Development of Bone Remodeling Model for Spaceflight Bone Physiology Analysis

Jim Pennline$^1$, Chris Werner$^2$, Beth Lewandowski$^1$, Bill Thompson$^1$, Jean Sibonga$^3$ and Lealem Mulugeta$^4$

1. NASA Glenn Research Center, Cleveland, OH
2. ZIN Technologies, Cleveland, OH
3. NASA Johnson Space Center, Houston, TX
4. Universities Space Research Association, Division of Space Life Sciences, Houston, TX
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.
**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.

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

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

**BVF Rate of Change = Rate of Formation – Rate of Resorption \approx 0 \ (Balance\ Healthy\ State)**
### Model Description (2/2)

**Mathematical System**

**Variables**

<table>
<thead>
<tr>
<th>Bone Volume Fractions</th>
<th>Rates of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{M} ) Mineralized V F</td>
<td>( \dot{\sigma} ) Osteoid V F</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell population</th>
<th>Rates of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{B} ) Active Osteoblasts</td>
<td>( \dot{C} ) Active Osteoclasts</td>
</tr>
<tr>
<td>( B_r ) Responding Osteoblasts</td>
<td></td>
</tr>
</tbody>
</table>

**Driving Process**

- **Removal and Replacement of Bone Packets (Remodeling Units)**

**Dependencies**

- Activation Density
- Bone Remodeling Units
- BRU Area Resorbed
- BRU Area Formed
- Active Resorbing Cell Population
- Active Forming Cell Population

**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
The model gauges 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**

$NO$ and $PGE_2$ synthesis are defined to be proportional to SL

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

$S_N = \frac{p_N}{f_s(\varepsilon) \times Y_d \times BVF}$

Mathematical model of the Mechanostat.
Given Initial vBMD

BMD Converted to Ash density

Initial BVFs Computed By Math Algorithm

Modulus Value Computed Keyak Model

$E \propto \text{ash density}$

Stress value at Center of Dead Zone Computed

Strain $\varepsilon(t) = \frac{\sigma(t)}{E(t)}$

Elastic Modulus

Stress/Strain Value per Exercise via FEM Input to DLS Formula

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

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>

### Bone Density Measurements

<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></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Change</td>
</tr>
<tr>
<td>791</td>
<td>5000</td>
<td>365</td>
<td>0.130</td>
<td>0.130</td>
<td>-0.001</td>
</tr>
<tr>
<td>791</td>
<td>7500</td>
<td></td>
<td>0.131</td>
<td>0.131</td>
<td>0.000</td>
</tr>
<tr>
<td>791</td>
<td>10000</td>
<td></td>
<td>0.131</td>
<td>0.131</td>
<td>0.000</td>
</tr>
<tr>
<td>565</td>
<td>5000</td>
<td></td>
<td>0.129</td>
<td>0.129</td>
<td>-0.002</td>
</tr>
<tr>
<td>565</td>
<td>7500</td>
<td></td>
<td>0.131</td>
<td>0.131</td>
<td>0.000</td>
</tr>
<tr>
<td>565</td>
<td>10000</td>
<td></td>
<td>0.131</td>
<td>0.131</td>
<td>0.000</td>
</tr>
</tbody>
</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="QCT Simulation" /></td>
<td><img src="image2.png" alt="DXA Simulation" /></td>
<td>565</td>
</tr>
<tr>
<td>10000</td>
<td><img src="image3.png" alt="QCT Simulation" /></td>
<td><img src="image4.png" alt="DXA Simulation" /></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
### Validation Sample Results

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

<table>
<thead>
<tr>
<th>Trabecular</th>
<th>Cortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>% Change</td>
</tr>
<tr>
<td>Change</td>
<td>SD</td>
</tr>
<tr>
<td>-4.3%</td>
<td>±10.8%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Duration</th>
<th>N</th>
<th>Change</th>
<th>SD</th>
<th>Model</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 days</td>
<td>4</td>
<td>-1.8</td>
<td>±2.5%</td>
<td>-1.7%</td>
<td>±0.6%</td>
</tr>
<tr>
<td>120 days</td>
<td>18</td>
<td>-1.6</td>
<td>±3.2%</td>
<td>-3.9%</td>
<td>±1.4%</td>
</tr>
</tbody>
</table>

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

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)