Computational modeling have become a routine and powerful strategy for academic research and clinical care. Consequently, significant scientific discoveries were made, innovative products were launched, and individualized delivery of healthcare has become a possibility. The scientific and clinical domain of knee biomechanics is no exception. The knee is a major site of orthopaedic problems resulting in annual physician visits on the order of tens of millions. Modeling and simulation offers a cost-effective and prompt path to respond to the pressing medical needs for restoration of knee function. However, the reproducibility of simulation results, to inform scientific and clinical decision making, is questionable. Reproducibility is a pressing issue in scientific conduct. For modeling and simulation, there is added scrutiny particularly with the desire to repurpose and reuse virtual specimens for prospective solutions of diverse scientific and clinical problems. A significant portion of the modeling and simulation workflow includes development, evaluation, and simulation. This workflow, while based on objective scientific principles, commonly requires intuition during implementation; therefore relies on the knowledge and expertise of the modeler. This ‘art of modeling’ can be a fundamental source of diminished reproducibility. The goal of this study is to understand how modelers’ choices to build models, even when using the same data, may influence predictions and therefore the reproducibility of simulation results. Five modeling and simulation teams will independently develop, calibrate and benchmark computational models of knees based on the same data sets and reuse these models to simulate the same scientifically and clinically relevant scenarios. Ideally, predicted joint and tissue mechanics will be the same. In practice, the skills and experiences of model developers will reflect upon their modeling choices; and as a result, discrepancies will exist. The proposed activity will document the magnitude and potential sources of such discrepancies through comparisons of model components and simulation results. This project will examine and critique the current state of model development and simulation reproducibility in joint and tissue mechanics. This will translate into reliable models of the knee joint for simulation-based discoveries and in silico design and evaluation of medical devices and interventions. The required exchange of data, model components, and simulation results among the teams and with the public will also impact developers and users of such resources. Specifications, to facilitate data and model exchange and to develop data and modeling standards, and guidance, to inform modeling and simulation workflows, will likely emerge as by-products of the research activity. The investigators are leaders in simulation-based explorations of knee biomechanics and include representatives of prominent research laboratories and clinical institutions worldwide. With this project, they will establish the necessary scientific rigor to recognize computational modeling and simulation as a dependable component of knee research and the joint's clinical care.

The potential of modeling and simulation to enable significant scientific discoveries and to improve clinical care is not limited to knee biomechanics. Yet, realization of simulation-based approaches as routine and dependable strategies for healthcare delivery requires establishing their reproducibility to be independent from the analyst's preferences. By understanding the influence of modelers' approaches and decisions (essentially their art) throughout the lifecycle of modeling and simulation, this project will demonstrate the uncertainty of delivering consistent simulation predictions when the founding data to feed into models remain the same.

Knee joint injury and pathology are very common in the United States, resulting in more than 10 million visits to orthopedic clinics[1]. Osteoarthritis, for example, is at an alarming level, i.e., impacting approximately 27 million adults in the United States[2,3]. It is a leading cause of musculoskeletal disablement with prevalence rates for the knee reaching 16%[2]. Trauma to the knee is also a major healthcare issue, resulting in ligament ruptures and meniscal tears[4], leading to early onset of osteoarthritis. Scientific and clinical studies of knee biomechanics are therefore vast and computational modeling has found significant utility in cost-effective and prompt explorations of knee biomechanics to enable scientific discoveries, to realize engineering innovations, and eventually, to improve clinical care. Simulations allow predictions of joint and tissue mechanics, which in turn provide a platform to understand structure-function relationships within the knee in health and disease[5]. The causality of data associations can be established to understand risk factors and to improve diagnosis and prognosis[6]. Virtual prototyping has radically influenced intervention design and evaluation through which effective surgical reconstruction[7,8], rehabilitation[9], and joint replacement[10] can be devised for recovery of joint function. The magnitude of work in computational biomechanics of the knee is immense; a recent PubMed search has revealed almost 10,000 hits relevant to knee biomechanics and modeling and simulation (Figure 1). The knee biomechanics community has also taken significant strides to share anatomical and mechanical data relevant to modeling[11–14] and to deliver software to build individualized knee representations[15,16]. The Grand Knee Challenge[17] is an example of a recent initiative to enhance the predictive capacity of modeling and simulation for its specific application for determining implant forces. Modeling and simulation projects have also started to deliver virtual knees[13,18] to quantify detailed joint and tissue mechanics of the natural knee as a reference state, and allow repurposing for virtual experimentation on diseased, injured and reconstructed states.

Modeling and simulation in biomechanics inherit the same challenges of computational approaches in any scientific discipline[19,20]. These challenges are associated with credibility of model predictions in general and reproducibility of predictions in particular. Within this context, an unappreciated concept in the broad scientific community and by healthcare professionals, but a commonly acknowledged practice among modeling and simulation experts, is the “art of modeling”. Utilization of raw data to build models and assumptions to reach desired modeling fidelity may be subjective, depending on the knowledge, expertise, and preferences of the developer. As a consequence, different knee modeling workflows may result in different flavors for the virtual representation of the same knee specimen. The long term goal of this project is to understand whether choices made by the modeler during the modeling and simulation workflow influence the conclusions made by relying on the scientific and clinical interpretation of simulation predictions. The overall objective is to answer the following question: “*Do the predictions of natural knee biomechanics depend on modeling decisions of separate development teams when the target simulation scenarios and the source data to build models remain the same?*” Our specific aims are:

Specific Aim 1. To quantify the influence of variations in modeling and simulation workflows on the reproducibility of **joint level predictions** in computational knee biomechanics.

Specific Aim 2. To quantify the influence of variations in modeling and simulation workflows on the reproducibility of **tissue level predictions** in computational knee biomechanics.

