TITLE

Disuse-related bone loss prediction using a multiscale mechanobiological model of bone remodeling

ABSTRACT
Disuse during immobilization or microgravity results in excessive bone loss. The magnitude of bone loss is site dependent and even within a specific location, bone mineral is not lost homogenously. The interaction of bone loss with measures of lifestyle or environment are difficult to assess *in vivo,* as different combinations of these factors cannot be investigated in the same person. ESA bedrest studies offer very well controlled study settings and despite small single study data sets, the level of standardization is unique. This allows to employ mathematical models of bone remodeling to simulate different scenarios and their effects on bone health, while enabling calibration of the models with the available high-quality ESA data sets. Mechanistic mechanobiological models of bone remodeling allow to investigate anabolic and catabolic regulatory pathways and have been used extensively in the assessment of bone loss in osteoporosis research. We propose to adapt the existing models to the bedrest studies and implement countermeasure effects based on the requested real data with the goal to personalize the bone models by using optimization approaches. With this, we aim to enable prediction of the individual response to disuse and countermeasures and extrapolate our findings to longer duration space flight (e.g. crewed mission to Mars or living in Moon habitats). While extrapolation can be based on statistical methods, given the complex cellular and mechanobiological interactions in bone remodeling, bone models may be able to enhance the accuracy of such predictions. We have assembled a highly qualified science team complementing longtime experience in computational modeling of mechanobiological regulation of bone, optimization and optimal control in biomechanics, and extensive experience in microgravity research of the musculoskeletal system resulting in additional available data sets related to those available in this ESA AO.

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Please provide the title and name of the proposal coordinator.

PD Dr Anna-Maria Liphardt

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ACRONYM*

Please provide an abbreviation or acronym for your proposal.

BoLoMo

SCISPACE SPOTLIGHT*

Please select one or more of the SciSpacE spotlights that the proposed science activity can contribute to addressing.

X Humans Living on Moon and Mars
X Astronaut 2.0
Space Travel and Transport
Extraterrestrial Life
Fundamentals of Nature
Nature of Exploration Destinations

RESEARCH QUESTION*

Please add here as precisely and briefly as possible the research question. Please find under this link an explanation of what is expected as research question.

With our here proposed project we aim to investigate the following research questions:

1. Primary research questions
    1.1. Can existing state-of-the-art mechanobiological models of bone remodeling predict bone loss during mechanical disuse scenarios?
    1.2. What is the best way to integrate imaging and biomarker data in mechanobiological models of bone remodeling?
    1.3. How are subject-specific characteristics linked to personalized model parameters in mechanobiological models of disuse?

2. Secondary research questions
    2.1. Can the bone model be used to extrapolate the time effect of disuse on bone health (e.g. including microgravity and longer space mission times > 6 months)?
    2.2. Can countermeasures such as nutrition and exercise be integrated into mechanobiological models of bone remodeling?
    2.3. Is it possible to optimize countermeasures to minimize bone loss due to mechanical disuse based on mechanobiological models of bone remodeling?
    2.4. Can mechanobiological modeling support the identification of the most preferable characteristics for an ideal skeleton for exploration missions?
    2.5. How can the effect of radiation exposure be integrated in mechanobiological models of bone remodeling (based on clinical and animal data)?

SCIENTIFIC JUSTIFICATION AND HYPOTHESIS*

Please describe what will be accomplished or tested in the project.
Please list the different hypothesis(es) clearly and succinctly. How does the proposed research extend our understanding of the phenomena being investigated? How does it elaborate, extend, or fill in gaps in our present knowledge? (2000 words)

General

It is well known that disuse during immobilization or microgravity results in excessive bone loss (Vico and Hargens 2018). The magnitude of bone loss is site dependent and even within a specific location, bone mineral is not lost in a homogenous way (Armbrecht et al. 2011; Belavy et al. 2011). The interactions of bone loss with measures of lifestyle (e.g. exercise), nutrition, or environment (e.g. radiation) are difficult to assess *in vivo,* as usually different combinations of these factors cannot be investigated in the same individual. ESA bedrest studies offer very well controlled study settings and even though single study data sets are rather small, they are unique in the high level of standardization. This opens the door to employ mathematical models of bone remodeling (that require high quality data sets for calibration) to simulate different scenarios and their effects on bone health. The duration of bedrest studies is often not sufficient to detect effects with imaging techniques (pQCT) - however, the systemic response in bone biomarkers shows a strong response to disuse that could be integrated using mathematical models.

