The Digital Astronaut Project Bone Remodeling Model

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INTRODUCTION: Under the conditions of microgravity, astronauts lose bone mass at a rate of 1% to 2% a month, particularly in the lower extremities such as the proximal femur [1]. The most commonly used countermeasure against bone loss has been prescribed exercise [2]. However, current exercise countermeasures do not completely eliminate bone loss in long duration, 4 to 6 months, spaceflight [3,4], leaving the astronaut susceptible to early onset osteoporosis and a greater risk of fracture later in their lives. The introduction of the Advanced Resistive Exercise Device, coupled with improved nutrition, has further minimized the 4 to 6 month bone loss. But further work is needed to implement optimal exercise prescriptions [5]. In this light, NASA's Digital Astronaut Project (DAP) is working with NASA physiologists to implement well-validated computational models that can help understand the mechanisms of bone demineralization in microgravity, and enhance exercise countermeasure development.

METHODS: The objective of the DAP computational modeling effort is to enable simulations in time of changes in bone mineral density (BMD) and Bone Volume Fractions (BVF) under the conditions of skeletal unloading and changes in physiological processes encountered in microgravity. Since the geometry of the remodeling units or bone packets that are removed and replaced during remodeling differ, separate modules for trabecular bone and cortical bone are developed. Key elements of the computational model include: Bone resorption (formation) rate varies with activation density, volume of remodeling unit removed (replaced), and active osteoclast (osteoblast) population. The active osteoblast and osteoclast populations vary according to the cellular dynamics mediated by hormones, proteins, ligands and receptors. The well-known adaptive response theory of Frost drives the bone response to variations in skeletal loading. Within the expressions for rates of changes of the cellular populations, assumptions for the ligand and receptor expressions are modeled in accordance with the American Society of Bone and Mineral Research educational literature.

INITIAL MODEL DEVELOPMENT The model's initial development focuses on the femoral neck. Remodeling unit dimensions for the femoral neck (particular for cortical bone) were identified in the literature to make the model specifically applicable to the femoral neck, although many other model parameters were based on general bone knowledge. For model validation, we used BMD changes of control subjects in the current 70 bed rest study and available data from the 17-week bed rest studies conducted in the past (Figure 1). Volumetric bone densities for the 70 bed rest were obtained at pre and post bed rest via Quantitative Computed Tomography (QCT). However, bone densities from past bed rest studies were obtained via Dual-energy X-ray Absorptiometry (DXA). Given that DXA is 2-D integrated cortical and trabecular, and the computational model tracks BVF changes, the DXA values were mapped to equivalent QCT integral volumetric density values in order to run simulations with the DXA data. Our poster will discuss in detail how the model tracks BVF and the preliminary model validation results.

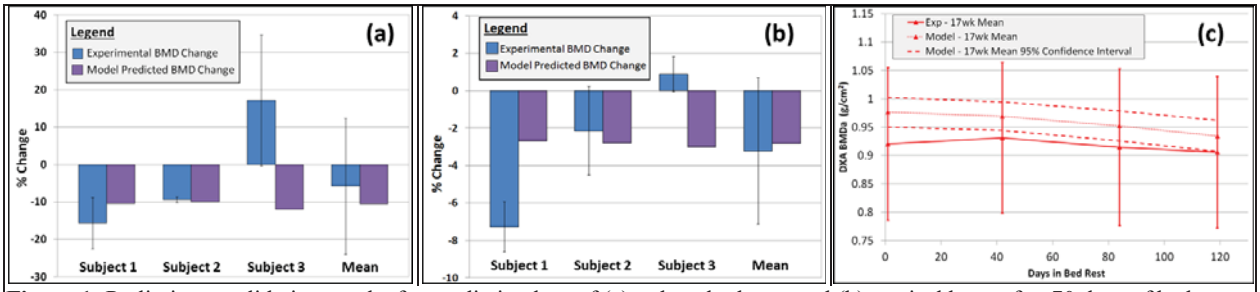

Figure 1: Preliminary validation results for predicting loss of (a) trabecular bone, and (b) cortical bone after 70 days of bed rest, as well as (c) time course change of mean DXA BMD for 18 control subjects during 17 weeks of bed rest.

