The Digital Astronaut Project Computational Bone Remodeling Model (Beta Version) Bone Summit Summary Report

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1 PURPOSE OF THE DAP BONE REMODELING MODEL

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 has shown that existing exercise countermeasures are not as effective as desired for preventing bone loss in long duration, 4 to 6 months, spaceflight [1,3,5,6]. This spaceflight related bone loss may cause early onset of osteoporosis to place the astronauts at greater risk of fracture later in their lives. Consequently, NASA seeks to have improved understanding of the mechanisms of bone demineralization in microgravity in order to appropriately quantify this risk, and to establish appropriate countermeasures [7].

In this light, NASA's Digital Astronaut Project (DAP) is working with the NASA Bone Discipline Lead to implement well-validated computational models to help predict and assess bone loss during spaceflight, and enhance exercise countermeasure development. More specifically, computational modeling is proposed as a way to augment bone research and exercise countermeasure development to target weight-bearing skeletal sites that are most susceptible to bone loss in microgravity, and thus at higher risk for fracture. Given that hip fractures can be debilitating, 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, proximal femur and calcaneus.

The DAP has currently established an initial model (Beta Version) of bone loss due to skeletal unloading in femoral neck region. The model calculates changes in mineralized volume fraction of bone in this segment and relates it to changes in 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.

The DAP bone model is unique in several respects. In particular in takes former models of volume fraction changes one step higher in fidelity and separates 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. In another respect, the modules allow the functional description of the time rate of change of other parameters and variables in the model during a computational simulation. More detailed description of the model, preliminary validation results, current limitation and caveats, and planned advancements are provided in sections 2 through 5.

The DAP bone model is being developed primarily as a research tool, and not as a clinical tool like QCT. Even if it transitions to a clinical tool, it is not intended to replace QCT or any other clinical tool. Moreover, the DAP bone model does not 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. This data can then be used as input to the Keyak [8] (or equivalent) FE analysis method to gain insight on how bone strength may change during and after flight. This information can also be useful to help optimize exercise countermeasure protocols to minimize changes in bone strength during flight, and improve regain of bone strength post-flight. To achieve this goal, the bone model will be integrated with DAP's exercise countermeasure models to simulate the effect of exercise prescriptions on preserving bone. More specifically, 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. Figure 1 illustrates this application process.

The bone remodeling model will be particularly be useful for providing data for time periods where QCT is not available. Currently, because only few QCT scans can be acquired from each crewmember, FE strength analyses can only be done at specific snapshots in time. Furthermore, there is currently no way to track or predict bone changes during flight to accurately track changes in cortical and trabecular bone. Therefore, the model can be used to estimate the time course change of vBMD during an exploration mission and between the scans astronauts undergo after they return to Earth. This data can then be used for FE strength analysis method to gain insight on how bone strength may change over time and to refine exercise countermeasure protocols to minimize changes in bone strength during flight, and improve regain of bone strength post-flight (Figure 1).

