

A Computational Model for Simulating Spaceflight Induced Bone Remodeling

James A. Pennline¹

NASA Glenn Research Center, Cleveland, OH, 44135

and

Lealem Mulugeta²

Universities Space Research Association, Houston, TX, 77058

An overview of an initial development of a model of bone loss due to skeletal unloading in weight bearing sites is presented. The skeletal site chosen for the initial application of the model is the femoral neck region because hip fractures can be debilitating to the overall performance health of astronauts.

The paper begins with the motivation for developing such a model of the time course of change in bone in order to understand the mechanism of bone demineralization experienced by astronauts in microgravity, to quantify the health risk, and to establish countermeasures. Following this, a general description of a mathematical formulation of the process of bone remodeling is discussed. Equations governing the rate of change of mineralized bone volume fraction and active osteoclast and osteoblast are illustrated. Some of the physiology of bone remodeling, the theory of how imbalance in remodeling can cause bone loss, and how the model attempts to capture this is discussed. The results of a preliminary validation analysis that was carried out are presented. The analysis compares a set of simulation results against bone loss data from control subjects who participated in two different bed rest studies. Finally, the paper concludes with outlining the current limitations and caveats of the model, and planned future work to enhance the state of the model.

Nomenclature

<i>aBMD</i>	=	Areal Bone Mineral Density (g/cm^2)
<i>BMD</i>	=	Bone Mineral Density
<i>BVF</i>	=	Bone Volume Fraction
<i>DAP</i>	=	Digital Astronaut Project
<i>DXA</i>	=	Dual-energy X-ray Absorptiometry
<i>FE</i>	=	Finite Element
<i>vBMD</i>	=	Volumetric Bone Mineral Density (g/cm^3)
<i>QCT</i>	=	Quantitative Computed Tomography

I. 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 [1–3]. The most commonly used countermeasure against bone loss in microgravity has been prescribed exercise [4]. However, data have shown that existing exercise countermeasures do not completely eliminate bone loss in long duration, 4 to 6 months, spaceflight [1, 3, 5, 6]. This spaceflight related bone loss may lead to early onset osteoporosis and place the astronauts at greater risk of fracture later in their lives. Consequently, NASA seeks to improve understanding of the mechanisms of bone remodeling and demineralization in microgravity in order to appropriately quantify the long term risk, and to establish appropriate countermeasures [7].

¹ DAP Bone Modeling and Simulation Lead, Mechanics and Life Prediction Branch, Structures and Materials Division, 21000 Brookpark Rd. MS 49-7.

² DAP Project Scientist, Division of Space Life Scientist, 3600 Bay Area Blvd.

In this light, NASA's Digital Astronaut Project (DAP) is working with bone specialists in the Human Research Program to develop a validated computational models to help predict and assess bone loss during spaceflight, and enhance exercise countermeasure development. More specifically, proposed computational modeling augments bone research and exercise countermeasure development by elucidating changes in weight-bearing skeletal sites that are most susceptible to bone loss in microgravity, and thus at higher risk for fracture. Given that hip and proximal femur are dynamic load bearing sites susceptible to microgravity induced demineralization and potentially debilitating fractures the initial model development focused on the femoral neck. Future efforts will focus on including other key load bearing bone sites such as the greater trochanter, lower lumbar vertebrae, proximal femur and calcaneus.

The DAP has currently established a beta model of bone loss due to skeletal unloading in the femoral neck region. The model, as applied to the femoral neck region, calculates changes in mineralized volume fraction of bone that can be related to changes in volumetric bone mineral density (vBMD) measured by Quantitative Computed Tomography (QCT). The model is governed by equations describing changes in bone volume fraction (BVF), and rates of changes in bone cell populations that remove and replace bone in packets within the bone region. For a given volumetric element, BVF is defined as the unmineralized plus mineralized bone volume divided by the total volume.

The DAP bone model is considered unique in how it tracks volume fraction changes. In particular it has a higher physiological fidelity than models of volume fraction changes reported in the literature. This higher physiological fidelity is achieved by separation of the BVF into separate equations for mineralized and osteoid volume fractions governed by a mineralization rate. This more closely follows the physiology of the remodeling unit cycles where bone is first resorbed and then followed by the action of osteoblasts to lay down collagen matrix which eventually becomes mineralized. More detailed description of the model, preliminary validation results, current limitation and caveats, and planned advancements are provided in sections II through V.

The DAP bone model is being developed primarily as a research tool, and not as a clinical tool. The DAP bone model is not being developed, nor will it be validated, to predict bone fracture. Its purpose is to provide valuable additional data via "forward prediction" simulations for during and after spaceflight missions to gain insight on, (1) mechanisms of bone demineralization in microgravity, and (2) the volumetric changes at the various bone sites in response to in-flight and post-flight exercise countermeasures. These data can then be integrated with Finite Element Modeling similar to the methods proposed in [8, 9] to gain insight on how bone strength may change during and after flight. Such information could also contribute to optimizing exercise countermeasure devices and protocols designed to minimize changes in bone strength during flight. Figure 1 illustrates this application process.

II. Overview of the DAP Model of Bone Remodeling

Bone remodeling, the physiological mechanism for maintenance, renewal, and repair in the adult skeleton, is the process done through the replacement of bone in units by the coupled action of bone cells on the same cell surface. The bone resorbing cells, *osteoclasts*, remove old or damaged bone. The bone forming cells, *osteoblasts*, form an initial collagen matrix and then mineralize the collagen. Within bone, *osteocytes*, cells derived from the bone forming cells, form what is understood to be a signaling network. The replacement unit or bone remodeling unit differs between trabecular bone (the spongy interior tissue in bone marrow) and cortical bone (the compact bone that forms the outside shell that encloses bone marrow). In trabecular bone, the structural unit is a packet shaped like a shallow crescent, hemi-osteon, on the surface of a rod or plate like element. In cortical bone, the structural remodeling unit is a single Haversian system, osteon, shaped like a cylinder, singly referred to as a tunnel or cutting cone while forming. Osteons run almost parallel to the longitudinal axis of bone enclosing blood vessels or nerves within the Haversian canal [10].