Space travel will be of longer duration in the future, especially in light of a foreseen crewed mission to Mars and living in Moon habitats. Current study settings and even space missions do not offer research data from studies or flights going beyond one year and extrapolation based on statistical methods alone is not a reliable method, given the complex cellular and mechanobiological interactions in the bone remodeling process. On the other hand, mechanistic mechanobiological models of bone remodeling allow the investigation of different anabolic and catabolic regulatory pathways and have extensively been used in the assessment of bone loss in osteoporosis and for the assessment of efficacy of single and multiple-drug treatments of osteoporosis (Lavaill et al. 2020; Pivonka et al. 2013; Lerebours et al. 2016; Martin et al. 2019; Martínez-Reina and Pivonka 2019; Martonová et al. 2023; Pivonka et al. 2008; Scheiner et al. 2014).

While these models have not yet been used to investigate the effects of space-flight on bone loss, some modeling studies have investigated the effects of mechanical disuse on femur midshaft bone mineral density (Lerebours et al. 2016) and combined drug and exercise to increase bone mineral density (BMD) in the spine and hip (Lavaill et al. 2020; Lerebours et al. 2016; Martin et al. 2019). However, such studies did not have strong experimental data to validate these models and consequently are theoretical in nature. The existing bedrest data would allow to calibrate and validate mechanobiological models of bone remodeling with the objective to be applied in simulations of bone remodeling during space missions. Furthermore, once the model has been validated for the existing time points, one can perform forward simulations to extrapolate bone loss at later time points.

Given that mechanobiological models of bone remodeling contain a significant amount of parameters including mechanosensitivity of osteocytes, cell differentiation and apoptosis rates, rate of bone turnover at a respective bone site, habitual mechanical loading etc., it is essential to use state-of-the-art optimization algorithms to identify these parameters. Once this has been achieved, one may be able to link model parameters with subject characteristics. It has been shown that in individuals with high BMD, the rate of bone loss is higher resulting in excess calcium loss which might lead to damage of organ systems such as the kidney (Buckey, Thamer, and Lan 2023). Furthermore, it is unclear if those sites with greatest bone loss are at highest risk of injury. Having a mechanistic insight in the disuse-related bone loss will allow to identify

indviduals with lower risk of bone loss due to their particular mechanobiological makeup described with a unique set of model parameters.
Despite strong attempts to develop effective countermeasures (e.g. exercise and/or nutritional supplements), the best combination of countermeasures that ideally halt or at least significantly slow down bone loss remains unclear. Especially the inter-individual differences in the response to disuse and the responsiveness to countermeasures could be better understood with the use of model approaches. Mechanobiological models of bone remodeling offer the possibility to include molecular, cellular and tissue level regulatory mechanisms, where these countermeasures may act. Subsequently, optimization algorithms can be used to identify the best combination of countermeasures to reduce bone loss and to even personalize this.
Another risk factor for long term space travel such as the Mars mission is the high radiation exposure for the crew. Ground-based studies show the detrimental effect of ionizing radiation on bone health (Farley et al. 2020; Farris et al. 2020). Mechanobiological models of bone remodeling may help to better understand this response in the scope of long duration exploration missions.

To enable an accurate prediction of the biological response to disuse by a simulation model, calibration of the model with high quality data sets is required to yield personalized parameters. For this personalization as well as to answer further specific research questions, it is necessary to solve a constrained optimization problem. In general, this reads as $\min_x f(x)$ subject to $c_i(x) \leq 0$, where $f(x)$ is an objective function that we want to minimize, x is a vector of unknown model parameters and c_i are the constraint functions, defining certain restrictions that the unknown vector x has to satisfy. Usually, the objective and constraint functions are physiologically motivated, include model equations (describing e.g. bone remodeling or bone loss) and take meaningful bounds on the model parameter values into account. Such model-constrained optimization problems result in complex equations that cannot be solved analytically and therefore require appropriate numerical techniques. Thus, one of the challenges is to formulate a well-defined constrained optimization problem, and then to approximate it with a suitably accurate numerical method (Leyendecker et al. 2010; Betts 2010; Gerdts 2012; Penner and Leyendecker 2020).

