The Digital Astronaut Project Bone Remodeling Model

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Background

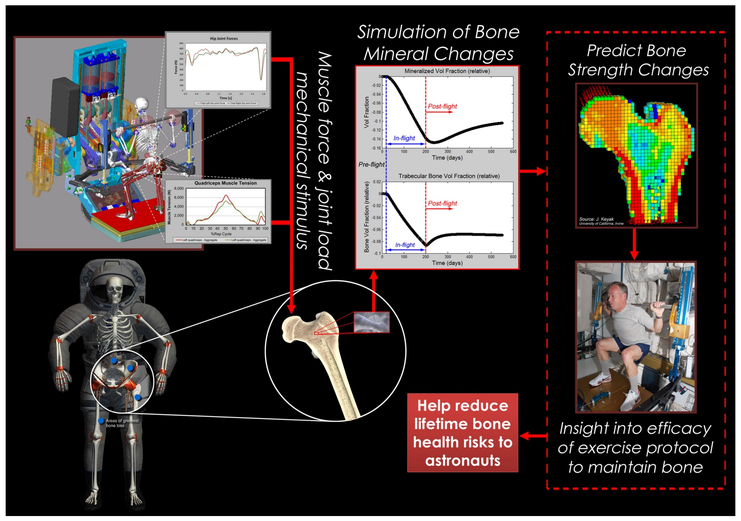
Why Quantifying Change in Bone via Bone Remodeling is Objective of NASA Digital Astronaut Project (DAP)

- 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 cellular mechanism of bone remodeling to maintain bone.
  - Exercise induced loading, with appropriate 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	$\frac{dB_r}{dt} = D_{B_P}\cdot E_{TGF} - D_{B_r}\cdot((1-E_{TGF})+E_{PGE})\cdot B_r$	**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 (#BRUs 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_P}	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

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

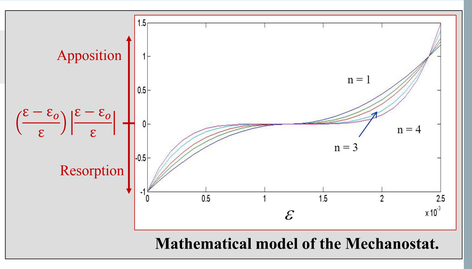
- PGE_2
  - Mediates differentiation of osteoblasts induced by TGF-β
  - Stimulates proliferation of osteoblasts
- NO
  - Stimulates production of OPG
  - Inhibits production of RANKL

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

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

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



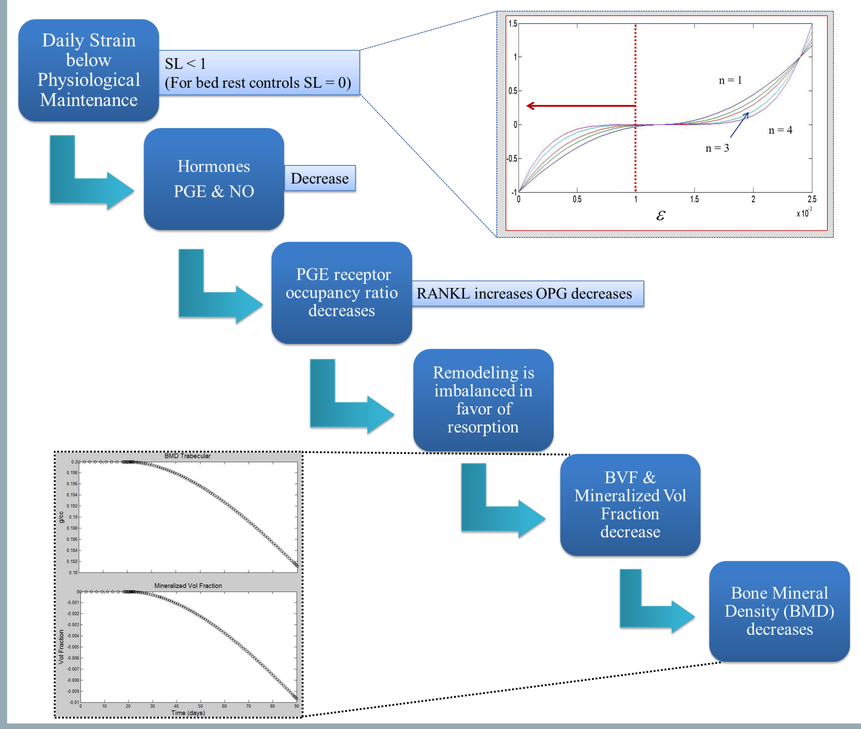
Mathematical model of the Mechanostat.

