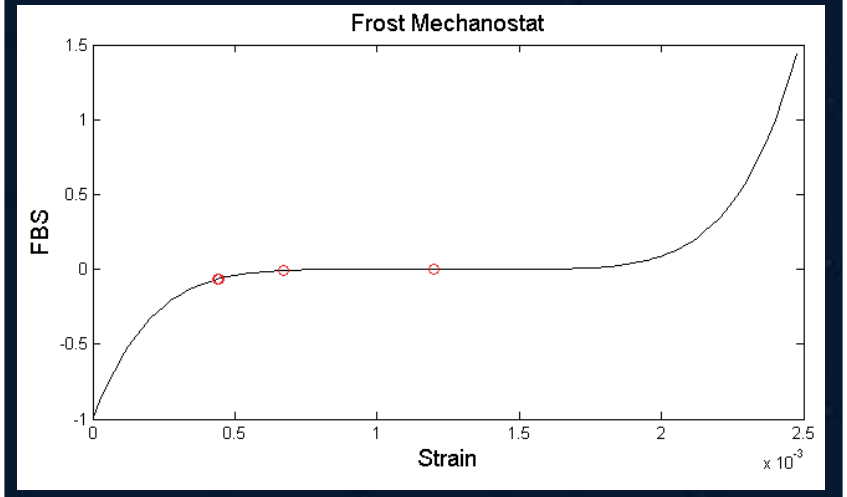
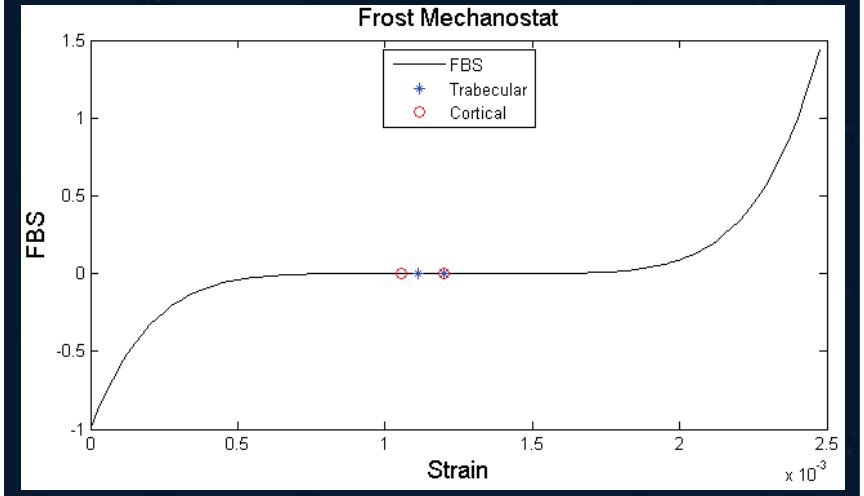
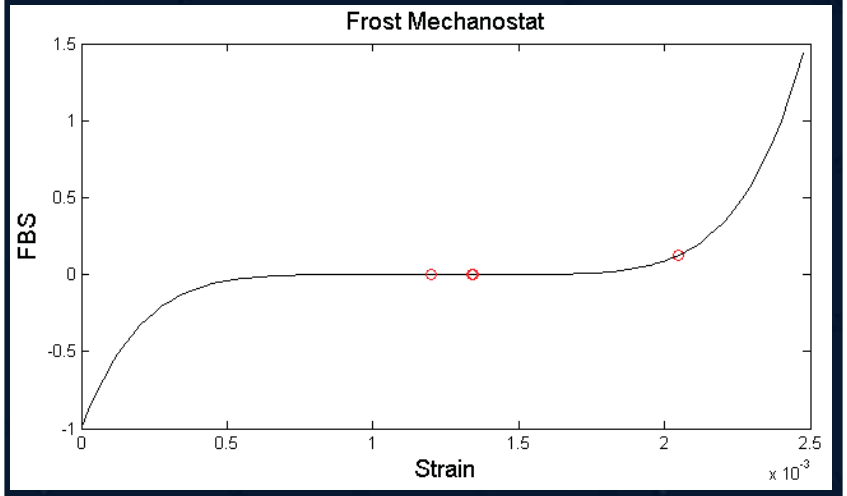
Time integration reveals change in BVF and in turn change in vBMD