With the use of same source data, uncertainties due to modeling choices will be highlighted, i.e., they will not be masked by variations within a population, from which different samples for modeling may be selected arbitrarily by modeling teams. We anticipate that discrepancies in tissue level predictions will be more pronounced than the variations in joint level predictions. With explicit documentation of individual workflows and access to derivative data, model components, and models themselves, it will be possible to isolate the sources of discrepancies in simulation predictions. As a result, dependable prediction of natural knee biomechanics, which will be agnostic to the selected modeling and simulation workflow, will be possible. This will provide the foundations for reproducible virtual knees to conduct virtual experiments of healthy, pathological, and reconstructed joint states. Through sharing of data, models, and results between participating teams and with the public, the requirements for data and model exchange standards in computational biomechanics will be established in a grassroots manner. The knowledge gained by this project will have direct impact on appropriate modeling and simulation of any musculoskeletal joint and will also be important for the broad community of biomedical computing. For credibility, the modeling and simulation community has recognized the need for the development of competing implementations to check the influence of modeling workflow on scientific conclusions[21]. This activity will be a hands on demonstration of this guidance.

A. Significance. The proposed project has implications for modeling and simulation of knee mechanics with significance relevant to the understanding of natural knee function and management of knee health. By improving our understanding of reproducibility in modeling and simulation, this study will also have implications for biomedical sciences and computational biomechanics. The collaborative and open science approach that we propose will also provide the foundations for pragmatic exchange of data and models. All these significance areas are elaborated in the following to establish the scientific premise of the proposed work.

A.1. Knee biomechanics in health and disease. Prevention of knee problems and restoration of knee mechanics require a thorough understanding of the natural biomechanical function of the joint and its tissue structures. Knee mechanics is a function of articulating surface geometries, individual mechanical properties of connective tissue, and mechanical interactions between tissue components. Knee mobility and its mechanical capacity accommodates healthy locomotion and large forces commonly endured during daily activities. The compromise of the whole joint or its tissues may diminish knee biomechanics, which will likely result in performance loss, pain, and disability. Injury and pathology of the knee are very common, illustrated by ~10 million clinical visits in 2010, only in the United States[1]. In osteoarthritis, prevalence rates for the knee has been reported as high as 16%, the highest among other joints[2]. Considering that ~27 million are affected by this debilitating disease in the United States[2], knee osteoarthritis is at an unsustainable level. It is a leading cause of disability, which frequently leads to joint replacement procedures[2]. Sports injuries in the knee such as anterior cruciate ligament damage and meniscal tears are also prevalent[4]. Among the highest of work related musculoskeletal injuries are meniscal tears, requiring surgery and physical therapy[22]. Such injuries influence knee mechanics and may result in cartilage degeneration due to the altered mechanical state[23]. Therefore, many tissue reconstruction techniques and rehabilitation protocols have been devised with the goal of restoring the joint's natural mechanics[24]. Gender can be influential on incidence of knee problems. For example, female athletes exhibit higher rates of anterior cruciate ligament injury[25]. Complications of patellofemoral joint are also a main reason for knee related clinical visits as anterior knee pain is common among active young people[26]. Consequently, fundamental research on knee biomechanics and clinical trials to evaluate strategies for management of knee conditions are actively pursued.

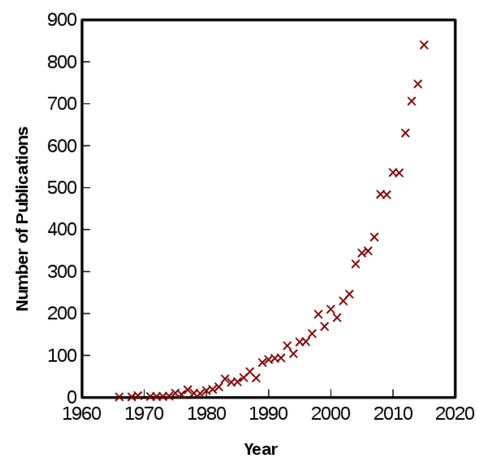

Figure 1. Publications associated with knee and modeling and simulation amount to a total of 9,687. Number of citations per year (1960-2015) are shown using data acquired from PubMed on August 25, 2016 with the search term "knee AND (model OR simulation)". Not all of these studies may pertain to computational knee biomechanics. Nonetheless, the PubMed results imply an exponentially increasing interest level in simulation-based explorations of the knee joint. Similar data exist for other musculoskeletal joints and in general, for the use of modeling and simulation in healthcare.

A.2. Impact of modeling and simulation in knee biomechanics. Computational modeling, when performed correctly and effectively, has the premise to reduce testing on animals, cadaver experimentation, human subjects testing, and physical prototyping. The popularity of simulation-based explorations has been increasing asymptotically (Figure 1). In silico strategies, e.g., finite element analysis, have been used routinely for the knee to explore joint and tissue function[5,27–29], to understand injury mechanisms[30,31], to study pathological joint mechanics[32,33], to evaluate surgical performance[34,35], to prototype tissue reconstruction techniques[36,37], and to facilitate implant design[10,38,39]. Numerous models have been developed[5], sometimes to investigate the same scientific question or clinical problem[8,40]. Explorations of cartilage mechanics are wide spread as a result of this tissue's importance for load bearing, its degeneration due to age, osteoarthritis, or injury, and the variety of interventions available to restore its function[41,42]. Simulations also explored mechanical role of ligaments and menisci, on the overall joint response and on the stress distribution within the knee[28,43,44] and were used to predict the outcome of tissue interventions and injury[45,46]. With increased robustness of simulation software and significant improvements in computing capacity, multiscale simulations are emerging, coupling knee biomechanics to body level movements[47–49] and deformations of cells[50,51]. The potential to transform knee joint models into clinical tools for patient assessment and personalized care is emerging[32]. There is also a pressing need to leverage modeling and simulation as a virtual prototyping platform for design of medical devices and their regulation[52], e.g., as pursued by the U.S. Food and Drug Administration (FDA)[53].