A remodeling unit's cycle consists of 5 phases: activation, resorption, reversal, formation, and quiescence. Activation involves conversion of a small area of bone surface from quiescence to activity requiring the recruitment of osteoclasts, a means for them to gain access to bone and a mechanism for attachment to the surface. Briefly, the cycle proceeds as follows. Surface bound molecules, referred to as RANKL (Receptor Activator for Nuclear Factor κ B ligand) are expressed on the surface of osteoblasts while membrane protein RANK receptor is expressed on the surface of preosteoclasts. The binding of RANK with RANKL causes the derivation of *active osteoclasts* from preosteoclasts which begin to erode bone, resorption, in the shape of a shallow crescent or cutting cone. Following a reversal period, formation by *active osteoblasts*, derived from a different precursor cell, begins at the same location where bone was eroded. Osteoprotegerin (OPG) is released by osteoblasts and acts as a decoy receptor for RANKL blocking RANK-RANKL binding and inhibiting differentiation into active osteoclasts[11]. During the time span of formation, some active osteoblasts become osteocytes embedded in the bone while others die or become surface lining cells.

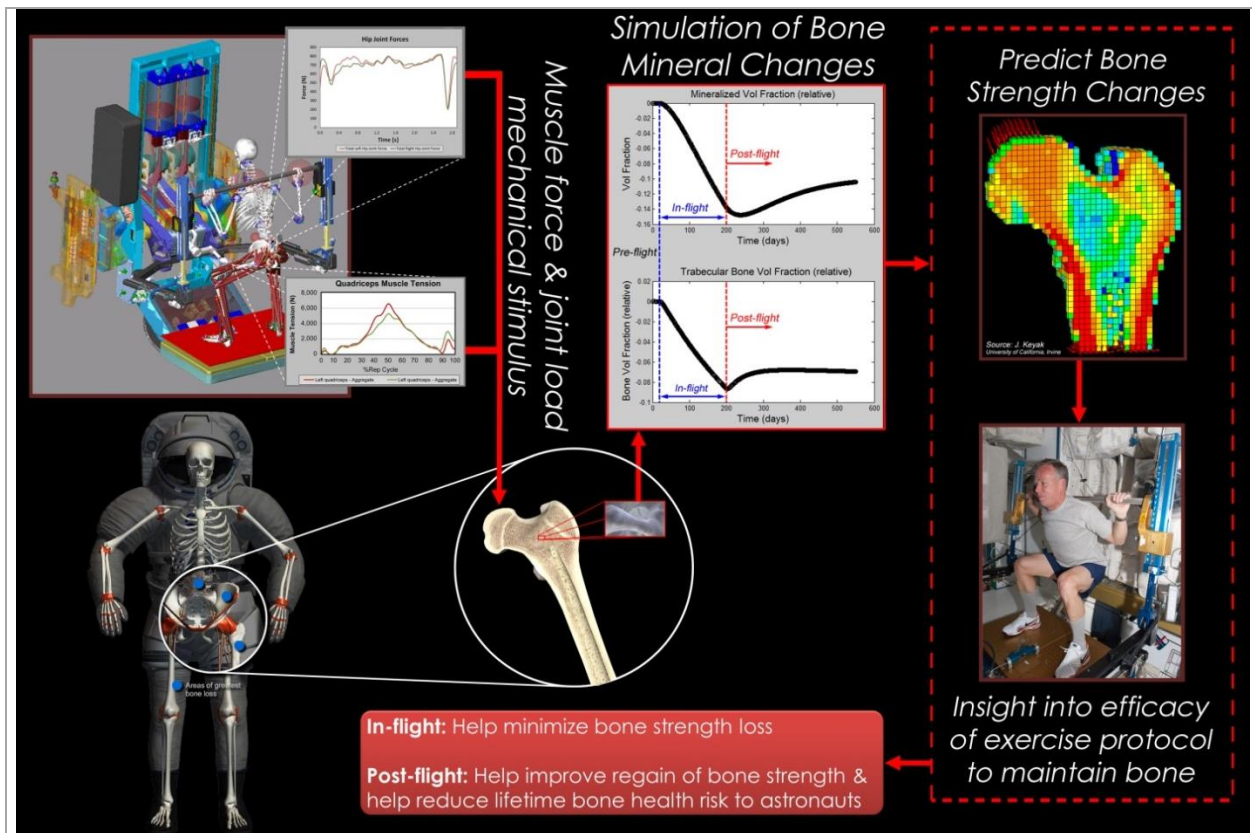


Figure 1. Illustration of how the DAP bone remodeling model will be used to perform “forward prediction” simulations to gain insight on the volumetric changes in bone and how bone strength is affected based on FE method. The model will accept loading history due to muscle and joint force on bone and produce quantified remodeling within the bone region under influence of the applied stress. Furthermore, because they tend to respond differently, the bone remodeling model includes both trabecular bone and cortical bone.

The DAP bone remodeling computational model consists of a system of 1st order, nonlinear differential equations shown in Table 1 that govern the time rate of change in bone via the bone remodeling process. The model consists of three major topics, (1) the mechanics of the removal and replacement of bone packets via remodeling units, (2) the biology and physiology of cellular dynamics of remodeling units, and (3) mechanotransduction which describes the function of skeletal loading and its role in maintaining bone health. The basic biological assumption used in the cellular physiology can be stated as such: Cell proliferation (anti-proliferation) is directly proportional (inversely proportional) to receptor occupancy ratio [12].

The model is designed to track BVF (Eq. 1 - base equation) of a representative volume element of a specific skeletal site or bone segment, which is divided into the *mineralized volume fraction* plus the *osteoid volume fraction* as shown in the expression of Eq. 2 and Eq. 3. Assuming the areal volume fraction is equivalent to the volume fraction [13], the time rate of change of the volume fractions are functions of the areas removed and replaced in a cross section of a representative volume element by the cells in the *remodeling units*, *activation frequency*, and *normalized active cell populations*.