Based on the above and in relation to our primary research questions, we are hypothesizing that:

1.1 Existing state-of-the-art mechanobiological models of bone remodeling are able to predict bone loss during mechanical disuse scenarios.

1.2 Integration of imaging and biomarker data improves models of bone remodeling

1.3 Subject-specific characteristics allow the optimization of the model parameters in mechanobiological models of disuse.

With respect to our secondary research questions we further test and explore the following hypothesis:

2.1 Models of bone remodeling can be used to extrapolate the time effect of disuse including microgravity on bone health to longer space mission times.

2.2 High quality data from bedrest studies allow integration of the effects of countermeasures (e.g. nutrition and exercise) into mechanobiological models of bone remodeling.

2.3 Mechanobiological models of bone remodeling can be used to optimize countermeasures for minimizing bone loss during mechanical disuse.

2.4 Mechanobiological models of bone remodeling can be used to support the identification of an ideal skeleton for a mission.

2.4 Effects of radiation exposure based on clinical and animal data can be integrated in mechanobiological models of bone remodeling.

APPROACH*

This section should include the research plan, planned data analysis, and significance of the study. (max. 2000 words)

Requested data

For our proposed analysis we are requesting all bone biomarker data (urine and blood biomarkers) and bone imaging data (DXA, pQCT, HR-pQCT, 3D pQCT) from all available studies and all available study groups. Additionally, subject characteristics (age, sex, height, body mass) and body composition (from DXA) are requested. Skeletal loading history will be estimated from muscle and cardiovascular performance data. More specifically we are requesting:

- Core data
- Bone system biomarkers in blood and urinary bone markers
- DXA variables and DXA body composition
- pQCT data
- 3DpQCT (HRpQCT) outcomes
- Maximum voluntary contraction and muscle fatigue
- Vertical jump test
- Blood variables
- Plasma volume outcomes
- Aerobic fitness assessment
- Dynamic gait index test
- Computerized dynamic posturography
- Body mass

Work packages / Research plan

The proposed work packages (WPs) group the diverse aspects thematically and show the planned development and the relation to the respective hypothesis.

WP1 (data management): In case of a successful application, FAU, UKER and QUT will set up a formal data and research agreement between each other. This agreement will regulate data use, data storage and joint publications.

After receiving the files with the requested data, we will use R and Python software to merge all the files. In this way, a master file with all the requested data will be created that is highly consistent in terms of variable names, study of origin, and time of data collection, for example. In addition, this strategy provides a high level of traceability and transparency since we can share the codes used. The next step will be to automatically import all data into a data management system specifically designed for clinical trials and human studies, namely Research Electronic Data Capture (REDCap). This system complies with current European data protection regulations (GDPR) and is offered and supported by the institution of the proposal coordinator. Access to the data set can be granted by the above mentioned data and research agreement between the institutions. This will allow the research team to share data across countries and laboratories in a secure and efficient manner.

Data will only be extracted by members of the research team for specific analysis. Importantly, any access or activity in/with the REDCap database will be logged, so that it can be tracked. For the implementation of the data into the bone model, relevant parameters can then be exported from REDCap into csv files. Implementation of the data into the model will be done locally on FAU and QUT computers and networks. For long-term data storage of the code

needed for the model and optimization, the GitHub repository will be used. It includes all relevant data and information ensuring reproducibility of all results at any time. Additionally, as a natural routine, all files will be professionally secured and managed as part of the institute-based and university-wide cascade backup system.

The plan described here is preliminary and based on information available to PIs at the time of submission (September 22nd, 2023). Final decisions on the data management plan will be formulated once the research team receives the data and will depend on the nature of the data (e.g., type of files, size of files, etc.).