A.3. Problem of reproducibility in computational biomechanics. Reproducibility in scientific conduct cannot be taken for granted. Recent investigations have documented the lack of rigor, which challenged the reproducibility potential in the broad scientific community[19] and for computational approaches[20]. Modeling and simulation and in relevance to the proposed activity, computational biomechanics inherit the reproducibility problem. Increased access to computational resources and ease of conducting simulations; yet, increasingly convoluted workflows and undisclosed model development processes and simulation code have made the issue more pressing. The fundamental requirement for appropriate and effective modeling and simulation is the development of a reliable and robust computational model, capturing anatomical and physiological realism at such a level that meaningful simulations can be performed. Many initiatives in computational biomechanics are applicable for appropriate use of simulations to explore joint and tissue mechanics in the knee. These range from guidance for implementation of verification and validation strategies in simulations of the musculoskeletal system[54], for predictions of muscle forces and body level movements[55], and in finite element analysis using anatomically realistic representations of the joints, for predictions of joint level movements and tissue deformations[56,57]. For finite element analysis, perspectives for appropriate and adequate reporting of studies have also been published[58]. For the knee, there has been work incorporating detailed strategies in their workflow to validate the outcome of models[59], and a large number of investigations have explored the sensitivity of model parameters on simulation predictions[44,60,61]. Uncertainties in model parameters can be due to both variability of source data and modeling choices. When someone glances over the aforementioned guidance documents, the number of decisions that need to be made to develop models and implement simulation scenarios can be daunting. The modeler's intuition may a have a significant role when making decisions against lack of data or computational constraints. As a result, a modeling and simulation workflow may have a different outcome depending on who does it, how and when, even when the source data remain the same. In computational biomechanics, and specifically for knee mechanics, there is a void in the literature to understand the influence of modeling decisions on simulation predictions.

A.4. Preventing reinventing the wheel in computational biomechanics. In computational biomechanics, guidance and standards for exchange of data, models, and simulation results are not readily available. Exceptions are noted, e.g., FieldML for modeling[62], yet adoption has been severely limited. This issue has to be resolved if the community aspires to reuse data, repurpose models, and transparently assess data quality and simulation performance. In recent years, biomechanics community has become increasingly open in terms of development of simulation software[63,64] and by launching platforms for sharing of data[65]. For the knee, a handful of groups have provided their models[18,66–68] and anatomical and mechanical data to build virtual knees[11–14]. Nonetheless, data and model formats are fragmented due to information heterogeneity, non-standard and proprietary approaches for storage, and unconventional formats for exchange. Projects requiring hands-on exchange of data, model, and simulation results can identify challenges and opportunities in this area. The proposed activity therefore has an important scientific premise driven by the required interactions among diverse modeling groups to fulfill the specific aims.

B. Innovation. The novelty of the proposal is grounded on the reproducibility potential of predictive simulations in knee biomechanics. Additional, and equally important, innovations are related to the processes that will be implemented during the execution of the project. These will provide novel and generally applicable pathways for the practices of regulatory science and collaborative modeling and simulation. Innovation potential of the project is expanded in the following sections.

B.1. Establishing credible practice of modeling and simulation for knee biomechanics. The novelty of this proposal rests on the documentation of simulation uncertainties due to modeler’s choices for the development of virtual knees. Over the past six years, an exciting project, the Grand Knee Challenge[17,69], has provided some insight into this issue by launching a competition for prediction of load sharing in total knee replacement. This project specifically dealt with the use of patients' locomotion data along with musculoskeletal models and implant representation to resolve muscular force patterns and therefore the loading on the medial and lateral compartments of the implant. Apart from the emphasis on the artificial knee, the investigations focused at the interface of body level locomotion and joint mechanics. Modeling and simulation of the intact knee, in a healthy state or for pathological conditions, bring additional challenges for model developers. Tissues and their nonlinear mechanical behavior, which can understandably be neglected for implant simulations, need to be represented, e.g., cartilage, meniscus, cruciate ligaments. When virtual specimens are of interest[18], the burden on the model developer increases, i.e., to predict natural knee mechanics correctly to establish reference functional mechanics of the joint and its tissue structures, and to repurpose models to simulate the influence of disease or joint and tissue reconstruction on this reference mechanical response. The proposed project will fill in the gap in literature, which currently lacks the influence of model development decisions on predictions of knee mechanics. To ensure comprehensive evaluation of data utilization, model components, and simulation results, the project will also provide dedicated resources for multiple teams to execute and document their modeling and simulation workflow.

B.2. A rigorous strategy to understand the role of modelers' choices on reproducibility. The proposed project is an innovative collective activity to establish the bounds of simulation predictions as a consequence of modeling decisions. The implications of this is beyond knee biomechanics; it will provide a comprehensive strategy that can be implemented to assess reproducibility of any computational modeling effort. The need for such strategies have become pressing. For example, recent funding programs have explicitly requested third-party evaluation of computational models used for multiscale simulations of physiological and behavioral systems[70]. Subsequently, comparisons of independent implementations of a model have been recognized by the biomedical computation community as an important part of a holistic approach to establish credibility in modeling and simulation[21]. Exemplar studies relevant to these concepts are appearing in the literature. In a recent study, which also involved the investigators of this project, integration of model sharing and reproducibility analysis to scholarly publishing in computational biomechanics was documented[71]. The authors served as the reviewers of two musculoskeletal models; they downloaded them and conducted simulations to replicate predictions reported by their developers. This study provided significant insight into the seemingly simple process of running the same model to repeat the same simulations. Rebuilding models from scratch was not explored. In another study, this time for spine biomechanics, independent research teams used their existing spine models to simulate the same scenarios[72]. They attributed the differences in predictions to high inter-subject variability, possibly dictated by the use of different models based on different subjects' data. This situation may have masked the influence of model development decisions, i.e., contributions of modeling assumptions may have been misconstrued as subject variations. To our knowledge, for representation of natural physiological systems, structured studies, where independent research teams build their own models relying on the same data and simulate the same scenarios, do not exist or are severely scarce. Herein lies the novelty of the proposed study as we will understand the role of modeling choices, which are usually in response to data limitations and computational challenges.

