Fiscal Year:	FY 2014	**Task Last Updated:**	FY 05/02/2014
PI Name:	Pennline, James Ph.D.		
Project Title:	Digital Astronaut: Bone Remodeling Model		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Bone Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (2) **Osteo**:Risk Of Early Onset Osteoporosis Due To Spaceflight		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	Directed Research
Start Date:	04/01/2011	**End Date:**	09/30/2017
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: Extended to 9/30/2017 per D. Griffin/GRC (HRP monitor)--Ed. 10/9/15		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Mulugeta, Lealem (Universities Space Research Association)		
Grant/Contract No.:	Directed Research		
Performance Goal No.:			
Performance Goal Text:			
	Background 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. The most commonly used countermeasure against bone loss in microgravity has been prescribed exercise. However, data has shown that existing exercise countermeasures are not as effective as desired for preventing bone loss in long duration spaceflight. 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.		

Task Description:	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. Methods 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 or anti-proliferation is respectively either directly proportional or inversely proportional to receptor occupancy ratio. In implementation, the bone remodeling model is based on a first principles physiological and mathematical description of the components of bone physiology, including responses by the endocrine, biochemical, autocrine, and paracrine systems. The model mathematically formulates the key elements based on well-accepted knowledge and experimental studies of bone. In particular, the model uses the RANK-RANKL-OPG signaling pathway to describe the cellular dynamics. For skeletal loading, the model includes the effects of nitric oxide and prostaglandin E2. In the computational model, reduced skeletal loading triggers a decrease in nitric oxide (NO) and rostaglandin E2 (PGE2), 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 bone volume fraction (BVF). The loading portion of the model is based on the concept of a minimum effective strain stimulus, which takes into consideration strain rate as opposed to strain magnitude only. Specific Aims 1. For individuals in the age range of the astronaut corps, predict changes in trabecular and cortical volumetric bone mineral fraction and density as a function of time since measurement, gravity level, and applied loads 2. Support the bone fracture standard by accepting and providing data in the same form as that of a Quantitative Computed Tomography (QCT) scan.
Rationale for HRP Directed Research:	This research is directed because it contains highly constrained research, which requires focused and constrained data gathering and analysis that is more appropriately obtained through a non-competitive proposal. This task meets the requirements for being tightly coupled with NASA efforts and therefore not amenable to solicitation because it: 1. Must be tightly coupled with integrated exercise biomechanical/device models that NASA is currently developing in-house. Otherwise, the bone remodeling model will have little utility for NASA because it will not be able to predict the time course change of vBMD in reduced gravity as a function of time and how exercise prescription can be optimized to counteract bone loss. 2. Must be tightly integrated with the QCT-based NASA bone strength standard. The bone remodeling model will provide valuable additional data via "forward prediction" simulations for during and after spaceflight missions to be used as input to the new bone strength FE analysis method to gain insight on how bone strength may change during and after flight. The bone remodeling model will be particularly be useful for providing data for time periods where QCT is not available, such as during flight. Under such cases, the model will 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 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.
Research Impact/Earth Benefits:	The discoveries made through this work can have spin-off benefits to terrestrial healthcare by providing fundamental methods that can be further built upon to: (1) Gain further insight on the mechanisms and influence on the bone remodeling process and its implications in bone health and other health risks to patients who are bed-ridden or immobilized due to: * Long term illnesses; * Post-op surgery; * Limb fractures; and/or * Spinal injury, to name a few (2) Design exercise prescriptions for patients who have experienced bone demineralization from bed-ridden or immobilized disuse indicated in 1, in order to help them recover bone and minimize bone fracture. (3) Investigate the level of regular activity or exercise people should be engaged in to ensure healthy bones throughout their lives, particularly in minimizing or preventing age related osteoporosis.
	A mathematical model of bone remodeling, the physiological mechanism for maintenance, renewal, and repair in the adult skeleton, was developed. The model consists of three major aspects of the remodeling process: (1) The removal and replacement of bone packets via remodeling units, which is done by the coupled action of bone cells on the same cell surface. Bone resorbing cells, osteoclasts, remove old or damaged bone. Then bone forming cells, osteoblasts, fill in new bone. (2) The biology and physiology of the cellular dynamics of remodeling units. This includes the effects of hormones and biochemical mediators that drive the dynamics. (3) Mechanotransduction, which describes the function of skeletal loading in maintaining bone health and strength. The model includes the release of NO and PGE2 by the sensing cells, osteocytes, as a result of cyclic loading, which can act as anabolic mediators. The mathematical formulation that captures the aspects of the bone remodeling process consists of a system of 1st order nonlinear differential equations. The basic state variable is the rate of change of Bone Volume Fraction (BVF) of a