WP2 to WP7 address the research questions/hypothesis. For the proposed research project, we will use the mechanobiological model of bone remodeling developed by Dr Pivonka's group (Lerebours et al. 2016). This model is formulated on a representative volume element (RVE) scale and contains different types of bone cells which are coupled through mechanobiological regulatory factors including RANKL, OPG, RANK and TGF-beta to name a few. These can be related to the biomarkers measured in the ESA bedrest studies. Active osteoclasts resorb bone matrix, while active osteoblasts form bone tissue in the RVE. Given a particular bone site (spine, hip etc) the habitual loading or lack thereof is taken into account in the model by considering the induced stress/strain state in the RVE which is sensed by osteocytes to regulate sclerostin and in turn the anabolic Wnt pathway. Mechanical disuse will induce catabolic regulatory mechanisms linked to RANKL upregulation by osteocytes which will lead to increased osteoclast numbers and consequently increased bone loss (Lavaill et al. 2020; Lerebours et al. 2016; Martin et al. 2019). Mechanobiological feedback is incorporated into this model (Lavaill et al. 2020; Lerebours et al. 2016; Martin et al. 2019) based on Frost's mechanostat theory.

WP2 (hypothesis 1.1)
1.1 Existing state-of-the-art mechanobiological models of bone remodeling are able to predict bone loss during mechanical disuse scenarios.

Modeling: To address hypothesis 1.1, we will (i) estimate the pre-bedrest habitual loading status of individual subjects. For the hip, this will be achieved through estimation of the stress/strain loading state during gait (e.g. either based on data from the ESA bedrest studies if available or from literature values), which is assumed the most prevalent habitual loading on the femur bone. (ii) Depending on the available experimental bone density data, we will estimate the pre-bedrest BV/TV data at the particular bone site as the initial condition for our simulations. (iii) Depending on the bone metabolism of individual subjects, different rates of bone turnover need to be assigned to each bone site. The latter are reflected in different bone cell numbers in the RVE. (iv) With the so selected initial conditions, we will simulate homeostatic conditions characterized by BV/TV=const, no bone loss or gain at different bone sites; (v) Bedrest experiments will be simulated by reducing the habitual loading state to account for reduced mechanical loading. While the habitual loading will be reduced for most bone sites, some sites such as the skull might experience increased loading during bedrest.

WP3 (hypothesis 1.2)
1.2 Integration of imaging and biomarker data improves models of bone remodeling.

Modeling and optimization: To address hypothesis 1.2, it is necessary to derive mathematical relations between measured data (from imaging and biomarkers) and the model output quantities, such that the prediction accuracy of the model can be assessed and improved.
In particular: (i) Different measured biomarkers (e.g. BAP, CTX, NTX) can be linked to the concentrations of the osteoblasts and osteoclasts used in the model (global, site-unspecific

quantities). (ii) The model output quantity BV/TV can be either compared directly with the measured data or via a transformation function between BV/TV and the measured BMD. (iii) Many other model parameters can be linked to physiological subject specific characteristics by using a meaningful transformation function.

WP4 (hypothesis 1.3)
1.3 Subject-specific characteristics allow the optimization of the model parameters in mechanobiological models of disuse.

Optimization: The described computational model includes many parameters which need to be fitted to the experimental data, respectively individually personalized. For that, we initially test the model sensitivity and identify a set of the most sensitive model parameters denoted by μ. Identification of the most sensitive parameters will first be achieved by statistical methods (e.g. repeated measures analysis of variance (ANOVA) or mixed-effects regression models, Saltelli et al. 2004). Subsequently, these parameters are calibrated to fit the experimental data at different times t well. Thus, the following optimization problem is solved

$$min_{\mu}|BV/TV_{measured,t} - BV/TV_{modeled}(\mu, t)|,$$

where $BV/TV_{measured,t}$ and $BV/TV_{modelt}(\mu, t)$ represent the measured BV/TV (either directly measured or obtained via transformation from the measured BMD, see WP3) and the modeled BV/TV at different times t, respectively.

WP5 (hypothesis 2.1)
2.1 Models of bone remodeling can be used to extrapolate the time effect of disuse including microgravity on bone health to longer space mission times.