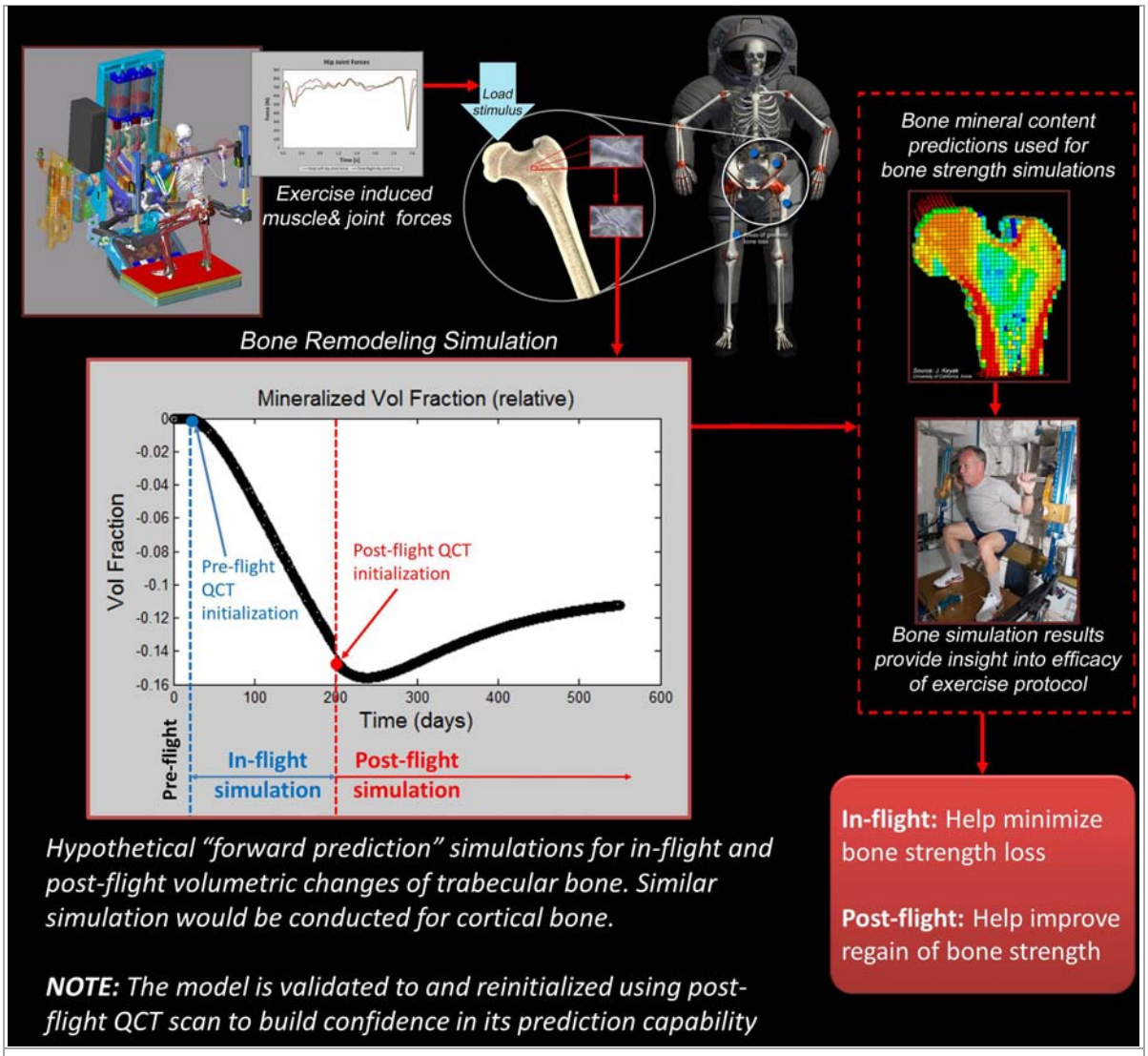

Figure 1: Illustration of how the DAP bone remodeling model will be used to perform "forward prediction" simulations to gain insight on the volumetric changes in bone and how bone strength is affected based on FE method.

2 OVERVIEW OF THE DAP MODEL

The Digital Astronaut Project (DAP) bone remodeling computational model (Beta Version) consists of a 1st order nonlinear system of differential equations that govern the time rate of change in bone via the bone remodeling process. To account for change, the model tracks BVF 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*. 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 differences between trabecular bone and cortical bone are captured in part by the differences in the geometry and the process of removal/replacement in the remodeling units. In trabecular, the structural unit is a packet shaped like a crescent (hemi-osteon) on the surface of a rod or plate like element. In cortical bone the structural unit is a single Haversian system (Osteon) shaped like a cylinder and referred to as a cutting cone [9]. Differences in other parameters, like activation density also distinguish trabecular bone from cortical bone. Thus, there are two separate computational modules: one for trabecular bone and one for cortical bone.