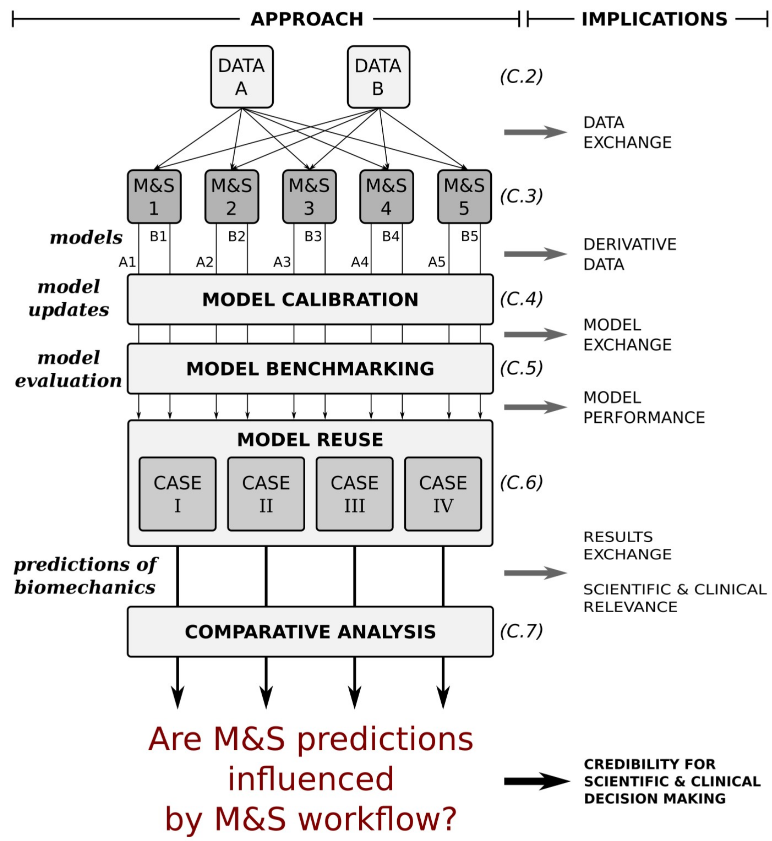

Figure 2. The overall approach adopted for the proposed research activity is outlined here. Each modeling and simulation (M&S) team will build two specimen-specific models; one for each data set, utilizing anatomical information and when available, tissue mechanical properties. Iterative simulations informed by joint mechanics data will assist in the calibration of the models to capture specimen-specific response. Model benchmarking on data sets that are not used for calibration will provide the platform for evaluation of the predictive capacity of models. Each team will reuse their models to simulate four simulation cases where joint and tissue level biomechanics will be predicted and reported for additional comparative analysis. Comparisons between simulation results of each team at various levels in M&S lifecycle (specifically model calibration, model benchmarking, and model reuse) will indicate the role of M&S choices on the final predictive outcome. The final and intermediary products of the proposed activity will have significant implications for M&S development, reuse, and utility for scientific and clinical decision making. Sections relevant to different steps of research methodology are italicized.

B.3. A collective approach to computational biomechanics. A novel contribution of the proposed activity, while being a by-product of the overarching reproducibility analysis, is the need based determination of the requirements for exchange of data, models, and simulation results. In the computational biomechanics community, comprehensive standards for data and model exchange do not exist. Some standards are available for specific data types, e.g. DICOM for anatomical imaging[73], and are adapted from manufacturing, e.g. STEP for geometric representation[74]. Reliance on de facto exchange formats are common, e.g., STL for triangulated representation of surfaces[75]. Initiatives for comprehensive model representation for field problems are promising, e.g., FieldML[62]. However, they are not widely adopted. Identifying commonalities in both data and model formats is at the heart of resolving exchange of data and models, which is the core requirement of collaboration, third-party quality assurance of data and models, and their effective sharing for prospective

Table 1. Milestones and timeline for the proposed research activities. Documentation, publications, dissemination, and progress meetings will occur regularly.

Activities	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
Curation & selection of data sets (C.2)	■															
Model development (C.3)		■	■	■	■	■										
Model calibration (C.4)						■	■	■								
Model benchmarking (C.5)								■	■	■						
Model reuse (C.6)										■	■	■	■	■		
Comparative analysis (C.7)							■		■		■				■	■
Outreach meetings (C.8)	■			■				■				■				■

reuse. Our activities will result in a bottom up approach, driven by independent modelers and informed by the desire to reuse existing data. This is not commonly employed in development of modeling and simulation formats, markups, and standards.

C. Approach. Reproducibility of simulation-based predictions of joint and tissue mechanics will be evaluated by developing a total of ten models based on two data sets (Figure 2). The data originate from the University of Denver group and from the Open Knee(s) project. For each data set, a model of the knee joint will be developed by contributing research teams, who will rely on their own modeling and simulation workflow: Open Knee(s) from Cleveland Clinic, University of Denver, Auckland Bioengineering Institute, Cleveland State University, and the Hospital for Special Surgery. The workflows will be staged to include model development, calibration, benchmarking, and reuse. All models will be reused to simulate scientifically and clinically relevant loading cases to characterize the overlaps and differences in predictive capacity of the models. Members of the Division of Applied Mechanics at the U.S. FDA will have an active role for absolute and relative assessment of model components and simulation performance at all stages (see letter of support). The activities and choices of the teams during the modeling and simulation workflow will be documented through a structured process. Before executing each of the model development, calibration, benchmarking, and reuse stages, the participating teams will submit detailed specifications (or standard operating procedures) to the project website to publicly describe their protocols. If their protocol changes during execution, they will submit a protocol deviation at the project website including a justification. Such approaches have been used in the Open Knee(s) project, where specifications are regularly documented before execution[76], i.e., using wikis, and amended when necessary through the use of reporting mechanisms provided by SimTK, an online collaboration infrastructure[65] (also see section C.8). The following sections provide the scientific rigor through an in-depth description of the proposed procedures. The timeline and milestones are provided in Table 1.

C.1. Project administration. Ahmet Erdemir, PhD, Principal Investigator, and his team will be responsible for day-to-day management of the project site, curation and distribution of models and simulation results, communication within the contributing teams, and outreach activities (see section C.8). Organization of the activities will be guided by a steering committee, which will consist of all contributing team leaders (Drs. Halloran, Besier, Erdemir, Imhauser, Laz, Shelburne) and support from regulatory science perspective (Dr. Morrison). The steering committee will meet quarterly online via video conferencing and in person at least once a year (see section C.8.2). These meetings will focus on scientific progress, challenges, opportunities, and outreach. Note that Dr. Erdemir has implemented a similar administrative infrastructure for Open Knee(s).

C.2. Data sources. Specimen-specific data from two data sets (Figure 3), which were publicly disseminated by two of the participating teams[12,13], will be used to feed the model development and simulation workflows. The steering committee will select two specimens (one from each data set, including female and male donors) to conduct modeling. The content of these data sets are described in detail in the following sections.