The normal maintenance of bone is achieved by balanced processes of bone formation and bone resorption described at the beginning of this section, which can be influenced by endocrine regulation, local biochemical mediators, and skeletal loading. When the processes are balanced, the rate of change of BVF of the whole skeletal site or bone segment is approximately zero. When the processes become unbalanced in favor of resorption, integration of the equations in time yields a decrease in mineralized volume fraction and BVF. The differences between trabecular and cortical bone compartments are captured in part by the differences in the shape of the remodeling unit, hemi-osteon vs. cutting cone, and the process by which bone mass is removed and replaced. Differences in other parameters, like activation density also distinguish trabecular bone from cortical bone. These differences are reflected in the specific values used for the variables listed in the second column of Table 2 when applying the model to specific bone sites.

Table 1. System of Equations

Bone Volume Fraction	$\frac{dBVF(t)}{dt} = A_F(t) \cdot \bar{f}_a \frac{B(t)}{B_0} - A_R(t) \cdot \bar{f}_a \frac{C(t)}{C_0}$	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	$\frac{dC}{dt} = D_{C_p} \cdot E_{RL} - k_C \cdot E_{TGF} \cdot C$	Eq. 6

Table 2. State Variables and Definitions

$BVF(t)$ = Bone Volume Fraction	$A_R(t)$ = Cross Sectional Bone Area Resorbed per BRU (mm ²)
$M(t)$ = Mineralized Volume Fraction	$A_F(t)$ = Cross Sectional Bone Area Formed per BRU (mm ²)
$O(t)$ = Osteoid Volume Fraction	\bar{f}_a = Activation Density in Normal State (#BRUs activated per day per mm ²)
$B(t)$ = Concentration of Active Osteoblasts (pM)	r_r = ($A_R \cdot \bar{f}_a$) Resorption Rate per Normalized Osteoclast Population
$C(t)$ = Concentration of Active Osteoclasts (pM)	r_f = ($A_F \cdot \bar{f}_a$) Formation rate per Normalized Osteoblast Population
$B_r(t)$ = Concentration of Responding Osteoblasts (pM)	r_m = Mineralization Rate

The normalized active cell populations are governed by Eq. 4 through Eq. 6 to model the physiology of resorption and formation via the dynamics of the active bone resorbing cells, *osteoclasts*, the active bone forming cells, *osteoblasts*, and the *responding osteoblasts*. Considered a composite of several phenotypes (i.e., early *osteoblasts* or *preosteoblasts*), the term *responding osteoblasts* is not considered a true cell type [14]. Rather, the uncommitted progenitors commit to differentiating into this category. *Osteoblasts progenitors* are modeled implicitly as a reservoir source as well as the *osteoclasts precursors* through the differentiation rate parameters listed in Table 3, which also defines the quantities involved in the endocrine regulation, biochemical mediation, and skeletal loading.

Table 3. Parameters and Receptor Occupancy Functions in the Cell Equations

D_{B_p} = Differentiation Rate of Osteoblast Progenitors	E_{TGF} = TGF-beta Receptor Occupancy Ratio Dependencies – C, r_r
D_{B_r} = Differentiation Rate of Responding Osteoblasts	E_{PGE} = Prostaglandin PGE-2 Receptor Occupancy Dependencies – M, O
D_{C_p} = Differentiation Rate of Osteoclast Precursors	E_{PTH} = Parathyroid Hormone Receptor Occupancy Dependencies – Rate of synthesis S_p
k_B = Rate of Elimination of $B(t)$	E_{NO}^\dagger = Nitric Oxide effect on RANKL Dependencies – M, O
k_C = Rate of Elimination of $C(t)$ (Apoptosis)	E_{RL} = RANKL Receptor Occupancy Ratio Dependencies – B_r, B, E_{NO}, OPG
B_0 = Reference Osteoblast Population (pM)	C_0 = Reference Osteoclast Population (pM)

[†] It is important to note that the effect of NO on RANKL, E_{NO} , does not appear explicitly in the equations and nor does an Osteoprotegerin (OPG) function but both are dependencies of E_{RL} . To avoid complicating a description of the system, the functional expressions of the receptor occupancy ratios are omitted but their dependencies are listed in the tables.

Bone remodeling literature encompasses a vast amount of research on the endocrine, biochemical, autocrine, and paracrine interactions involving receptors and ligands. With regard to bone-cell communication and the role played by receptor-ligand pathways, a large number of hypotheses have been postulated. Although there is much that is not understood about the process, the DAP bone remodeling model mathematically formulates the key elements based on well accepted knowledge and experimental studies of bone [15]. In particular, the RANK-RANKL-OPG signaling pathway discovered in the mid-90s is the essential part of the cellular dynamics. As explained at the beginning of section II it's the balanced signaling pathway that's followed through the sequence of each complete remodeling unit cycle. Causes of bone loss or effects of therapeutic drugs can often be traced to disturbances in this pathway, and it is the fundamental principle under which this model is implemented computationally [12, 16, 17].

Another key element is the mathematical formulation of the effects of nitric oxide and prostaglandin E_2 which takes into account the contribution of skeletal loading to the normal maintenance of bone through balanced processes of bone formation and bone resorption. Osteocytes (and possibly bone lining cells), which are assumed to be the mechanosensors, have been shown experimentally to release the cellular signaling molecule NO and the paracrine PGE_2 in response to mechanical loading [18–21]. Although they can have an inhibiting effect as well as a stimulating effect, both have been found to contribute to bone formation either by direct mediation in the RANK-RANKL-OPG pathway or by indirect promotion of cell differentiation [22, 23]. In the computation model, reduced skeletal loading triggers a decrease in NO and PGE_2 , which in turn triggers an imbalance in the pathway in favor of resorption. This leads to a decrease in mineralized volume fraction M and osteoid volume fraction O , and hence a decrease in BVF.

