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.

\[ \text{BVF Rate of Change} = \text{Rate of Formation} - \text{Rate of Resorption} \approx 0 \quad (\text{Balance Healthy State}) \]

\[ \text{BVF} = \frac{\text{Bone Volume Fraction}}{} = \frac{\text{BV}}{\text{TV}} = \frac{\text{BA}}{\text{TA}} \]

\[ \text{TA} = \text{Total Area}; \quad \text{BA} = \text{Bone Area}; \quad \text{TV} = \text{Total Volume}; \quad \text{BV} = \text{Bone Volume} \]

\[ \text{BVF} \]

Mineralized Volume Fraction (MVF) M + Osteoid Volume Fraction (OVF) O
### Model Description (2/2)

**Mathematical System**

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

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

<table>
<thead>
<tr>
<th>Disuse</th>
<th>Adapted State</th>
<th>Overload</th>
<th>Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

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 $\varepsilon$ in Frost’s Mechanostat Theory:

- Sensing strength or sensing level (SL) defined in relation to bone strain
  \[ SL = f_s(\varepsilon) = [S(\varepsilon, \varepsilon_0) + 1] \]

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

\textit{NO} and PGE$_2$ synthesis are defined to be proportional to SL

\[ S_G = \frac{p_G}{f_s(\varepsilon)} \times Y_d \times BVF \]

\[ S_N = \frac{p_N}{f_s(\varepsilon)} \]

Mathematical model of the Mechanostat.
Computational Implementation

Given Initial vBMD

1. BMD Converted to Ash density
2. Initial BVFs Computed By Math Algorithm
3. Stress value at Center of Dead Zone Computed

\[ \text{Strain} \; \varepsilon(t) = \frac{\sigma(t)}{E(t)} \]

\[ \text{Stress/Strain Value per Exercise via FEM Input to } DLS \text{ Formula} \]

\[ E \propto \text{ash density} \]

Modulus Value Computed Keyak Model

Below PR = Negative BVF rate of change
In PR = 0 BVF rate of change
Above PR = Positive BVF rate of change

PR = Physiological Range

Time integration reveals change in BVF and in turn change in vBMD
## Verification Analysis (1/2)

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

### Table:

<table>
<thead>
<tr>
<th>Weight (N)</th>
<th>Steps</th>
<th>Duration (days)</th>
<th>Trabecular vBMD (g/cm³)</th>
<th>Cortical vBMD (g/cm³)</th>
<th>DXA aBMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>791</td>
<td>5000</td>
<td>365</td>
<td>0.130</td>
<td>0.131</td>
<td>0.891</td>
</tr>
<tr>
<td></td>
<td>7500</td>
<td></td>
<td>-0.001 (-0.76%)</td>
<td>0.131</td>
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<td></td>
<td>10000</td>
<td></td>
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<td>565</td>
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</table>
## Verification Analysis (2/2)

<table>
<thead>
<tr>
<th># of Steps</th>
<th>QCT Simulation Results</th>
<th>DXA Simulation Results</th>
<th>Weight (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td>565</td>
</tr>
<tr>
<td>10000</td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
<td>791</td>
</tr>
</tbody>
</table>
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
Comparison of deconditioning simulation results against 70-day bed rest control subject QCT vBMD (N=4)
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
References

Abstract

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