C.2.1. Data A: a specimen from Open Knee(s) data. The first experimental data set originates from the Open Knee(s) (Figure 3-A), an ongoing activity funded by NIH (R01GM104139, PI: Erdemir) with disseminated data on eight cadaver knees[13]. Detailed specifications are available at the Open Knee(s) wiki[76]. In summary, cadaver specimens matched a cross-sectional sample of the population, which were delineated by sex, age, cartilage health[77], and “normal” ranges of physiology (height, weight, BMI). To highlight the various tissue types, magnetic resonance imaging was adapted from the Osteoarthritis Initiative[78]. Multiple image sequences were collected[79]: (i) a general purpose setting including the tibiofemoral and patellofemoral joints and registration markers, (ii) a setting focusing on cartilage, (iii) axial, sagittal, and coronal image sets focusing on ligaments, tendons, and menisci. After imaging, kinematics and kinetics of the tibiofemoral joint were characterized at 0°, 30°, 60°, and 90° of flexion using a robotics testing system (the Universal Musculoskeletal Simulator[80]) and real-time force feedback using simVITRO™ software (Cleveland Clinic, Cleveland OH). Conducted tests included (i) laxity testing: internal rotation (±5 Nm), varus (±10 Nm), anterior translation (±100 N), and (ii) combined loading[81]. Preconditioning was performed and repeatability tests ensured no substantial damage to the specimen was realized. A separate test of the patellofemoral joint measured kinematics, kinetics, and contact pressures as a function of quadriceps load (up to 600 N in steps of 100 N) and knee flexion (0°, 15°, 30°, 45°, and 60°)[82]. During loading, the quadriceps tendon was held by a custom wire mesh grip (DCD Design and Manufacturing Ltd., Richmond BC, Canada) and frozen with liquid nitrogen. A Tekscan (Boston, MA) sensor (5051, 1,200 psi range) provided quantification of patellofemoral contact mechanics throughout the testing. Following joint mechanics testing (tibiofemoral and patellofemoral), tissue samples were collected from cartilage (medial & lateral femoral condyles and tibial plateau, trochlear groove, patella), meniscus (medial & lateral), ligaments (anterior & posterior cruciate, medial & lateral collateral, patellar), and quadriceps tendon. Tissue samples were frozen for uniformly shaped test sample preparation. Specimen-specific tissue testing is in progress (thirty tests for each knee specimen). Cylindrical compression samples have been acquired from cartilage and menisci. Planar dumbbell shaped tensile samples have been acquired from ligaments, tendons, cartilage, and menisci. Multi-step stress-relaxation tests under confined and unconfined compression and under tension (for relevant sample types) will allow time-dependent characterization of tissue mechanical behavior.

C.2.2. Data B: a specimen from University of Denver data. A second experimental data set from the University of Denver (Figure 3-B), which was funded through NIH (R01EB015497, PI: Shelburne) and completed in partnership with the University of Kansas, will be used to support model development and validation. The complete protocols and data sets can be found in Harris et al.[67] and Ali et al.[83], and on the data sharing site[12]. In brief, magnetic resonance images of the lower limb (femoral head to toes) from four fresh-frozen cadaver specimens (3 male, 51 ± 15 years old, 26 ± 10 BMI,) were taken after 24 hours of thawing at room temperature. Images were captured with T2 weighting and true fast 3D gradient echo sequence with in-plane resolution of 0.5-0.6 mm and slice thickness of 0.5 to 1.0 mm. For testing, all tissue approximately 20 cm proximal and distal to the joint line was retained. High-speed optical motion tracking arrays (collection frequency = 100 Hz) were rigidly attached to the femur, tibia, and patella and knee joint motion was captured using an Optotrak 3020 camera system (accuracy = 0.1 mm, Northern Digital Inc., Waterloo, ON). Passive laxity tests were performed at 0°, 15°, 30°, 45° and 60° knee flexion by consecutively applying up to ±10 Nm varus-valgus (VV) torque, ±8 Nm internal-external rotation torque, and ±80 N anterior-posterior force. Applied loads were measured with a six degree of freedom load cell attached to the distal tibia. Laxity testing was repeated for each knee with all soft-tissue intact and again after controlled resection of the anterior and posterior cruciate ligaments and the lateral and medial meniscus. Following experimental testing, each knee was completely dissected. Attachment site locations of the major bundles (if applicable) of the cruciate and collateral ligaments were digitized. Experimental knee laxity motion and loading information were processed using the radial basis function technique described by Cyr and Maletsky[84]. In addition, kinematics and loading data from an experiment that used quadriceps force to extend the knee were provided. Accordingly, imaging and six degrees of freedom joint movement and loading information are available to support modeling of the tibiofemoral and patellofemoral articulations of the knee.

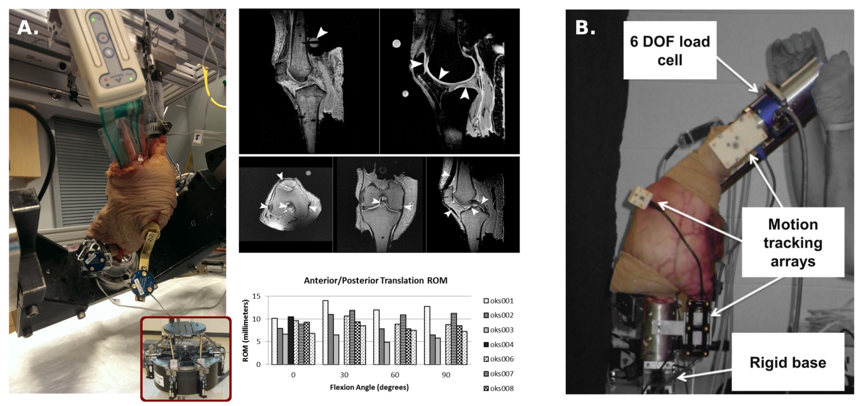

Figure 3. The project will rely on two publicly available data sets: Open Knee(s) from Cleveland Clinic and Natural Knee Data from University of Denver. A. For Open Knee(s) project, robotics testing was conducted to collect joint kinematics-kinetics. A cadaver specimen is shown during patellofemoral joint testing, where contact pressures were also recorded. Different types of magnetic resonance imaging were acquired to assist anatomical reconstruction of the tissues. The specimen variations in anterior-posterior translation range of motion during laxity testing are also shown. Additional tissue testing to characterize tissue material properties are in progress. B. The Natural Knee Data provides similar data on cadaver specimens. The knees were manually loaded, during which joint kinematics-kinetics were collected. Joint mechanics data are also available after resection of cruciate ligaments and menisci.