Thus the current model considers the endocrine hormone signal PTH, as well as the autocrine and paracrine substances that include the protein TGF- β , protein cytokine receptor OPG, protein ligand RANKL, the autocrine or paracrine hormone PGE_2 and the biochemical NO. Although numerous proteins, hormones, ligands and receptors have been implicated in the bone remodeling process, the desire was to produce a tractable model than allow us to consider imbalances in the remodeling process caused by skeletal unloading. This motivated the isolation and consideration of only substances that play a direct role particularly in the RANK-RANKL-OPG pathway and to include substances that can play a significant role in bone response to mechanical loading.

Although the skeletal loading contribution to the maintenance of bone health has been modeled in, it is important to realize that mechanotransduction theory encompasses phases from mechanocoupling to the final effector response [24]. Mechanical signals can directly affect bone cells or be turned into chemical signals. However, the mechanisms by which effector cells, i.e., osteoblasts and osteoclasts, respond to the original stimulus are not fully established. Frost's mechanostat theory [25, 26] that relates loading-induced strain magnitudes to bone gain or bone loss, defines a lower threshold or minimum effective strain. Although the DAP bone model mathematical formulation develops a robust concept of a mechanical stimulus "magnitude" from dynamic loading, this aspect of the model needs testing and further development with regard to specific exercise-induced loading. The current beta version includes only the bone deconditioning due to mechanical unloading.

Parameter values referred to in the discussion are still under active research by the science community. Due to the parameter value uncertainty, our approach was to use average values based on experimental studies in the literature or assumed values based on experimental studies on ribs or the iliac crest. A selected example of these is as follows:

- **Resorption depth (depth of remodeling unit):** An average value of 0.05 mm for trabecular hemi-osteone was used based on reported values [27–30]. For cortical bone, femoral neck values for osteonal diameter and Haversian canal diameter, 0.0955 mm and 0.0271mm, that were reported for controls in studies of hip fractures and osteoarthritis [31, 32] were used. Resorption depth is used in the calculation of resorption area A_R , Table 2.
- **Activation frequency:** For cortical bone an average of the value reported for three age groups covering ages 30 to 59 from a histological study of ribs by Frost (1969) was used [33]. In the case of trabecular bone average values reported vary greatly. A sample includes 0.45/yr reported by Dempster et al. (1999) [34], 0.53/yr reported by Chapurlat et al. (2007) [35], 0.42/yr reported by (Mayo Clinic, personal communication). Since our model used a value in terms of #/day any value of about 0.36/yr to 0.53/yr gives a value rounded to three digits of 0.001/day. Activation frequency is used in calculating activation density f_a , Table 2.
- **TGF-beta 1:** Transforming Growth Factor has the ability to stimulate an increase in the osteoblast population, but can also inhibit final maturation in active osteoblasts. Because the amount of TGF-beta 1 involved in the remodeling process comes from the amount released during bone resorption a value of the

amount contained in bone is needed. A value of 200 $\mu\text{g}/\text{kg}$ is reported by Janssens et al. (2005) and Bonewald and Mundy (1990) [36, 37].

- **Receptor occupancy ratios:** For a given ligand receptor pair, the ratio has a dissociation constant reference value. For TGF-beta 1 a value for trabecular receptors reported by Tripathi et al. (1993) was used [38].

The shape of the femoral neck conforms approximately to a “short” cylindrical shape and acts like a cantilever during locomotion [39]. Trabeculae that accommodate tensile stresses and trabeculae that accommodate compressive stresses intersect at right angles in a significant part of the neck [40]. Currently, the model implementation is coded with a specific scheme to match mean vBMD values from QCT scanning technology presently use by NASA for flight and bed rest studies, and under consideration for use as part of an expanded standard for bone health. Correlation equations relating vBMD to ash density developed by Keyak [41] are used to relate ash density to mineralized volume fraction.

Validation of the the model’s capability to represent deconditioning of the femoral neck due to unloading uses data from control subjects participating in the current 70-day bed rest study (CFT70), a 17-week bed rest study reported in [42, 43], as well as literature data for BVF simulations. More specifically, pre-bed rest and post-bed rest QCT and DXA density scans obtained from control subjects are used to validate the model’s ability to track trabecular and cortical vBMD, and integral aBMD changes. Also the simulated BVFs are compared with experimental values reported in literature. Section III discusses the preliminary validation results for the beta version of the bone model.

III. Preliminary Validation Results

The NASA Human Research Program requires that all models and simulations (M&S) that can potentially impact the crew health or mission must be verified and validated in accordance to NASA’s Standard for Models and Simulations (NASA-STD-7009). In this light, we are working to verify and validate the DAP bone remodeling model to ensure that it can be used reliably for the intended application described in section I. This section will summarize the preliminary model validation results for bone deconditioning due to gravitational unloading under bed rest conditions.

It is important to note that the term “validation” does not mean the absolute substantiation of the model’s capability to capture the bone remodeling process. Validation refers to the degree which the model is able to reproduce the observed behavior under consideration (e.g. BMD or BVF) in comparison to an appropriate referent. In this case, either experimental data, real world observations or expert opinion. For example, if the model is compared against vBMD readings from bed rest control subjects, the validation activity is only indicative of the model’s capability to reproduce vBMD changes under bed rest conditions without countermeasure. It would not validate the behavior of any other parameters or variables. At best, it would only have indirect implications to other parameters or variables based on subject matter expert input and with appropriate justifications.

A. Bone Volume Fraction

Given that the fundamental formulation of the DAP bone remodeling model is based on BVF, it is important to ensure the model calculates BVF values within normal ranges of healthy adults.

We were not able to find literature that reports BVF for the femoral neck, but we were able to find trabecular BVF values for the intertrochanteric region of the proximal femur for both male and female adults between 18 and 49 year of age [45]. In addition, data presented in [46] shows that the trabecular vBMD for the femoral neck and the intertrochanteric region are $146.92 \pm 77.98 \text{ mg}/\text{cm}^3$ and $141.04 \pm 81.02 \text{ mg}/\text{cm}^3$, respectively. Therefore, it seems reasonable to assume the trabecular BVF of the femoral neck would be similar to the trabecular BVF for the intertrochanteric region.