The normalized active cell populations are themselves governed by equations in the system that 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 [10]. Rather, it is a category that uncommitted progenitors commit to differentiating into. *Osteoblasts progenitors* are modeled implicitly as a reservoir source as well as the *osteoclasts progenitors.* .

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. In particular, the RANK-RANKL-OPG signaling pathway discovered in the mid-90s is the essential part of the cellular dynamics. 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 fundamental principle under which the model is implemented computationally.

Another key element is the mathematical formulation of the effects of nitric oxide and prostaglandin E_2 which takes into account the contribution to the bone remodeling and bone density balance from skeletal loading. 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. 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. 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 M and osteoid volume O, and hence a decrease in BVF. Although the skeletal loading contribution to the maintenance of bone health has been modeled in, it is important to realize that mechanotransduction theory requires phases from mechanocoupling to the final effector response. Mechanical signals can directly affect bone cells or be turned into chemical signals. The effector cells, i.e., osteoblasts and osteoclasts, respond to the original stimulus via a complicated cascade of events, the details of which are not yet fully established. Frost's mechanostat theory that relates loading-induced strain magnitudes to bone gain or bone loss, defines a lower threshold or minimum effective strain. The model incorporates the more comprehensive concept of a minimum effective strain stimulus which can take into consideration strain rate as opposed to strain magnitude only. The mathematical formulation develops the concept of a mechanical stimulus "strength" that quantifies the average daily strain accumulated from dynamic loading. Other than a zero load for complete disuse, this aspect of the model needs testing and further development with regard to specific exercise-induced loading. Therefore, the current beta version of the DAP bone remodeling model considers only the bone deconditioning due to mechanical unloading.

In short, the model consists of three major research areas, (1) the orthopedic science or 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 [11].

Values associated with parameters referred to in the discussion thus far are still under active research by scientists. Due to the uncertainty and variability, 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 0.5 mm for trabecular hemi-osteon is used based on values reported in [12–15]. For cortical bone, femoral neck values for osteonal diameter and Haversian canal diameter were used that were reported for controls in studies of hip fractures and osteoarthritis in [16,17].
- ***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) can be used [18]. In the case of trabecular average values reported vary greatly. A sample includes 0.45/yr reported by Dempster et al. (1999) [19],

0.53/yr reported by Chapurlat et al. (2007) [20], 0.42/yr reported by (Mayo Clinic ppt). Since our model uses 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.

- ***TGF-beta 1:*** Because the amount of TGF-beta 1 involved in the remodeling process comes from the amount released during bone resorption we needed a value of the amount contained in bone. A value of 200 μg/kg is reported by Janssens et al. (2005) and Bonewald and Mundy (1990) [21,22].
- ***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) is used [23].

Given that remodeling is the normal physiological mechanism for bone replacement or repair in the adult skeleton, the computational model is best suited for the mature adult between 25 and 55 years of age, or typical age of an astronaut. The primary application of the DAP bone remodeling model is to track bone loss in astronauts during spaceflight and bone recovery post flight. Skeletal sites at high risk include the proximal femur (femoral neck), lower lumbar spine, and calcaneus. Our current efforts in developing the model are aimed at the femoral neck since the femoral neck has been identified as the site with the highest risk for fracture.

The shape of the femoral neck conforms approximately to a "short" cylindrical cylinder and acts like a cantilever during locomotion [24]. Trabeculae that accommodate tensile stresses and trabeculae that accommodate compressive stresses intersect at right angles in a significant part of the neck [25]. We assume that due to the approximate regular geometry of the femoral neck, the BVF of volume elements throughout the neck will not vary widely. Therefore the vBMD and BVF of the representative volume element of the computational model and its adaptive changes can be expected to represent an estimate of the average value of the femoral neck's volume elements.

Currently, the model implementation is coded with a specific scheme to match vBMD values from QCT scanning technology presently use by NASA for flight and bed rest studies, and under consideration for use as part of the new bone strength standard measure. Correlation equations relating vBMD to ash density developed by Keyak [8] are used in the first step of the scheme to eventually relate ash density to mineralized volume fraction.