Modeling: While bedrest somewhat mimics the effect of microgravity on bone tissue, the question arises, how the microgravity effect can most realistically be added to the mechanobiological model of bone remodeling. Gravity plays a pivotal role in cell biology, acting on cytoskeletal organization and cell structure. Cells can convert mechanical inputs into biochemical signals, initiating downstream signaling cascades in a process known as mechanotransduction. Therefore, any changes in mechanical loading, for example, those associated with microgravity, can consequently influence cell functionality and tissue homeostasis, leading to altered physiological conditions. One way to include the effect of microgravity would be by changing the regulation of osteocyte mechanobiological feedback. If indeed, long-term exposure of osteocytes to microgravity would permanently alter their cytoskeletal structure, this would also explain why astronauts returning to earth are not able to restore bone mass back to normal (Vico et al. 2017). First, the proposed model, including and not including effects of microgravity, will be extrapolated for a longer time scale and compared with available literature data.
Optimization: Subsequently, the model parameters, describing the gravity loss, will be optimized to fit the available experimental data from longer missions.

WP6 (hypothesis 2.2, 2.3, 2.4)
2.2 High quality data from bedrest studies allow integration of the effects of countermeasures (e.g. nutrition and exercise) into mechanobiological models of bone remodeling.
2.3 Mechanobiological models of bone remodeling can be used to optimize countermeasures for minimizing bone loss during mechanical disuse.
2.4 Mechanobiological models of bone remodeling can be used to support the identification of an ideal skeleton for an exploration mission.

Modeling: To address hypothesis 2.2, the mechanobiological model of bone remodeling will be extended to include the effect of nutrition countermeasures as available in the ESA data sets (e.g. protein & bicarbonate supplementation, inti-inflammatory / anti-oxidative supplement). Note that exercise is already included in the model based on the habitual loading state.
Optimization: Using such an extended model, it will be possible to address hypothesis 2.3. For this, by minimizing an appropriate objective function representing bone loss, we will determine an optimal loading (exercises) and nutrition which is needed for the subject to obtain a specific target BV/TV predicted by the model.
To address hypothesis 2.4 and thus to characterize an ideal skeleton for exploration missions, we determine an optimal initial condition for a crew member (i.e. optimal initial BV/TV, BMD, marker concentration before a mission) such that the bone loss after a mission does not exceed a specific threshold (e.g. maximum allowed bone density loss of 5% over 6 months).

WP7 (hypothesis 2.5)
2.5 Effects of radiation exposure based on clinical and animal data can be integrated in mechanobiological models of bone

Modeling: To address hypothesis 2.5, the mechanobiological model of bone remodeling will be extended to include radiation exposure. Long-term exposure of cells to radiation may lead to increased apoptosis and the combined effect of irradiation and disuse has been investigated before (Farley et al. 2020; Willey et al. 2021). Bone cell apoptosis rates of different types of bone cells are included in the current model. Consequently, radiation can be included in the model as either permanent increase of apoptosis rates of different bone cells (for the case of long term space flight) or temporary increase of apoptosis rates of bone cells (for the case of midterm space flight with returning to earth situation).
Optimization: The extended model is calibrated with the available published data including the radiation. Subsequently, the optimization from WP6 is repeated analogously for the extended model.

Timeline
WP1-6 can be carried out in three years by two researchers (PhD Students or Postdocs) working full time on the project. One researcher will work mainly on the modeling with Peter Pivonka, while the other researcher will work on the integration of the data and the related optimization problems with Anna-Maria Liphardt and Sigrid Leyendecker. The extension to model the effect of radiation and the integration of further data (not requested in this proposal) in WP7 is an outlook going beyond the first three years of work.
As a first milestone after one year, we will have first results for WP1, 2, 3 based on the data from one bedrest experiment. We will choose a data set containing the BV/TV values and concentrate on a specific site in the body (to be chosen such that the complexity of the model computations is kept as small as possible). In parallel, WP1 will be completed for the full data set.
In year two, WP2, 3 will be carried out for more data sets and WP4, 5 will be addressed.
In year three, the model extensions and predictions in WP6 are performed.