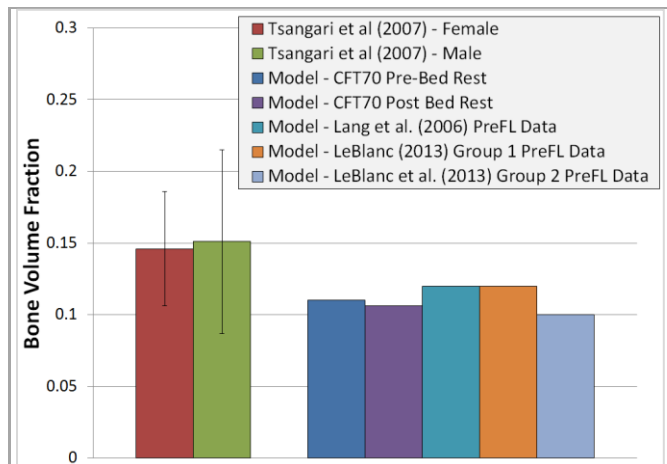


Figure 2. Validation of simulated trabecular bone volume fraction by comparing against experimental data presented in [6, 44, 45].

Comparing the BVF values calculated by the model using the group mean pre- and post-bed rest vBMD data from the CFT70 control subjects, and the pre-flight mean vBMD data presented by Lang et al. (2006) and LeBlanc et al. (2013) [6, 44], the model results are still within the standard deviation of the experimental trabecular BVF values reported in [45] (Figure 2). The two groups identified from LeBlanc et al. (2013) represent treated and untreated subjects in a Bisphosphonate spaceflight study. To ensure that our results were not confounded by the Bisphosphonate treatment or spaceflight exercise countermeasures, we only used the pre-flight and pre-treatment vBMD values for both groups in LeBlanc et al. (2013) and those presented by Lang et al. (2006). Overall, the results of the BVF predictions suggest a good foundation has been established for appropriately defining the base BVF equation to track trabecular bone remodeling. Validation of cortical BVF simulations remains to be attempted once appropriate cortical BVF data is identified.

B. Trabecular vBMD

The trabecular bone remodeling module was validated for prediction of vBMD change under disuse conditions by comparing femoral neck vBMD values from three control subjects who participated in CFT70. As seen in Figure 3, the model results match experimental values within one standard deviation for two of the subjects and for the group mean. The simulations for subject CFT-3 did not match the experimental data because the subject appears to have gained trabecular bone. Although the cause of this bone gain is unknown, the subject was identified to have a baseline trabecular and cortical vBMD that was consistent with values observed in an elderly person with age-related bone loss, and not of the astronaut-aged population. Therefore, it may not be appropriate to use the data from this subject for validation since the DAP bone model is intended to be used for simulating bone remodeling in healthy individuals between the ages of 25 and 55 who are representative of the astronaut population. We also acknowledge that this preliminary validation study uses a limited experimental data. Therefore, although the results show promise, we cannot make substantive conclusions on the model's capability to track trabecular vBMD changes for up to 70 days in bed rest without countermeasures. Additional QCT data are needed to assess the overall capability of the model to simulate trabecular bone loss at the femoral neck.

C. Cortical vBMD

We performed validation analysis of the cortical bone remodeling module for prediction of vBMD change under disuse conditions using the same methodology described for trabecular bone. As seen in Figure 4, the model successfully predicts bone loss trends for two out of the three subjects and for the group mean. Additionally, the model is able to match the post-bed rest vBMD experimental data within one standard deviation for CFT-2 and the mean vBMD for the control group. However, the model under predicts the amount of bone lost for CFT-1 and did not match the bone gain trend observed in subject CFT-3. The cause of these discrepancies between simulation

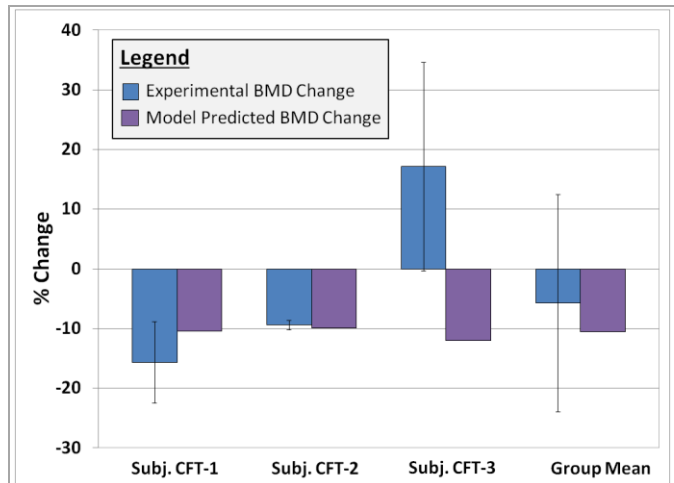


Figure 3. Comparison of model simulation results for percent change in trabecular vBMD with experimental data for three control subjects who participated in CFT70.

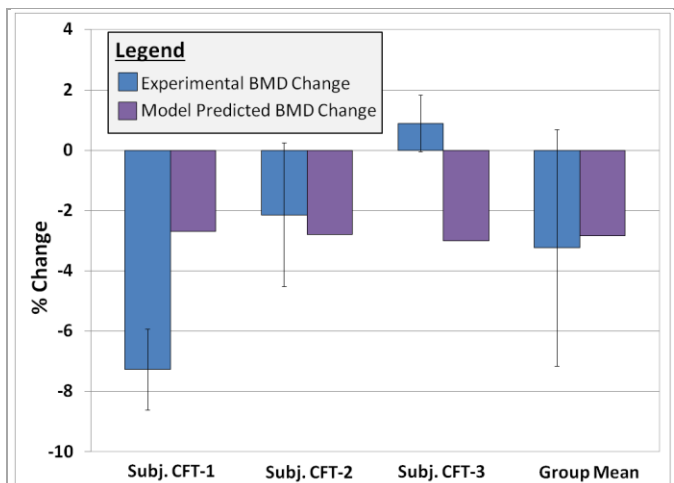


Figure 4. Comparison of model simulation results for percent change in cortical vBMD with experimental data for three control subjects who participated in CFT70.

results and experimental data is unknown. Additional data will help us understand if the rise in vBMD in the one subject is anomaly, and to assess the overall capability to simulate cortical bone loss at the femoral neck.