We are validating the model's capability to represent deconditioning of the femoral neck due to unloading using data from control subjects participating in the current 70-day bed rest study (CFT70), a 17-week bed rest study reported in [26,27], as well as literature data for BVF simulations. More specifically, we use pre-bed rest and post-bed rest QCT and DXA density scans obtained from control subjects to validate the model's ability to track trabecular and cortical vBMD, and integral BMDa changes. We also compare the simulated BVF with experimental values reported in literature. Section 3 discusses the preliminary validation results for the beta version of the bone model.

3 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 used for the intended application as described in section 1. 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 of a specific parameter or variable under consideration (e.g. BMD or BVF) in comparison to 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.

3.1 PRELIMINARY VALIDATION OF VOLUMETRIC BONE CHANGE SIMULATIONS

3.1.1 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 report 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 [28]. In addition, data presented in [29] shows that the trabecular vBMD for the femoral neck and the intertrochanteric region are 146.92 $\pm$ 77.98 mg/cm^3 and 141.04 $\pm$ 81.02 mg/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.

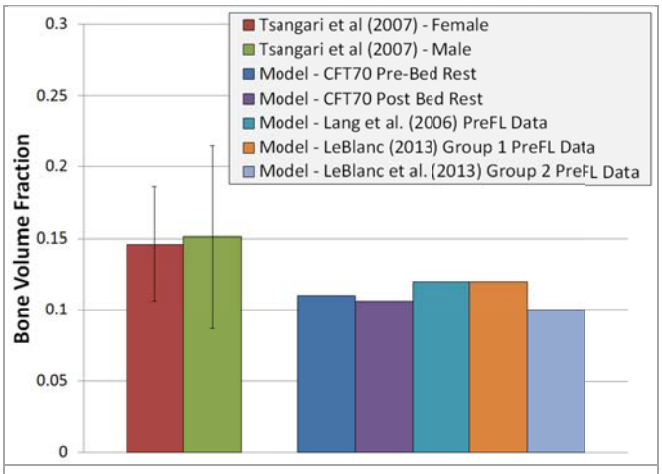

Figure 2: Validation of simulated trabecular bone volume fraction by comparing against experimental data presented in [28].

Comparing the BVF values calculated by the model using the group mean data from the CFT70 bed rest control subjects as well as those presented in [1,6], the model results are still within the standard deviation of the experimental trabecular BVF values reported in [28] (Figure 2). This suggests a good foundation has been established for appropriately defining the base BVF equation to track trabecular bone remodeling. We have not, however, yet validated for cortical BVF simulations because we were able not find cortical BVF data.

3.1.2 Trabecular vBMD

The trabecular bone remodeling module was validated 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 5210 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 more representative of an aged person, and not of the astronaut 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.

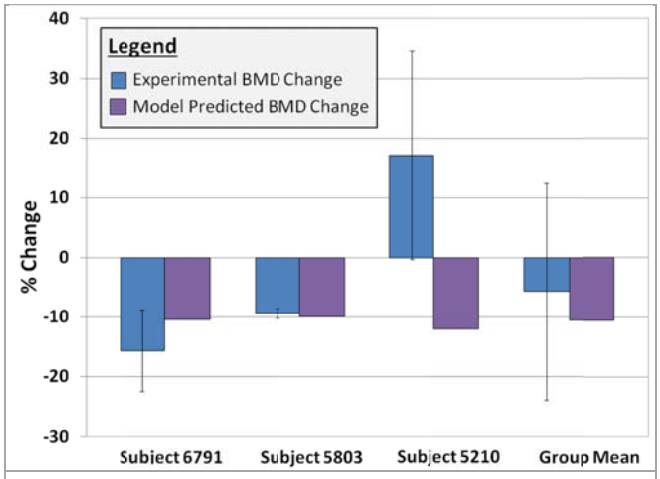

Figure 3: Comparison of model simulation results for percent change in trabecular vBMD with experimental data for three control subjects who participated in CFT70.