C.3. Model development. Multiple teams will develop knee models using their own modeling and simulation workflow based on the same anatomy and mechanics data (section C.2). While the software, formats for derivative data and models, and simulation techniques will differ (Table 2), the overall approach will likely be similar (Figure 4). Models require representations of anatomy and tissue mechanical properties, and application of boundary conditions to conduct meaningful simulations[58]. Mechanical interactions between tissue structures will be defined and boundary conditions will depend on simulation cases (sections C.4-C.6). Model parameters are often adjusted through iterative analysis, particularly at the stage of model calibration (section C.4). Individual teams are expected to conduct sensitivity analysis, e.g., mesh convergence, and will also use specimen-specific data, if available. Computational modeling requires many decisions that influence reconstruction of anatomy, implementation of constitutive response of tissues, and nonlinear solutions of the biomechanical system. These decisions will depend on the available data and may also be influenced by convenience, e.g., software capabilities and preferences. As a result, predictions may differ between the teams. Team-specific workflows are described below in more detail and examples are provided in Figure 5.

C.3.1. Workflow 1: Open Knee(s). The Open Knee(s) workflow emerged from the development of the first generation model[18] Figure (5-A), which was used for multiscale modeling of joint, tissue, and cell mechanics[50]. Freely available and open source tools are utilized, and detailed specifications are provided for the public[76]. In summary, manual segmentation using Slicer[85] results in volumetric representation of the tissue structures - specifically femur, tibia, patella; femoral, tibial, patellar cartilage; menisci; cruciate and collateral ligaments; patellar ligament; and quadriceps tendon. MeshLab[86] is used to generate surface representations, where the process includes noise and artifact removal to prepare the surfaces for meshing. Meshes are generated using Salome[87] (tetrahedral) and, if possible, using IA-FEMesh[88] (hexahedral). Clinically relevant coordinate systems are defined[89] and registration markers relate imaging and joint mechanics testing coordinate systems. Bones are assumed to be rigid; cartilage, menisci, ligaments, tendon are nonlinear elastic materials, incorporating anisotropy and inhomogeneity, with material properties determined from specimen-specific tissue testing data (which is planned for Open Knee(s) specimens, C.2.1). If tissue mechanical properties are not available, it is possible to rely on literature[18]. Frictionless contact are defined between all articulating surfaces. Simulations are conducted using FEBio[64], currently with version 2.5, and Python scripting allows automation of various pre- and post-processing steps. Ligaments commonly exhibit in situ strain at the imaged state of the knee, which is the reference state for the model[90]. Currently, data from literature were adapted[44,91]. It is possible to utilize Python and optimization routines in SciPy[92] to adjust ligament in situ strains in a way that joint kinematics-kinetics predictions of the model match measured specimen-specific joint response[67]. Simulation scenarios have demonstrated predictive capacity against population response, i.e., passive flexion[93] using Open Knee(s) - Generation 1[18] (Figure 5-A).

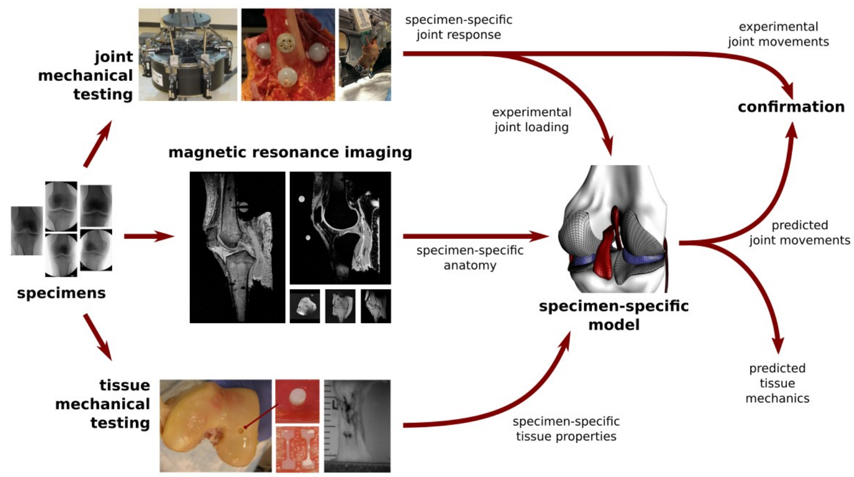

Figure 4. The general modeling and simulation approach requires joint anatomy and tissue mechanical properties to build the model (Open Knee(s) workflow is shown). While it is common to have access to imaging data to reconstruct anatomy, specimen-/subject-specific tissue properties may not be available. When joint mechanics response is collected, the models can be evaluated for authenticity and/or calibrated to better represent specimen-/subject-specific behavior. The accuracy of data analysis procedures to build the models and model developers' preferences to accommodate lack of required information, to select the level of anatomical and mechanical fidelity, and to exploit simulation software capabilities, may instigate uncertainties in the representations of model components. Therefore, discrepancies in simulation results are expected even when the same data set is used for modeling.

C.3.2. Workflow 2: University of Denver. The University of Denver's Abaqus-based (Dassault Systemes, Johnston, RI) simulation framework allows for interchangeable rigid and deformable representations of the tissues (Figure 5-B). Subject-specific three-dimensional anatomy are segmented from imaging using ScanIP (Simpleware, Exeter, UK). Reconstructed surfaces are then discretized and meshed with triangular shell elements for the cortical bone and 8-node hexahedral elements for the femur and tibia cartilage using HyperMesh (Altair, Troy, MI). A spectrum of representations have been used for ligamentous structures, ranging from bundles of tension-only nonlinear spring elements to full three-dimensional structures[67,94]. Ligament lines of action are determined using either imaging or experimentally determined attachment points. The following structures are typically included: posterior oblique ligament, popliteofibular ligament, lateral and medial posterior capsule, and anterolateral structure. Ligament parameters, including stiffness, reference strains, and attachment locations, can be calibrated. Specimen specific calibration consists of an adaptive simulated annealing optimization algorithm, which minimizes model predictions versus experimental data, across varus-valgus and internal-external rotation torques at 0°, 15°, 30°, 45°, and 60° knee flexion angles[67] (Figure 5-B). Our systematic approach also assures that the ligaments engage in agreement with their physiological function. Intersubject variability becomes an important consideration to extend cohorts of subject-specific models to larger populations. To this end, sensitivity and robustness will be assessed by perturbing sets of input parameters within physiological bounds to assess both the stability of the model and the impact on the output measures of interest. Our research team is experienced in performing these types of error assessments and probabilistic evaluations[94–96].