DISCUSSION AND FUTURE WORK: Our results show that a good foundation has been laid for establishing a physiologically accurate bone remodeling model. For example, mean BMD data for the 70-day bed rest is well within the 95% confidence interval of the model prediction. Future work will integrate the bone remodeling model with DAP's biomechanical exercise models to predict the benefits of exercise induced load stimulus from different exercise prescriptions for maintaining bone at the femoral neck. The model will also be extended to include predictions for the lower lumbar spine, calcaneus, trochanter and the integrated proximal femur.

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Background

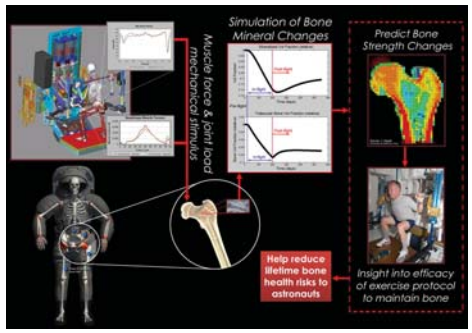
Why Quantifying Change in Bone via Bone Remodeling is Objective of NASA Digital Astronaut Project (DAP)

- One of the main objectives is to provide a tool to help HHC address Bone Gap **Osteo 4**: We don't know the contribution of each risk factor on bone loss and recovery of bone strength and which factors are the best targets for countermeasure application; and **Osteo7**: We need to identify options for mitigation of early onset osteoporosis before, during, and after spaceflight.
  - **Skeletal loading** along with endocrine regulation and local biochemical mediators are what drives the physiological mechanism of bone remodeling to maintain bone.
  - Exercise induced loading, with appropriately input to a model can approximately predict the effect of specific exercise prescription and thus help to evaluate its benefits as a countermeasure option. **Integrates with DAP Biomechanics Model** and the **DAP Muscle Model.**

Importance for the New Finite Element Based Strength Standard

- Other main objectives intend to inform the HHC Bone Discipline's efforts to address **Bone Gap Fracture 3**. We need a validated method to estimate the **Risk of Fracture** by evaluating the ratio of applied loads to bone fracture loads for expected mechanically-loaded activities during and after a mission
  - One effort is underway to evaluate **Finite Element (FE) estimates of bone strength** (aka bone fracture loads) as a potential standard for bone health.
  - A bone remodeling formulation that quantifies dynamic changes in bone has the potential of tracking changes in volume fractions that can relate to QCT BMD and ash density estimates, upon which FE bone strength is based [1]. In addition coupling a BR model with a QCT based FE model may also provide geometry changes.

Bone Remodeling Model Implementation Plan



General Description of the DAP Bone Remodeling Model

What does it do?

It tracks changes in the bone when the balance between formation and resorption in the bone remodeling process becomes unbalanced.

How does it do it?

The cellular physiology, remodeling unit mechanisms, and mechano-transduction theory that drive the process are described mathematically.

How does the computational algorithm work?

Rates of change of bone volume fraction and cell populations are set to zero (Balanced healthy state with steady bone density).

Balance is broken by skeletal unloading, and rate of change is no longer 0.

The system including bone properties and cell populations are integrated in time to estimate the change.

NOTE: Model parameters and methodology are currently focused on the femoral neck.

Mathematical Description

System of ordinary differential equations

Bone Volume Fraction	$\frac{dBVT(t)}{dt} = A_f(t)\cdot \bar{f}_a \frac{B(t)}{B_0} - A_R(t)\cdot \bar{f}_a \frac{C(t)}{C_0}$	Eq. 1 Base Equation
Osteoid Volume Fraction	$\frac{dO}{dt} = r_f \frac{B}{B_0} - r_r \frac{C}{C_0}\left(\frac{O}{O+M}\right) - r_m O$	Eq. 2
Mineralized Volume Fraction	$\frac{dM}{dt} = r_m O - r_r \frac{C}{C_0}\left(\frac{M}{O+M}\right)$	Eq. 3
Responding Osteoblasts	$\frac{dB_r}{dt} = D_{B_u}\cdot E_{TGF} - D_{B_r}\cdot((1-E_{TGF})+E_{PGE})\cdot B_r$	Eq. 4
Active Osteoblasts	$\frac{dB}{dt} = D_{B_r}\cdot((1-E_{TGF})+E_{PGE})\cdot B_r - k_B\cdot B\cdot(1-E_{PTH})$	Eq. 5
Active Osteoclasts	$\frac{dC}{dt} = D_{C_p}\cdot E_{RL} - A_C\cdot E_{TGF}\cdot C$	Eq. 6

