Model Credibility Update, August 2019

1. Project Title

A Lower Extremity Neuromusculoskeletal Human Simulator: Addressing Multiscale Challenges
U01 AR072989
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2. Brief description of the project

The overall goal is to create a comprehensive multiscale musculoskeletal model of the human lower extremity, which includes seamless connection between tissue and whole-body function during dynamic human activities and enables realistic investigations of musculoskeletal disease and treatment. A multiscale approach is essential because diseases and injuries often affect tissues at the microstructural scale and small-scale pathology impacts biomechanics at larger scales.

- Aim 1: Measure and share multiscale biomechanical data linking tissue and body movement mechanics. The dataset will consist of knee stereo radiography, MRI and CT imaging, EMG, ground force, and whole-body motion captured for healthy subjects, patients with knee OA, and patients following TKA.
- Aim 2: Develop subject-specific multiscale models of the lower extremity including deformable representations of the functional anatomy to improve realism and utility for dynamic simulation. Models will represent the major structural tissues, including bone, cartilage, ligament, muscle, tendon, and adipose tissue.
- Aim 3: Create realistic dynamic simulations to assess and predict the effects of disease state, surgical, and other biomechanical variables on a patient's function. Our target is understanding the effects of knee osteoarthritis on patient function and optimizing treatment through total knee arthroplasty.

3. Model credibility plan details

A. Planned actions as outlined

The model credibility plans as outlined in the original proposal can be summarized as follows:

- Year 1: Baseline models and detailed data collection planning for measurements needed in credibility assessments.
- Year 2: Completion of measurements needed for model and simulation development and credibility assessments.
- Year 3: Completion of first-generation complete lower body multiscale musculoskeletal models and simulations. Beginning of credibility phase involving outside collaborators testing model and simulation performance. Measurements of made in subjects with pathology and after treatment to assess model efficacy for clinical investigation.
- Year 4: Second generation model and simulations completed and prepared for credibility assessments, and application to clinical issues in osteoarthritis and joint replacement.

B. Brief description of information gained from each credibility action

The investigators have demonstrated a rigorous commitment to performing verification and validation of models. Prior finite element models have been based on the anatomy of specific specimens and then model-predicted outputs (e.g. kinematics) have been compared to results from cadaveric testing performed on the same specimen (e.g. Baldwin et al. 2012, Harris et al. 2016, Ali et al. 2016). Further, we have been leaders in the application of probabilistic and other numerical techniques to quantify the various uncertainties present and understand their impact. Recently, we have investigated the propagation of error in musculoskeletal modeling as measurement uncertainty is carried forward to influence kinematics, joint reactions, and muscle forces (Myers et al. 2015). This probabilistic analysis tool for OpenSim was made publicly available for use by other investigators (https://simtk.org/home/prob_tool). Using this tool, we examined the effect of parameter and measurement uncertainty on the joint loads reported in the Knee Grand Challenge dataset (Navacchia et al. 2016). Our commitment is further demonstrated by our open sharing of not only the models and simulations we build, but also the data we used to create them (https://simtk.org/projects/knee_model).

C. Actions & activities organized in the CPMS TSR framework

Rule	Actions and Activities
Rule 1 – Define context clearly	The goal is to create a comprehensive multiscale musculoskeletal model of the human lower extremity, which enables realistic investigations of musculoskeletal disease and treatment
Rule 2 – Use appropriate data	We will measure and share publicly multiscale biomechanical data linking tissue and body movement mechanics. The dataset will consist of knee stereo radiography, MRI and CT imaging, EMG, ground force, and whole-body motion and habitus
Rule 3 – Evaluate within context	Credibility will be assessed by direct comparison to measurements made from participants to determine how well the created models and simulations mimic human performance
Rule 4 – List limitations explicitly	As the models and data become available, limitations will be shared via a dedicated website used to host the dataset. Actively shared models and data are available at www.simtk.org/projects/knee_model and www.simtk.org/projects/kneehub
Rule 5 – Use version control	Version control is established by the version manager at the Center for Orthopaedic Biomechanics at the Univ of Denver. Data and models will include version information including version numbering and change logs maintained through the lifespan of the dataset.
Rule 6 – Document adequately	Documentation will follow guidelines being developed by R01EB024573 “Reproducibility in simulation-based prediction of natural knee mechanics”
Rule 7 – Disseminate broadly	Models and data will be shared via a dedicated project website which will include a Creative Commons attribution license. Datasets will also obtain a digital object identifier (DOI) to improve dissemination, sharing, and reuse
Rule 8 – Get independent reviews	Independent reviewers have agreed to test the project simulations starting in year 3 (2021)
Rule 9 – Test competing implementations	Competing implementations will be tested as they become available. Currently no other comparably detailed representations of the human lower extremities are available.
Rule 10 – Conform to standards.	We will adopt and promote applicable operating procedures, guidelines, and regulations. We will complete and share with the ASME V&V-40 subcommittee in credible modeling Credibility Assessment Matrices related to verification, validation, and uncertainty quantification