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representative volume element of a specific skeletal site or bone segment. Since a bone segment can have voids, BVF is defined as the volume of bone tissue divided by the total volume. The computational model can simulate the rate of change of BVF separately in the trabecular region (spongy interior bone) and in the cortical region (compact outer layer) by using the differences in the geometry of the remodeling units. In trabecular bone the cells remove and replace a crescent shaped hemi-osteon on the surface of trabeculae, while in cortical bone the remodeling unit is a cylindrical shaped cutting cone. Other parameter values, for example activation frequency of remodeling units, distinguish trabecular bone from cortical bone.

Given that hip and proximal femur are dynamic load bearing sights susceptible to microgravity induced demineralization and potentially debilitating fractures the initial model development focused on the femoral neck. Using average, cortical remodeling unit dimensions from experimental studies and estimates of other parameters, a computational beta model of bone loss due to skeletal unloading in the femoral neck was established.

In general, the computational simulations in time work as follows. Volumetric bone mineral density (vBMD) for cortical and trabecular regions of a skeletal site are provided by Quantitative Computed Tomography (QCT). A mapping converts vBMD to BVF through conversions to ash density. Until unloading is invoked, the equations maintain an approximate steady state or balance of the processes of bone resorption and bone formation, i.e., the rate of change of BVF is approximately zero. The balanced processes are influenced by endocrine regulation, biochemical mediations, and skeletal loading modeled in the equations. Since it eliminates any disturbances in the balance caused by disease, injury, or age related osteoporosis, the balanced assumption restricts the application of the model to the healthy adult in the age range of an astronaut. A simulation will maintain steady state until skeletal loading is decreased or the skeletal site is unloaded, which triggers a negative rate of change in BVF. Then, integration in time of the rate of change reveals a loss of BVF which is related to a loss in vBMD.

A preliminary validation of the model's capability to represent deconditioning of the femoral neck due to unloading was carried out for control subjects in two bed rest studies.

(1) The current 70-day bed rest study (CFT70). The model results were able to match experimental values within one standard deviation of two out of three of the control subjects and the group mean for both trabecular and cortical regions. The third subject, whose experimental data did not match simulation results, was identified to have a baseline trabecular and cortical vBMD consistent with values observed in an elderly person with age related bone loss. 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. This is still under investigation.

(2) A 17 week bed rest study reported in the literature. Since spaceflight missions are much longer than 70 days and QCT data for bed rest controls is not available for more than 70 days, DXA aBMD data was collected for 18 control subjects from a 17 week bed rest study (4 months). Because the model uses vBMD and BVF, a regression method was developed to map aBMD to vBMD using total femur DXA and QCT data from a previous flight study. Comparing to experimental data, model prediction of time course change through the 120 days of mean aBMD was found to be within one standard deviation of the experimental error.

The preliminary 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 bed rest conditions. It also shows some limited capability to predict subject specific trends in vBMD changes under bed rest 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.