State Variables and Definitions

$BVF(t)$	Bone Volume Fraction	$A_r(t)$	Cross Sectional Bone Area Resorbed per BRU (mm²)
$M(t)$	Mineralized Volume Fraction	$A_f(t)$	Cross Sectional Bone Area Formed per BRU (mm²)
$O(t)$	Osteoid Volume Fraction	$\bar{f}_a$	Activation Density in Normal State (#BRU's activated per day per mm²)
$B(t)$	Osteoblast Population (pM)	r_r	$(A_r\cdot\bar{f}_a)$ Resorption Rate per Normalized Osteoclast Population
$C(t)$	Osteoclast Population (pM)	r_f	$(A_f\cdot\bar{f}_a)$ Formation rate per Normalized Osteoblast Population
B_0	Reference Osteoblast Population (pM)	r_m	Mineralization Rate
C_0	Reference Osteoclast Population (pM)		

Symbol Definitions in the Cell Equations

B_r	Concentration of Responding Osteoblasts	A_C	Rate of Elimination of C(t) (Apoptosis)
B	Concentration of Active Osteoblasts	E_{TGF}	TGF-beta Receptor Occupancy Ratio
C	Concentration of Active Osteoclasts	E_{PGE}	Prostaglandin PGE-2 Receptor Occupancy
D_{B_u}	Differentiation Rate of Osteoblast Precursors	E_{PTH}	Parathyroid Hormone Receptor Occupancy
D_{B_r}	Differentiation Rate of Responding Osteoblasts	E_{NO}	Nitric Oxide effect on RANKL
D_{C_p}	Differentiation Rate of Osteoclast Precursors	E_{RL}	RANKL Receptor Occupancy Ratio
k_B	Rate of Elimination of B(t)		

Expressions for Osteroprotegerin (OPG) , RANKL and the ligand receptor complexes are derived via mass balance equations. The complete detailed set of cellular dynamics is a considerable modification of the work of Lemaire et al. [2] and Pivonka et al. [3] with the addition of effectors related to skeletal loading.

Modeling the Influence of Skeletal loading

The most likely intermediaries that enable sensor cells to trigger effector cells is NO and PGE-2 [5]. Released by Osteocytes and Osteoblasts under mechanical stimulation

PGE_2:
- Mediates differentiation of osteoblasts induced by TGF-β
- Stimulates proliferation of osteoblasts

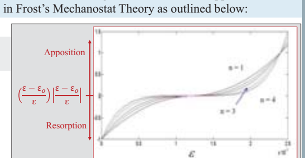
NO:
- Stimulates production of OPG
- Inhibits production of RANKL

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

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

$$SL = f(\varepsilon) = \left[\left(\frac{\varepsilon-\varepsilon_0}{\varepsilon}\right)\left|\frac{\varepsilon-\varepsilon_0}{\varepsilon}\right| + 1\right]$$

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



Mathematical model of the Mechanostat.

NOTE: Osteocytes are generally understood to be the sensor cells

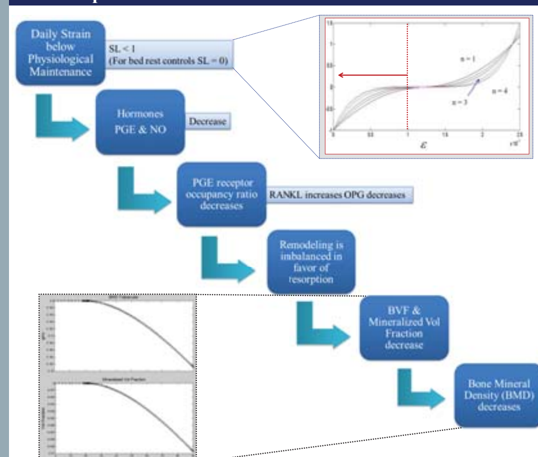
Production rate of NO and PGE_2 per cell are defined to be proportional to SL