C.3.3. Workflow 3: Auckland Bioengineering Institute. A typical modeling workflow at the Auckland Bioengineering Institute to simulate knee mechanics and investigate cartilage tissue stress distribution is composed of two levels to account for joint and tissue mechanics[97]. An initial parametric mesh of the knee joint is generated using cubic Hermite elements. Medical imaging data are used to obtain 'target points', which then drive a free form deformation of a parametric 'host mesh' to match an individual 'deformed mesh', which generates a patient-specific model and is available in the Musculoskeletal Atlas Project[98]. Further refinement is possible, which might be important for accurately representing cartilage thickness, for example. The whole joint knee model includes the major bone and soft tissue structures (Figure 5-C). While the model typically utilizes EMG-Driven OpenSim predicted muscle forces[99,100], for the purposes of this work, joint forces and moments will be applied to the finite element representation to quasi-statically solve for the deformations of the soft tissues for each simulation case (sections C.4-C.6). A tissue level model is integrated with the whole joint knee model, accounting for more detailed representations of cartilage, meniscus and ligaments, such as collagen fiber orientations with spatially varying stiffness and biphasic behavior[97] (Figure 5-C). The whole joint model is coupled with the tissue level models and both are solved using the Auckland Bioengineering Institute's nonlinear finite element analysis software, OpenCMISS[101] – a part of the IUPS Physiome Project.

C.3.4. Workflow 4: Cleveland State University. At Cleveland State University, finite element based knee models are solved using Abaqus/Explicit (Dassault Systemes Simulia Corp, Johnston, RI), though FEBio[64] is also being adopted. Models typically include the patella, tibia, femur, cartilage, and the following soft-tissue structures: superficial and deep medial collateral ligament, lateral collateral ligament, posterior cruciate ligament, anterior cruciate ligament, posterior capsules, and the anterolateral ligament (Figure 5-D). Manual segmentation is used to define all geometries (Slicer[85]). Ligaments are represented by surfaces and rely on sets of curves to define the cross sections. Curves are lofted (Salome[87]) and the created surface is subsequently meshed using membrane elements. Ligament geometries are easily updated, if desired. Custom scripts (Python 2.7) embed relatively stiff springs along the long axis of the native membrane mesh for each ligament (the expected collagen fiber direction). Along and cross-fiber stiffness values are adopted from the literature[102,103] and zero force reference lengths (the "slack" length) of each ligament bundle can be used as control variables during optimization[102]. Bones are modeled as rigid shells, hexahedral elements are utilized for cartilage[38]. Depending on the goals, cartilage properties are defined using various literature sources. For example, if efficiency is desired, cartilage is defined as a rigid body and a pressure-overclosure relationship is utilized[94,104,105], which Dr. Halloran has experience developing[104]. Boundary conditions are prescribed in a

Table 2. A large number of software, proprietary or open source, are commonly utilized by the modeling and simulation (M&S) teams. Modeling workflows can be heterogeneous based on the variety of software and the fragmentation of data formats.

	M&S 1 Open Knee(s) Cleveland Clinic	**M&S 2** University of Denver	**M&S 3** Auckland Bioeng. Institute	**M&S 4** Cleveland State University	**M&S 5** Hospital for Special Surgery
Segmentation **Geometric modeling** **Meshing**	Slicer ITK-Snap SimpleITK MeshLab SALOME Blender	Simpleware Solidworks Pro/Engineer Altair Hypermesh	Musculoskeletal Atlas Project AutoCAD OpenCMISS	Slicer MeshLab SALOME	Mimics Geomagic SOLIDWORKS Pro/Engineer
Simulation software	FEBio	Abaqus ANSYS	Abaqus OpenCMISS FEBio	Abaqus	Adams Abaqus
Data analysis **Programming**	Python NumPy SciPy npTDMS	Matlab Python	Matlab Python NumPy SciPy	Python NumPy SciPy	Matlab
Other M&S tools	Abaqus SOFA OpenSim	OpenSim Adams Nessus Unipass Isight	OpenSim CEINMS	OpenSim FEBio	
Data formats Image Geometry Data	.dcm, .ima, .nii .stl, .igs, .stp .tdms .xml, .txt, .hdf	.dcm .stl, .hm .txt, .csv	.dcm .stl .txt	.ima .stl .tdms .xml, .fcsv, .csv	.dcm .stl, .xmt_bin, .igs .xls, .txt, .cmd, .tab

clinically relevant coordinate frame[89] using experimental feedback data. To address the lack of specimen-specific soft-tissue behavior, optimization is used to determine the nonlinear properties of each ligament. A least squares fit based on the Levenberg-Marquardt algorithm ("leastsq" function in the Python/SciPy toolbox) is common in addition to other optimization methods.

C.3.5. Workflow 5: Hospital for Special Surgery. The modeling and simulation workflow of this team has been previously described[106]. In summary, imaged knees are processed using Mimics (Materialise Inc., Belgium) to develop three-dimensional models of the femur, tibia, fibula, cartilage, menisci, and registration markers. The surfaces of the three-dimensional models are smoothed using Geomagic Studio (Geomagic Inc., Research Triangle Park). Ligament insertion sites are obtained from images, dissection, and the literature[107–111]. The cruciate, collateral, and capsular ligaments, and the meniscal attachments are represented with at least 42 fibers (Figure 5-E). The anterior and posterior cruciate ligaments are represented by at least 6 and 7 fibers, respectively. Menisci are included[112] and the structural properties of each ligament fiber are described using a tension-only, nonlinear relationship from the literature[113,114,115]. Previous work established appropriate cartilage and meniscal contact definitions[106]. An optimization algorithm is utilized to determine the slack lengths of the ligament fibers, which identifies the fiber length at full extension that minimizes the differences between model predicted ligament forces and the corresponding experimental measurements. The optimization protocol follows a specific routine that is based on known bundle-specific recruitment as a function of flexion angle. All relevant geometries are imported into a multibody dynamics software (ADAMS, MSC Software, Newport Beach) where the equations of motion are solved using the "GSTIFF" integrator[116]. The outlined procedure has proven to be effective for simulation of passive flexion, with good agreement between model predicted and experimentally measured ligament forces and tibiofemoral kinematics[106] (Figure 5-E).