D. Preliminary Validation for Long Duration Simulation using aBMD Data

Given that current spaceflight missions are much longer the 70 days, and future exploration class missions be substantially longer, it is important to assess the model’s capability to simulate bone deconditioning for long durations. However, QCT data is not available for bed rest control subjects for more than 70 days. DXA data was collected, however, for 18 control subjects who participated in a 17-week bed rest study (4-months) [42, 43].

In order to be able to use the DXA aBMD to validate the model, we developed a regression method to map aBMD to vBMD using total femur DXA and QCT data from the flight study reported in [1], which was provided by NASA’s Life Science Data Archives. As it can be seen in Figure 5, the model predicts time course change of mean aBMD for 18 subjects who participated in a 17-week bed rest study well within one standard deviation of the experimental error. The 95% confidence interval of the simulation result is also within the one standard deviation of the experimental error.

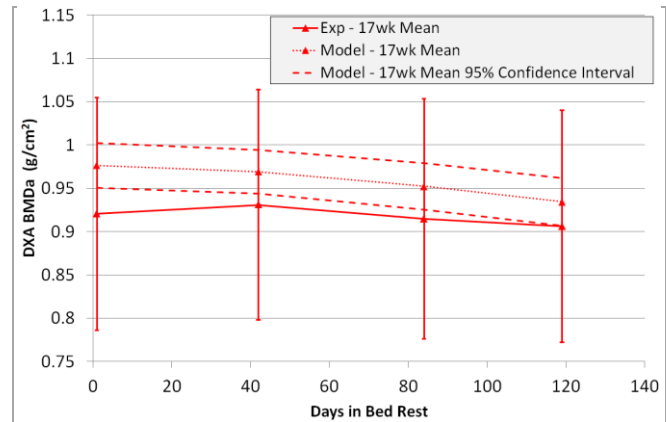


Figure 5. Comparison of model simulation results against experimental data for group mean predictions of time course change of aBMD for 18 control subjects who participated in a 17-week (4 months) bed rest study reported in [42, 43].

E. Overview of Preliminary Validation Results

The validation results suggest that the current state of the DAP bone remodeling model is most reliable for prediction of group mean BVF, vBMD and aBMD changes under bedrest conditions. It also shows some limited capability to predict subject specific trends in vBMD changes under bedrest conditions. These results suggest that we have laid a good foundation to establish a physiologically meaningful bone remodeling model that can simulate site specific bone adaptation due to mechanical unloading. In this light, we will continue to advance the state of the model by addressing the key limitations listed in section IV so that the model may be applied in the scheme outlined in section II and Figure 1.

IV. Limitations and Caveats

The DAP bone remodeling model has a number of limitations and caveats that should be noted. Some of these limitations and caveats are a direct consequence of the limited knowledge regarding bone remodeling process, while some will be addressed as we continue to develop the model further.

- 1) The bone remodeling formulation is limited to porosity, thus restricting it to density changes within the trabecular region and to intracortical density changes. It does not cover periosteal apposition or endocortical change. Furthermore, geometry changes in the bone site are not modeled.
- 2) Preliminary validation analysis of the computational predictions for deconditioning has only been done for up to 4 months in duration.
- 3) The validation data used is from bed rest control subjects as an analog to gravitational unloading due to exposure to microgravity. Although bed rest is viewed as a analog for microgravity, any differences that may exist between bed rest and microgravity with regards to the mechanisms of bone loss are not fully understood. Nevertheless, this is not a problem that is unique to the model, but rather due to the limited state of knowledge in bioastronautics bone science.
- 4) Age and gender differences are not yet factored in when initializing model variables and mapping the BMD or other initial types of data to the model’s state variables.
- 5) The bone model currently has a limited capability to make subject specific predictions.

- 6) The computational model is best suited for the mature adult between 25 and 55 years of age, or typical age of an astronaut.
- 7) The model does not include the effects of sclerostin, calcitonin, osteopontin, or Interleukins, some of which may play a role bone loss in microgravity and with disuse in 1 g.

Some key caveats that should be taken into consideration are included below. These are due to the inherent limitations imposed by the state of knowledge in bone science.

- 1) There is a degree of uncertainty and variation in remodeling unit geometry and dimensions reported in the literature. It is also difficult to guarantee that the values used in the model agree for the particular skeletal site of interest.
- 2) There is uncertainty in the way ash fraction is modeled, and the full potential range of values estimated from experimental studies is not completely understood.
- 3) Activation frequency and activation density are inherently difficult to appropriately model due to the lack of human values at skeletal sites other than the iliac crest or rib.
- 4) There are several potential algebraic schemes for mapping initial data values to model state variables. They depend on several possible definitions of ash fraction and how the steady state version of their respective equations are used.

V. Future Work

There are several areas of work that we need to complete before the model can be sufficiently mature to inform the bone research relating to bone strength standard development effort and exercise physiology. The areas of future development include:

- 1) Testing, evaluating, and resolving uncertainty in the model parameter values such as ash fraction, activation density, activation frequency.
- 2) Developing of appropriate methods for mapping experimental data to model variables must be developed.
- 3) Integrating with or leveraging data generated by biomechanics exercise models to predict the benefit exercise countermeasures for mitigating detrimental bone changes.
- 4) Extending the predictive capability of the model to simulate bone adaptation due to gravitational unloading and response to exercise countermeasures for up to one year.
- 5) Adapting the model to other skeletal sites such as the trochanter, total proximal femur and lumbar spine.
- 6) Performing rigorous verification, sensitivity and uncertainty analysis of the system of equations, as well as key parameters and variables that describe the bone adaptation process.
- 7) Tracking integral vBMD changes by accounting for the endocortical region in addition to the trabecular and cortical regions.
- 8) Adding age and gender related dependencies.
- 9) Enhancing the capabilities of the model to simulate subject specific bone changes.