PGE Production Rate → $S_G = p_G \times SL \times Y_d \times BVF$

NO Production Rate → $S_N = p_N \times SL \times Y_d \times BVF$

Rate per cell (p_G, p_N); Osteocytes density (Y_d)

Model Representation of Bone Loss Due to Insufficient Mechanical



Converting Experimental Data to Model Variables

Definitions

$$\text{Ash density } \rho_{ash} = \frac{\text{ash mass}}{\text{total vol}}$$

$$\text{Apparent (dry) density } \rho_{app} = \frac{\text{dry bone tissue mass}}{\text{total vol}}$$

$$\text{Ash fraction } \alpha = \frac{\rho_{ash}}{\rho_{app}} = \frac{\text{ash mass}}{\text{inorganic mass} + \text{organic mass}}$$

D_m – density Mineralizd bone D_0 – density of Osteoid

Ash fraction has a theoretical limit 0.7 [4].

$$\text{BVF} = \frac{\text{apparent density}}{\text{true tissue density } \rho_t} \quad \rho_t(g/cc) = 1.41 + 1.29\alpha \ [4]$$

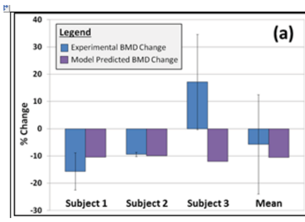
$$\alpha = \frac{M\cdot D_m\cdot 0.7}{M\cdot D_m + O\cdot D_c} \text{ or } \frac{M\cdot D_m + O\cdot D_o}{M+O} = \rho_t \text{ (Used in Model)}$$

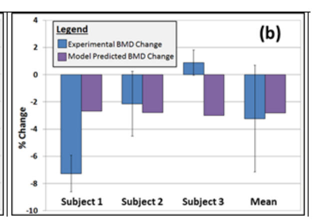
A Method for Mapping vBMD to BVF

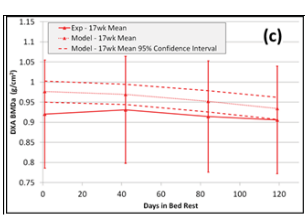
Given:
A Pre Bed Rest QCT BMD value.
A Bed Rest Duration Length of N days.
A Post Bed Rest QCT value.

1. (a) Convert ρ_{QCT} to ρ_{ash} (e.g. Keyak regression)
   (b) Convert ρ_{ash} to ρ_{app} (e.g. Schileo regression)
   (c) Compute initial ash fraction $\alpha = \rho_{ash} / \rho_{app}$
2. Initial value $M = \rho_{ash} / (0.7 \times D_m)$
   Solve for initial value O using α definition.
3. Run computational simulation subject to loading history (i.e. bed rest) for N days to track change in M, O, α, ρ_{ash}, ρ_{QCT} *(BMD)*, and *BVF*
4. Compare *BMD to* QCT *BMD*

Preliminary Validation Results for Bone Deconditioning Simulations







Preliminary validation results for predicting loss.of

(a) Trabecular bone

(b) Cortical bone   After 70 days of bed rest

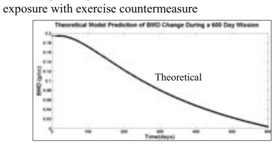
(c) Time course change of mean Dexa BMD for 18 control subjects during 17 weeks of bed rest.

The QCT bone analysis data was provided by the NASA JSC Bone Lab through the NASA Life Sciences Data Archive

Future Work

Near Term:
- Develop/formulate a daily load formula for quantifying exercise induced loading and test against exercise treated subjects (e.g. CFT70 study)

Long Term:
- Develop method for transforming force data from biomechanics modeling of specific exercise devices into stress/strain input
- Integrate the computational model with Finite Element Method
- Validate model using QCT data from spaceflight research
- Develop model for predicting bone adaptation for trochanter, total proximal femur and lower lumbar
- Bone adaptation prediction for more than 180 days of spaceflight exposure with exercise countermeasure



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