3.1.3 Cortical vBMD

We performed validation analysis of the cortical bone remodeling module 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 subject 5803 and the mean vBMD for the control group. However, the model under predicts the amount of bone lost for subject 6791 and did not match the bone gain trend observed in subject 5210. The cause of these discrepancies between simulation 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 of cortical bone loss at the femoral neck.

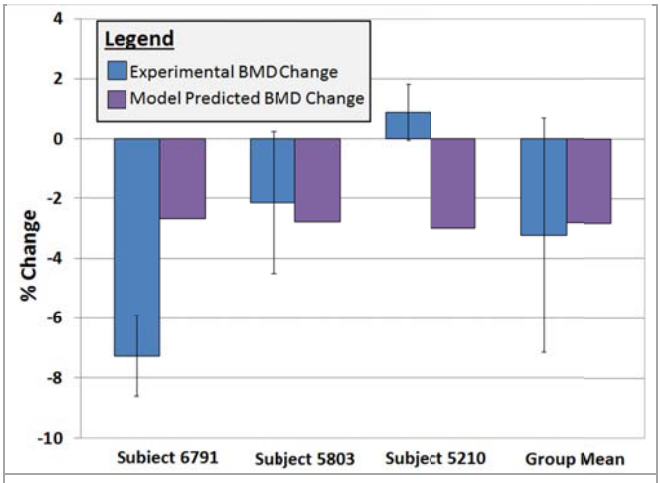

Figure 4: Comparison of model simulation results for percent change in cortical vBMD with experimental data for three control subjects who participated in CFT70.

3.1.4 Preliminary Validation for Long Duration Simulation using BMDa 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) [26,27].

In order to be able to use the use DXA BMDa to validate the model, we developed a regression method to map BMDa 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. The methods used to develop and verify the regression method for applicability to the available experimental data within the 95th confidence and prediction intervals are described in the DAP Bone Model Description report [30].

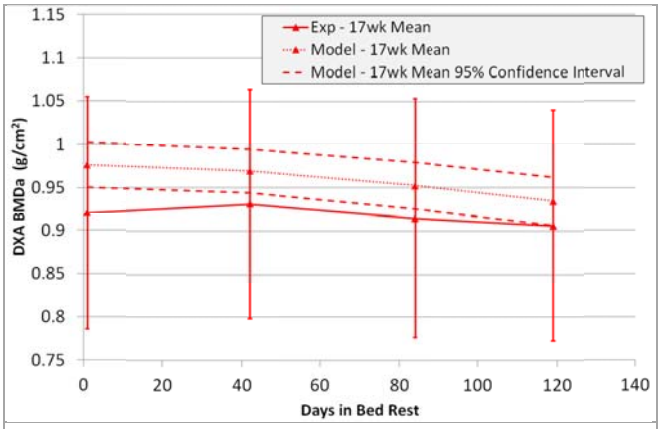

Figure 5: Comparison of model simulation results against experimental data for group mean predictions of time course change of BMDa for 18 control subjects who participated in a 17-week (4 months) bed rest study reported in [26,27].

As it can be seen in Figure 5, the model predicts time course change of mean BMDa 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.

4 LIMITATIONS AND CAVEATS

The DAP bone remodeling model has a number of limitation that should be noted by the users. Some of these limitations are a direct consequence of the limited knowledge regarding bone remodeling process, while some limitations 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. 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 good 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 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 model does not include the effects of sclerotin, calcitonin, osteopotin, or Interleukins, some of which may play a role in the difference between bone loss in microgravity and disuse bone loss 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. Changes can change the results.
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. Further testing with additional data is needed.

5 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 bone loss.
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 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 endosteal region in additional to the trabecular and cortical regions.
8. Adding age and gender related dependencies.

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