VI. Conclusions

We have summarized the mathematical structure and preliminary validation results of the DAP bone remodeling model which substantially advances various principles developed in the literature on models of volume fraction changes. More specifically, it represents BVF via separate equations for mineralized and osteoid volume fractions governed by a mineralization rates. By taking this approach, a closer representation of the physiology of bone remodeling process can be established.

We have attempted in this model to take these types of computational models forward to begin to focus on specific skeletal sites and to enhance their predictive capability. Our results show that a good foundation has been laid for establishing a physiologically based bone remodeling model that can simulate site specific bone adaptation due to mechanical unloading, and ultimately to exercise induced load. We will continue to advance the model by systematically addressing the limitations and caveats identified in the sections IV and V.

Acknowledgments

This work is funded by the NASA Human Research Program, managed by the NASA Johnson Space Center. Specifically, this work is part of the Digital Astronaut Project, which directly supports the Human Health and Countermeasures Element. We would like to thank Drs. Jean Sibonga, Adrian LeBlanc, Elisabeth Spector and Jerry Myers, as well as the other subject matter experts who have been very generous in sharing their expertise, constructive feedback and experimental data to help us advance the state of the model.

References

- ¹ Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A: **Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight.** *J Bone Min Res* 2004, **19**:1006–1012.
- ² Buckley Jr JC: *Space Physiology*. New York: Oxford University Press; 2006.
- ³ LeBlanc AD, Spector ER, Evans HJ, Sibonga JD: **Skeletal responses to space flight and the bed rest analog: a review.** *Journal of musculoskeletal & neuronal interactions* , **7**:33–47.
- ⁴ Layne CS, Forth KE: **Plantar stimulation as a possible countermeasure to microgravity-induced neuromotor degradation.** *Aviation space and environmental medicine* 2008, **79**:787–794.
- ⁵ Keyak JH, Koyama K, LeBlanc a, Lu Y, Lang TF: **Reduction in proximal femoral strength due to long-duration spaceflight.** *Bone* 2009, **44**:449–53.
- ⁶ LeBlanc A, Matsumoto T, Jones J, Shapiro J, Lang T, Shackelford L, Smith SM, Evans H, Spector E, Ploutz-Snyder R, Sibonga J, Keyak J, Nakamura T, Kohri K, Ohshima H: **Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight.** *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 2013.
- ⁷ NASA HRP: *Evidence Book: Risk of Bone Fracture*. Houston, TX; 2008(March):1–24.
- ⁸ Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB: **Predicting Proximal Femoral Strength Using Structural Engineering Models.** *Clinical Orthopaedics and Related Research* 2005, **&NA**:219–228.
- ⁹ Keaveny TM, Hoffmann PF, Singh M, Palermo L, Bilezikian JP, Greenspan SL, Black DM: **Femoral bone strength and its relation to cortical and trabecular changes after treatment with PTH, alendronate, and their combination as assessed by finite element analysis of quantitative CT scans.** *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research* 2008, **23**:1974–82.
- ¹⁰ Bronner F, Worrell R: *Orthopaedics: Principles of Basic and Clinical Science*. CRC Press LLC; 1999.
- ¹¹ Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Boyle WJ, Riggs BL: **The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption.** *J Bone and Mineral Research* 2000, **15**:2–12.
- ¹² Lemaire V, Tobin FL, Greller LD, Cho CR, Suva LJ: **Modeling the interactions between osteoblast and osteoclast activities in bone remodeling.** *Journal of theoretical biology* 2004, **229**:293–309.
- ¹³ Hernandez CJ: **Simulation of bone remodeling during the development and treatment of osteoporosis.** Stanford University; 2001.
- ¹⁴ Lemaire V, Tobin FL, Greller LD, Cho CR, Suva LJ: **Modeling the interactions between osteoblast and osteoclast activities in bone remodeling.** *Journal of theoretical biology* 2004, **229**:293–309.
- ¹⁵ Pennline JA: *Simulating Bone Loss in Microgravity Using Mathematical Formulations of Bone Remodeling*. Cleveland, OH: NASA Glenn Research Center; 2009.
- ¹⁶ Li J: **Signal Transduction in Osteoclast Biology: The OPG-RANKL-RANK Pathway.** In *TNF Superfamily*. Edited by Khare S. Lands Bioscience; 2007:37–46.
- ¹⁷ Jameson JL, Groot LJ De, Kretser D de, Grossman A, Marshall JC, Melmed S, John TPJ, Weir GC: **Disorders of RANK/OPG/RANKL/NF- κ B Signaling.** In *Endocrinology: Adult and Pediatric*. 6th edition. Elsevier; 2010.
- ¹⁸ Turner CH, Pavalko FM: **Mechanotransduction and functional response of the skeleton to physical stress: the mechanisms and mechanics of bone adaptation.** *Journal of orthopaedic science official journal of the Japanese Orthopaedic Association* 1998, **3**:346–355.
- ¹⁹ Bonewald LF: **Mechanosensation and Transduction in Osteocytes.** *BoneKEy Osteovision* 2006, **3**:7–15.
- ²⁰ Bonewald LF, Johnson ML: **Osteocytes, mechanosensing and Wnt signaling.** *Bone* 2008, **42**:606–615.
- ²¹ Scott A, Khan KM, Duronio V, Hart DA: **Mechanotransduction in human bone: in vitro cellular physiology that underpins bone changes with exercise.** *Sports Medicine* 2008, **38**:139–160.
- ²² Fan X, Roy E, Zhu L, Murphy TC, Ackert-Bicknell C, Hart CM, Rosen C, Nanes MS, Rubin J: **Nitric oxide regulates receptor activator of nuclear factor-kappaB ligand and osteoprotegerin expression in bone marrow stromal cells.** *Endocrinology* 2004, **145**:751–9.
- ²³ Machwate M, Harada S, Leu CT, Seedor G, Labelle M, Gallant M, Hutchins S, Lachance N, Sawyer N, Slipetz D, Metters KM, Rodan SB, Young R, Rodan GA: **Prostaglandin receptor EP(4) mediates the bone anabolic effects of PGE(2).** *Molecular Pharmacology* 2001, **60**:36–41.
- ²⁴ Duncan RL, Turner CH: **Mechanotransduction and the functional response of bone to mechanical strain.** *Calcified Tissue International* 1995, **57**:344–358.
- ²⁵ Frost HM: **Bone “mass” and the “mechanostat”: a proposal.** *The Anatomical record* 1987, **219**:1–9.