Verification Analysis (1/2)

Parameter	World-wide Measured Value	Source
Steps per day	5,000-10,000	Bassett et al. (2010); Tudor-Loke et al. (2011)
Average walking speed	~5 km/h	Levine and Norenzayan (1999)
Body mass	57.7 - 80.7 kg (565 to 791 N)	Walpole et al. (2012)

			Trabecular vBMD (g/cm^3)				Cortical vBMD (g/cm^3)				DXA aBMD (g/cm^2)			
Weight (N)	Steps	Duration (days)	Initial	Final	Change	% Change	Initial	Final	Change	% Change	Initial	Final	Change	% Change
791	5000	365	0.131	0.130	-0.001	-0.76%	0.532	0.531	-0.001	-0.19%	0.891	0.891	0.000	0.00%
	7500			0.131	0.000	0.00%		0.532	0.000	0.00%		0.891	0.000	0.00%
	10000			0.131	0.000	0.00%		0.532	0.000	0.00%		0.891	0.000	0.00%
565	5000			0.129	-0.002	-1.53%		0.528	-0.004	-0.75%		0.889	-0.002	-0.22%
	7500			0.131	0.000	0.00%		0.531	-0.001	-0.19%		0.891	0.000	0.00%
	10000			0.131	0.000	0.00%		0.532	0.000	0.00%		0.891	0.000	0.00%

Verification Analysis (2/2)

# of Steps	QCT Simulation Results	DXA Simulation Results	Weight (N)
5000			565
10000			791

Validations

- Deconditioning (skeletal unloading)
  - 4 control subjects 70 day bed rest
  - 16 control subjects 90 day bed rest
  - 3 control subjects ~ 50 days bed rest
  - 18 control subjects 17 week bed rest
- Daily Load Stimulus (Using walking)
  - 16 crewmembers post flight R0 & R+12
  - 6 control subjects post bed rest from 17 week bed rest R0 & R+60
  - 7 exercise treated subjects post bed rest from 17 week bed rest R0, R+60, and R+100

Validation Sample Results

Comparison of deconditioning simulation results against 70-day bed rest control subject QCT vBMD (N=4)

Trabecular			Cortical		
Experimental			Experimental		
Change	SD	Model	% Change	SD	Model
-4.3%	±10.8%	-10.2%	-2.7%	±3.7%	-2.6%

Comparison of deconditioning simulation results against 70-day bed rest control subject DXA aBMD

	Experimental			Model	
Duration	N	Change	SD	Change	95% CI
70 days	4	-1.8	±2.5%	-1.7%	±0.6%
120 days	18	-1.6	±3.2%	-3.9%	±1.4%

Comparison of Model DLS simulation results against post-flight QCT vBMD measurements from Lang et al. (2006) for 16 astronauts.

		Trabecular					Cortical				
Duration (days)	Number of steps	Experimental [7]			Model Output	Error	Experimental [7]			Model Output	Error
		Mean	SD	SE			Mean	SD	SE		
Post-flight	12,500	0.115	0.029	0.007	0.115	-	0.518	0.047	0.012	0.518	-
365		0.121	0.026	0.007	0.115	-0.006	0.516	0.044	0.011	0.518	0.002
Post-flight	18,000	0.115	0.029	0.007	0.115	-	0.518	0.047	0.012	0.518	-
365		0.121	0.026	0.007	0.119	-0.002	0.516	0.044	0.011	0.520	0.004

Future Work

- Enhance model representation of bone physiology
  - Adding age & gender dependencies,
  - Building in effects of other hormones and proteins,
  - Accounting for changes in geometry of trabecular and cortical regions,
  - Adapting to other skeletal sites (lumbar spine),
  - Evaluating and resolving uncertainty in model parameters
- Improve and advance credibility of the math model
  - Integrating capability to simulate loading from different exercise activities and validating against exercise countermeasures for exploration class missions
  - Refining the center of the physiological maintenance zone of Mechanostat scale
  - Testing, comparing, and evaluating methods for mapping experimental data to model variables
  - Performing rigorous verification, sensitivity and uncertainty analysis of the system of equations as well as key parameters in the model

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