Building the effects of exercise induced skeletal loading in spaceflight into the bone remodeling model has progressed as follows:

A literature review was conducted that focused on methods or results for determining the stress/strain in the proximal femur due to specific exercise activities, finite element methods used in performing estimates of stress/strain, and bone models predicting time course adaption of bone to loading or any related articles. Among articles found on determining bone stress/strain from exercise, a 1996 paper entitled "Biomechanical Analysis of an Exercise Program for Forces in the Hip Joint and Femoral Neck" calculated maximum stress for walking, jogging, and eight weight training exercises. However it was limited to a specific section of inferior surface of the cortex in a cross section of the femoral neck, using elementary beam theory. A more recent 2012 dissertation from Finland university, "Flexible Multibody Approach in Bone Strain Estimation during Physical Activity: Quantifying Osteogenic Potential," determined strain values from knee flexion, knee extension, leg press, squat, and walking but the work was restricted to the tibia. Several articles report on a finite element analysis of the stress distribution in the femoral neck and proximal femur. A 2004 article titled "Stress Fracture Analysis of the Human Femur based on Computational Biomechanics" simulates force transmitted through the hip joint during the single leg stance phase of normal running or jumping to estimate the Von Misses stress distribution in the proximal femur. A 2011 article titled "Finite Element Analysis of Femoral Neck Stress in Relation to Pelvic Width" compares maximum principle stress distribution in femoral neck for a narrow pelvic and a wide pelvic in a one-legged stance. There are inconstancies though in values used for compressive modulus and in the results. A 2011 article has a limited summary on "Estimating Lower Limb Skeletal Loading" and review techniques such as multibody dynamics and Ground Reaction Force (GRF), and inverse dynamics from commercially available software such as LifeMOD plus a finite element analysis. An important point made in this article is that estimating the magnitude of stresses and strains based on external forces only like GRF or joint moment and ignoring internal forces like muscle forces may lead to significant error in the calculations.

A through study was done on the concept of a Daily Load Stimulus (DLS) and an osteogenic potential associated with exercise induced cyclic loading. Since various formulae have been used in conducting experimental studies in humans as well as animals, a comparative study was conducted. It focused on the ability of the different expressions to relate to magnitude of stress or strain, strain rate, loading cycles or repetitions, as well as the potential to capture the effects of saturation of continuous loading and benefits of rest insertion combined with multiple shorter bouts. A NASA Technical Memorandum was written that summarizes these findings (TM NASA/TM-2014-218306 – In Press). Responses from email requests to authors and researchers in the area of time course adaptation of bone to loading from exercise or other activities was limited. Two researchers, one from the University of California, Davis, Biomedical Engineering and one from the Indiana U-Purdue U Indianapolis (IUPUI) Department of Biomedical Engineering, discussed some of the issues regarding quantification of bone loading. While adaptation due to disuse can be modeled, quantification of bone loading and response to loading is difficult and challenging.

	Ultimately a finite element model (FEM) will be needed to determine the strains/stresses within the femoral neck and pass these results to the computational model to track changes in bone volume fraction. Since the biomechanical models have not progressed to the point of being able to provide estimates of forces and loads on joints at skeletal sites from exercise that can be passed to a FEM, a plan for an interim solution is being developed. Based on knowledge gaps and lack of examples of DLS formulae that have summed a daily load contribution from more than one specific exercise, development of a conceptual method of estimating load contribution is part of the plan. Translation of the conceptual load contribution via a DLS in terms of a daily strain or stress and the resulting bone remodeling response into an algorithm to be tested is another part of the plan.
Bibliography Type:	Description: (Last Updated: 09/10/2018)
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NASA Technical Documents	Chang KL, Pennline JA. "Predicting bone mechanical state during recovery after long-duration skeletal unloading using QCT and finite element modeling." Cleveland, Ohio : NASA Glenn Research Center, 2013. NASA Technical Publication NASA/TM - 2013-217842. http://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20130011517.pdf , Feb-2013
Papers from Meeting Proceedings	Pennline J, Mulugeta L. "A Computational Model for Simulating Spaceflight Induced Bone Remodeling." 44th International Conference on Environmental Systems, Tucson, Arizona, July 13-17, 2014. 44th International Conference on Environmental Systems, Tucson, Arizona, July 13-17, 2014. ICES Paper ICES2014-513-83. , Jul-2014