- ²⁶ Frost HM: **Bone's mechanostat: a 2003 update.** *The anatomical record Part A Discoveries in molecular cellular and evolutionary biology* 2003, **275**:1081–1101.
- ²⁷ Parfitt AM: **Osteoporosis: Etiology, Diagnosis, and Management.** In *Osteoporosis: etiology, diagnosis, and management.* Edited by Riggs BL, Melton LJ. New York: Raven Press; 1988:45–93.
- ²⁸ Eriksen EF, Langdahl B, Vesterby A, Rungby J, Kassem M: **Hormone replacement therapy prevents osteoclastic hyperactivity: A histomorphometric study in early postmenopausal women.** *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 1999, **14**:1217–21.
- ²⁹ Brixen K, Hansen TB, Hauge E, Vahl N, Jørgensen JO, Christiansen JS, Mosekilde L, Hagen C, Melsen F: **Growth hormone treatment in adults with adult-onset growth hormone deficiency increases iliac crest trabecular bone turnover: a 1-year, double-blind, randomized, placebo-controlled study.** *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2000, **15**:293–300.
- ³⁰ Hernandez CJ, Beaupré GS, Carter DR: **A model of mechanobiologic and metabolic influences on bone adaptation.** *Journal of rehabilitation research and development* 2000, **37**:235–44.
- ³¹ Power J, Poole KES, Van Bezooijen R, Doube M, Caballero-Alías AM, Lowik C, Papapoulos S, Reeve J, Loveridge N: **Sclerostin and the regulation of bone formation: Effects in hip osteoarthritis and femoral neck fracture.** *Journal of bone and mineral research the official journal of the American Society for Bone and Mineral Research* 2010, **25**:1867–1876.
- ³² Bell KL, Loveridge N, Jordan GR, Power J, Constant CR, Reeve J: **A novel mechanism for induction of increased cortical porosity in cases of intracapsular hip fracture.** *Bone* 2000, **27**:297–304.
- ³³ Frost HM: **A determinant of bone architecture. The minimum effective strain.** *Clinical Orthopaedics and Related Research* 1983, **175**:286–292.
- ³⁴ Dempster DW, Parisien M, Silverberg SJ, Liang XG, Schnitzer M, Shen V, Shane E, Kimmel DB, Recker R, Lindsay R, Bilezikian JP: **On the mechanism of cancellous bone preservation in postmenopausal women with mild primary hyperparathyroidism.** *The Journal of clinical endocrinology and metabolism* 1999, **84**:1562–6.
- ³⁵ Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux JP, Portero-Muzy N, Delmas PD: **Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: a bone biopsy study.** *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2007, **22**:1502–9.
- ³⁶ Janssens K, Ten Dijke P, Janssens S, Van Hul W: **Transforming growth factor-beta1 to the bone.** *Endocrine Reviews* 2005, **26**:743–774.
- ³⁷ Bonewald LF, Mundy GR: **Role of transforming growth factor-beta in bone remodeling.** *Clinical orthopaedics and related research* 1990:261–76.
- ³⁸ Tripathi RC, Borisuth NS, Kolli SP, Tripathi BJ: **Trabecular cells express receptors that bind TGF-beta 1 and TGF-beta 2: a qualitative and quantitative characterization.** *Investigative Ophthalmology & Visual Science* 1993, **34**:260–263.
- ³⁹ Zebaze RMD, Jones A, Welsh F, Knackstedt M, Seeman E: **Femoral neck shape and the spatial distribution of its mineral mass varies with its size: Clinical and biomechanical implications.** *Bone* 2005, **37**:243–252.
- ⁴⁰ Tobin W: **The Internal Architecture of the Femur and its Clinical Significance.** *Journal of Bone and Joint Surgery* 1955, **37A**:57–72.
- ⁴¹ Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB: **Predicting Proximal Femoral Strength Using Structural Engineering Models.** *Clinical Orthopaedics and Related Research* 2005, **&NA**:219–228.
- ⁴² LeBlanc AD, Driscoll TB, Shackelford LC, Evans HJ, Rianon NJ, Smith SM, Feeback DL, Lai D: **Alendronate as an effective countermeasure to disuse induced bone loss.** *Journal of musculoskeletal & neuronal interactions* 2002, **2**:335–43.
- ⁴³ LeBlanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM: **Bone mineral loss and recovery after 17 weeks of bed rest.** *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 1990, **5**:843–50.
- ⁴⁴ Lang TF, Leblanc AD, Evans HJ, Lu Y: **Adaptation of the proximal femur to skeletal reloading after long-duration spaceflight.** *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2006, **21**:1224–30.
- ⁴⁵ Tsangari H, Findlay DM, Fazzalari NL: **Structural and remodeling indices in the cancellous bone of the proximal femur across adulthood.** *Bone* 2007, **40**:211–7.
- ⁴⁶ Bousson VD, Adams J, Engelke K, Aout M, Cohen-Solal M, Bergot C, Haguenaer D, Goldberg D, Champion K, Aksouh R, Vicaud E, Laredo J-D: **In vivo discrimination of hip fracture with quantitative computed tomography: results from the prospective European Femur Fracture Study (EFFECT).** *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2011, **26**:881–93.