Management approach

Overall coordination
The three PIs of this project will jointly coordinate all the activities included in this proposal from the Queensland University of Technology (Peter Pivonka), the Friedrich-Alexander-Universität Erlangen-Nürnberg (Sigrid Leyendecker) and the Universitätsklinikum Erlangen (Anna-Maria Liphardt). The resources to compile and merge the data, and to start the analyses

suggested here (WP1) are already in place and secured by the PIs. As a first step, all the acquired data will be merged into a general database with granted access for the different international groups involved, and complying with the current European data handling regulations. Then, the team will work on the different work packages. To ensure that the proposed timeline is accomplished, the three PIs will work together to obtain additional staff and funding resources for the project. With the current funding and resources, we believe WP1 and preliminary data for WP2 and WP3 can be achieved well in time for the ESA Preliminary Results Workshop (i.e., spring 2025). It is foreseen that sections of this project will serve as material for students to complete their master's thesis. To ensure consistency of analysis and workflow, the PIs will meet (virtually) once every month during the duration of the project. All science team members will be involved in data interpretation and preparation of the potential manuscripts that can originate from the work presented in this proposal. Any publication presenting results from this project will be published in open-access format.

Significance of the study

The current project will deliver important and novel knowledge to better understand bedrest-induced alterations in bone tissue and the effects of duration and countermeasures on disuse induced bone loss by using mechanobiological models of bone remodeling. We propose the use of such models for personalized prediction of bone loss, especially for missions of long duration. This method has a lot of potential to advance the identification of individual factors that accelerate bone loss and thus personal fracture risk and musculoskeletal degeneration during microgravity. This ESA *announcement of opportunity*, together with the experience and knowledge of the current research team, offers a unique opportunity to investigate the use of mechanobiological models of bone remodeling in the context of bone loss in space. This information has the potential to help fine tune selection processes for space exploration missions and to personalize countermeasure use during exploration missions. Furthermore, this work will as well increase the understanding of clinical populations suffering from severe inactivity.

RELEVANT EXPERIENCE AND BACKGROUND*

Provide information on relevant team expertise, background and achievements. Please also refer to the science criteria section on the overview page for additional guidance (max. 2000 words).

Research team

To guarantee the success of this project, we have formed a highly qualified team of specialists with many years of experience in microgravity research and musculoskeletal modelling. The researchers included in this application have a productive history of successful scientific collaboration. Anna-Maria Liphardt and Sigrid Leyendecker work together since many years, in particular in the context of the DFG (German Research Foundation) funded Collaborative Research Centre EmpkinS (SFB 1483), where they investigate hand motion patterns and their prediction based on biomechanical modeling and data from the advanced EmpkinS sensing technology, with a focus on inflammatory arthritis. Other common projects address spine mobility as well as degradation of bone and cartilage in the metacarpal joint of the hand. Jointly, they are actively publishing and supervising young researchers (journal publications 1 published, 2 submitted, conference papers 1, conference talks 10, student theses 12). Peter Pivonka and Sigrid Leyendecker have been collaborating for about two years. This resulted in research stays (Sigrid Leyendecker at QUT: March to August 2022, Denisa Martonová at QUT: May to August 2022), research visits (Peter Pivonka at FAU in March 2023), the joint organization of special session `Modelling and simulation of musculoskeletal mechanobiology' at 8th International Symposium on Computer Methods in Biomechanics and Biomedical

Engineering (Peter Pivonka, Sigrid Leyendecker, Areti Papastavrou; May 2023, Paris, France) and joint publications (Martonová 2023). Since February 2022, Sigrid Leyendecker holds an adjunct professorship at QUT. Furthermore, together with a team of twelve researchers from FAU, QUT, UKER and THN, Sigrid Leyendecker, Peter Pivonka and Anna-Maria Liphardt have established a virtual colloquium on the mechanobiology of musculoskeletal systems and are working on the establishment of an DFG funded international research training group for doctoral researchers on this topic.