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

Rate per cell
PGE Production Rate → $S_G = p_G \times SL \times Y_d \times BVF$
NO Production Rate → $S_N = p_N \times SL \times Y_d \times BVF$
Osteocytes density
Rate per cell

Model Representation of Bone Loss Due to Insufficient Loading



Converting Experimental Data to Model Variables

Definitions

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

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

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].

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

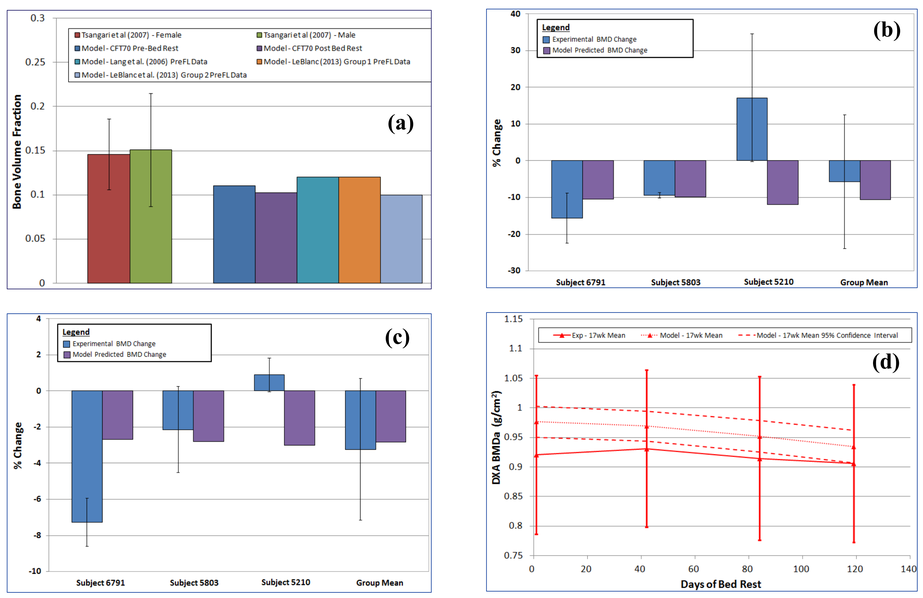
$\alpha = \frac{M\cdot D_m\cdot 0.7}{M\cdot D_m + O\cdot D_c}$ or $\frac{M\cdot D_m + O\cdot D_o}{M+O} = \rho_t$ (Used in Model)

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:
(a) Group mean BVF [9-11].
(b) Loss of trabecular bone after 70 days of bed rest.
(c) Loss of cortical bone after 70 days of bed rest,
(d) Time course change of mean DXA BMD for 18 control subjects during 17 weeks of bed rest [12].

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

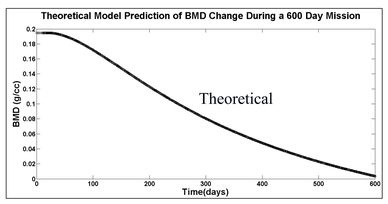
Future Work

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



References

1. Keyak J. *et al.* (2009), *Bone* Volume 44, pp. 449-453.
2. Lemaire, V. *et al.* (2004), *Journal of Theoretical Biology* Volume 229 (3), pp. 293-309.
3. Pivonk, P. *et al.* (2008), *Bone* Volume 43, 249-263.
4. Hernandez, C. *et al.* (2001), *Bone* Volume 29 (1), 74-78.
5. Turner, C. and Pavalko, F. (1998), *Journal of Orthopedic Science* Volume 3, 346-355.
6. Yoshida, K. *et al.*(2002), *PNAS*, Volume 99 (7), pp. 4580-4585.
7. Kaneko, T. *et al.* (2003), *Mechanical Engineering and Physics*, Volume 25, pp. 445-454.
8. Schileo, E. *et al.* (2008), *Journal of Biomechanics*, Volume 41, pp. 2483-2491.
9. Tsangari, H. *et al.* (2007), *Bone,* Volume 40, pp. 211–217.
10. Lang, T.F. *et al.* (2006), *Journal of Bone and Mineral Research*, Volume 21, pp. 1224-1230.
11. LeBlanc, A. *et al.* (2013), *Osteoporosis International*, Volume 24 (7), pp. 2105-2114.
12. LeBlanc, A.D. *et al.* (2002), *Journal of Musculoskeletal & Neuronal Interactions*, Volume 2, pp. 335–343.

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