D. How will these activities lead to a credible model?

Our proposed in vivo data collections will allow for the simultaneous measurement of whole body and joint level motions for subjects performing a variety of activities of daily living. Further, to consider adaptation, data will be collected for healthy subjects and those with osteoarthritis and after total joint replacement. The availability of multiscale experimental data will uniquely allow for subject-specific model validation at individual scales and across scales. With subject data from multiple activities and measurement domains, some activities will be used for model calibration, while other activities will be

used for verification and validation. Even so, we recognize that some measurements cannot be performed in-vivo, and so we will likely use data from other sources in model development. For example, to develop the anatomic representation data from multiple sources: MR and CT imaging, segmented structures from the Visible Human, and marker data from the data collection may be merged. Similarly, mechanical properties will be derived from prior cadaveric data considering the sequential resection of structures, as well as the literature. There are limitations when applying data from one specimen or subject to other subjects. We will employ probabilistic methods to characterize the variability in the model inputs and to assess the sensitivity of the model outputs.

We have identified independent investigators with complementary interests and requisite expertise to evaluate the developed models for completeness, accuracy, and credibility. While we are confident these respected researchers will perform unbiased, independent evaluations, we will also have this group identify additional researchers to provide truly blinded evaluations. The project budget includes support for these individuals to perform their evaluations and these efforts will take place in years 3 and 4 per the timeline. Finally, open dissemination of the results, model code, and associated data sets will enable independent evaluation by others.

E. Progress to date & plans for next reporting cycle

During the first year we laid the foundation to create a comprehensive multiscale neuromusculoskeletal model of the human lower extremity, along with the measurements needed for model assessment. During the first year we accomplished work important to credibility on all three aims:

- Aim 1: As part of our effort to measure and share comprehensive multiscale biomechanical data linking tissue and body movement mechanics we obtained IRB approval and completed plans and pilot studies for comprehensive measurements of the geometry and function of healthy volunteers. As part of this planning process, we designed, constructed, and tested new fixtures for the Human Dynamics Laboratory to assist in obtaining repeatable measurements with high-speed stereo radiography.
- Aim 2: We created our first template model extending from the lumbar spine through the toes. This model includes the major structures including bone, cartilage, ligament, muscle, and tendon. In addition, we completed detailed plans for in vitro measurements of the healthy lower limb and knee. These data will enable reverse engineering to create, calibrate, and validate musculoskeletal models of the normal healthy knee.
- Aim 3: We applied our starting template model described in Aim 2 in proof of concept simulations of rising from a chair. This simulation tested the full lower extremity finite element multiscale musculoskeletal model with a detailed representation of the natural knee. This single-framework finite element simulation used an optimization-based strategy to concurrently estimate muscle forces and tissue deformation. Development of these simulations and the data to drive them lays the foundation for Year 3 credibility assessments.

By the next reporting cycle, we expect to be able to report on the data that will be used for model development and credibility assessments. In addition, first-generation pilot models are currently under construction and we will present results from simulations using those models.

4. Issues/concerns identified as critical or problematic

None so far. The reduced award budget prompted some concern for the activities of collaborators to test our models, however, we believe these activities can be supported to a sufficient degree by the current budget and subsidy through other projects with similar needs.

5. What other factors contribute to credibility but cannot be reported within the TSR structure?

The inherent variability in normal human anthropometry and function is a challenge – it is difficult to assure the models created will be credible for all subjects and conditions. For this reason, we will use probability methods to assess the sensitivity of our models to uncertainty in measurements and geometric and material representations.