Anna-Maria Liphardt

Anna-Maria is leading an independent research group (Musculoskeletal Function and Mechanobiology) at the Friedrich-Alexander-Universität Erlangen-Nürnberg, Universitäts-klinikum Erlangen, Department of Internal Medicine 3, Erlangen, Germany. She has actively conducted spaceflight related research since 2003, initially as a co-investigator and coordinating scientist and for several years now as PI in bedrest, countermeasure and space flight studies (see also below). Her space related studies focus on the adaptation of articular cartilage, bone and muscle to bedrest and microgravity based on blood and urine biomarkers and imaging modalities (e.g. MRI, HRpCT) and with that she (together with Co-I A. Niehoff) significantly contributed to the understanding of cartilage health during bedrest. She has access to fully equipped research facilities for molecular analysis of blood and urine samples, imaging facilities (clinical MRI and CT, HRpQCT), clinical data management and statistical analysis. Anna-Maria is a member of the International Society for Gravitational Physiology's board of directors since 2023 and a co-chair of the society's Young Investigator subcommission that she initiated in 2021. She participated in the following space related studies:

Completed:

- DLR-VBR Study, (Cologne, Germany – 2003/ 2004: 14 days of bedrest, vibration training 10 x 10 min daily) (Baecker et al. 2012; Liphardt et al. 2009; Zange et al. 2009),
- ESA-NUC- Study (Cologne, Germany - 2009/ 2010: 21 days of bedrest - nutrition countermeasure) (Liphardt et al. 2018),
- ESA-MEP-Study (Cologne, Germany - 2010/2011: 21 days of bedrest - nutrition countermeasure) (Liphardt et al. 2018),
- ESA-SAG- Study (Cologne, Germany - 2010/2011: 5 days of bedrest - locomotion replacement training) (Liphardt, Mündermann, et al. 2020),
- ESA-MNX-Study (Toulouse, France – 2012/2013: 21 days of bedrest - nutrition + exercise) (Liphardt, Bolte, et al. 2020),
- ESA Cartilage Health (CO-I, PI: Brueggemann, Niehoff, pre/post ISS, 2013 - 2018) (Niehoff et al. 2016),
- CSA T-Bone (CO-I, PI: SK Boyd, 2014 - 2019, pre/post ISS) (Gabel et al. 2021, 2022),
- HyperGCart (Co-PI, PI: Niehoff; ambulatory, artificial gravity countermeasure and cartilage biomarker) (Dreiner et al. 2020; Dreiner et al. 2022),

Ongoing:

- NASA CIPHER (PI, Bone health experiment (Joint Health), ISS crew - joint health parameters),
- ESA BRACE/BRAVE (PI; Joint health experiment, 60 days bedrest – artificial gravity and exercise countermeasures),
- Vivaldi - MSK (PI, Response of the musculoskeletal system to 5 days dry immersion),
- ESA Cartilage Degeneration (PI, pre/post ISS, USOS crew)

Peter Pivonka

Peter Pivonka is Professor and Chair of Biomedical Engineering and Spinal Disorders at Queensland University of Technology. He has focused strongly on advancing current

musculoskeletal research, particularly multiscale imaging and computational modeling over the last 16 years. His work on mechanobiological regulation of bone and cartilage, with its application to osteoporosis and arthritis is nationally and internationally recognised. He has contributed significantly to the development of experimental- and computational methods to assess bone mechanobiology with the five most significant being: (1) Formulation of a bone cell population model which takes into account biochemical and biomechanical regulatory mechanisms based on a set of ordinary differential equations. (2) Development of a multiscale bone remodeling model including mechanobiological feedback of osteocytes. (3) Cellular scale models of the basic multicellular units (BMUs). (4) Multiscale model of cartilage and bone interactions. (5) Multiscale model of endocortical bone loss.

Sigrid Leyendecker

Sigrid Leyendecker is Professor of Applied Dynamics at the Friedrich Alexander Universität Erlangen-Nürnberg. Her research topics are situated in the field of computational mechanics, in particular dynamics and applied mathematics with focus on the development of efficient techniques for the simulation and optimization of dynamical and control systems with applications to modern engineering and biomechanical questions. Different optimization techniques have been utilized in the group of Professor Leyendecker, spanning from calibration of computational models with experimental data (Martonová et al. 2023; Holz et al. 2023; Martonová et al. 2021), through finding an optimal secretion and drug dosing pattern of PTH (Martonová et al. 2023) to solving optimal control problems via discrete mechanics and optimal control for constrained systems (DMOCC), being based on a discrete variational principle (Leyendecker et al. 2010). A key advantage of this formulation is that the structure preserving properties of the integrator enable the simulation to account for large, rapid changes in muscle paths without the usual numerical problems (Penner and Leyendecker 2020). An extension to multiobjective optimal control can be found in (Ringkamp, Ober-Blöbaum, and Leyendecker 2013). Furthermore, complex control problems, where a multibody system is actuated by several artificial muscles modeled as dielectric elastomers actuators are investigated in (Schlögl and Leyendecker 2017; Huang and Leyendecker 2023).

Professor Leyendecker provides as well an expertise in musculoskeletal models, in particular in Hill muscle actuated arm models with dynamic muscle paths (Penner and Leyendecker 2020), human hand models including grasping (Phutane, Roller, and Leyendecker 2022) as well as knowledge in the numerical simulation of systems with dynamics on different time scales (Gail, Ober-Blöbaum, and Leyendecker 2017; Wenger, Ober-Blöbaum, and Leyendecker 2016).

Research environment

A vivid international exchange between FAU, UKER and QUT has been established over the last years and is going to be further developed in terms of collaborations at different levels. In February 2021, FAU and QUT officially agreed to cooperate in research and teaching. This allows for example that PhD Students can work on their PhD thesis in both locations. Currently, there are several open calls for student theses and projects jointly supervised at FAU and QUT including the possibility of a research stay for the students at QUT.

Contributions

Anna-Maria Liphardt is the coordination PI of this research proposal and will be responsible for data management of this study (WP1). With her background in space life sciences she will (together with Co-Is L. Vico and A. Niehoff) phrase the relevant research questions to be answered with the modeling and optimization approaches in WP2 to WP7. In this context, she will together with the science team members decide on the to be included parameters and be responsible for the interpretations of the outcomes in the space lifesciences context.

Peter Pivonka will be responsible for the modeling approach in the study (WP2, WP3, WP5, WP6, WP7), With his expertise in modeling of bone remodeling, he and his team will formulate (WP2) and further incrementally extend the proposed multiscale model of bone remodeling (inclusion microgravity in WP5, inclusion of nutrition and exercise in WP6 and inclusion of radiation exposure in WP7).

Sigrid Leyendecker will be responsible for the optimization approach in the study (WP3, WP4, WP5, WP6, WP7). With her scientific experience in optimization and optimal control problems in biomechanics, together with the science team, she will formulate the corresponding optimization problems. This includes the definition of appropriate optimization variables, objective functions and constraints for the inclusion of data in WP3 and model calibration in WP4 as well as for answering the secondary research questions in WP5, WP6 and WP7. Furthermore, she will choose (or develop if required) appropriate numerical techniques to solve the resulting complex nonlinear optimization problems.

OTHER RELEVANT INFORMATION

Please provide here any other relevant information that may support your proposal.

Addition of other data sets:

Since some of the science team members have been PIs in various bedrest and space flight studies (see above), the core data set we apply for with this proposal can be amended by our own data sets. More specifically the available data sets in our team are:

Previous studies:

- MEP, NUC, Cocktail (various cartilage biomarkers; AML)
- MNX (cartilage biomarkers, imaging data (HR-pQCT bone, MRI knee joint, thigh muscle and fat; AML, AN)
- ESA Cartilage Health (AML, AN)
- CSA T-bone (HR-pQCT bone, bone biomarkers; AML)
- Four-month bedrest: (a bone histomorphometric study, LV)
- MIR space station (pQCT and bone markers, LV)
- EDOS 1 (HR-pQCT bone, bone biomarkers, LV)

Ongoing studies

- ESA Cartilage Degeneration (cartilage biomarkers, imaging data (HR-pQCT bone, MRI knee joint, thigh muscle and fat) AML, AN)
- CIPHER (cartilage biomarkers, AML, AN)
- EDOS 2 (LV)
- ESA BRAVE & BRACE (all muscle, bone and cartilage data; AML, AN, LV)
- ESA Vivaldi 1 & 2 (musculoskeletal data, bone and cartilage biomarkers; AML, AN, LV)

PRIVACY NOTICE CONSENT FORMS* *

Please upload here the signed and dated Privacy Notice Consent Forms (one for each science team member). Please submit the forms in PDF format and name them as "LastName_FirstName_PN_Consent".

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