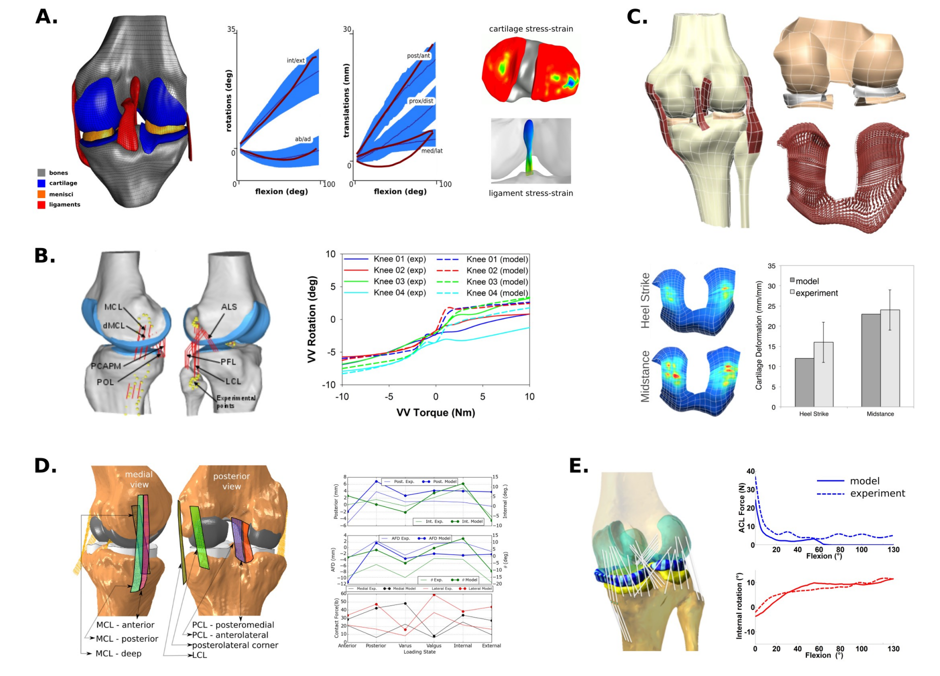

Figure 5. Knee models and simulation results from collaborating teams illustrate modeling variations and the investigators' capacity to build and utilize models for scientific conduct. A. Open Knee(s) from Cleveland Clinic; joint kinematics during passive flexion are shown. Tissue stress-strain distributions can also be obtained. B. A knee model from University of Denver. Joint kinematics-kinetics predictions are compared against measurements. C. The knee model developed by the Auckland Bioengineering Institute was used for predictions of cartilage stresses and deformations. D. Investigators at Cleveland State have been exploring the role of ligament representation on joint movements and contact mechanics. E. The predictive capacity of a computational model from the Hospital for Special Surgery was evaluated by comparing ligament forces and joint movements against experimental measurements.

C.4. Model calibration. Both data sets provide comprehensive information to build knee models. Nonetheless, the data may not be in a form to directly prescribe some model parameters, e.g., ligament slack lengths (or in situ ligament strain). A model calibration step can utilize the data sets to identify such missing or uncertain model parameters. For example, it is common to use experimental joint loads to drive a knee model and compare predicted joint movements to those that are measured experimentally and adjust ligament slack lengths in an iterative fashion until the deviations between model results and experimental data are minimized [67]. Such a process results in 'optimal' specimen-specific ligament slack lengths, which are calibrated to match specimen-specific response. The modeling teams will be allowed to use a pre-defined subset of the Open Knee(s) and University of Denver data for model calibration purposes. For Open Knee(s) data set, the tibiofemoral joint kinematics-kinetics data (only for the laxity tests[13,81]) and patellofemoral joint kinematics-kinetics[13,82] data will be available for calibration of model parameters. For University of Denver data set, the tibiofemoral joint kinematics-kinetics data (only for the intact joint retaining all ligaments and menisci[12,67]) will be available. The model calibration step will likely provide a fit error, i.e., how well the models can match specimen-specific response. This metric can be utilized as an indicator of the model's predictive capacity. The extent of model calibration, e.g., which parameters to tune for, will be left to individual teams.

C.5. Model benchmarking. The availability of comprehensive specimen-specific data for model development does not guarantee that a model will authentically predict specimen-specific joint and tissue biomechanics. A common approach to understand the 'validity' of models is to evaluate simulations of predictions against known 'withheld' behavior[57]. The proposed model benchmarking stage will accommodate such an analysis. A pre-defined subset of the Open Knee(s) and University of Denver data will form the basis for benchmarking. This data set will be strictly allocated for this purpose, i.e., the modeling teams will not be permitted to use these data for development and calibration. For Open Knee(s), the tibiofemoral joint kinematics-kinetics data from combined loading scenarios[13,81] will be the 'validation' data set. Simulations will be conducted with specimen-specific experimental loading and predictions of joint movements will be compared against measured joint kinematics. Cartilage contact pressure predictions will be compared against those measured during patellofemoral joint testing in Open Knee(s)[13,82]. Simulations will be conducted with patellofemoral joint loading of experiments to achieve this. For the University of Denver data set, the tibiofemoral joint kinematics-kinetics collected on the joint after resection of cruciate ligaments[12,117] will be the 'validation' data set, where model predictions obtained under specimen-specific experimental loading will be compared against measured joint kinematics. All these comparisons will indicate specimen-specific predictive capacity in an absolute fashion.

C.6. Model reuse. In the lifecycle of modeling and simulation, model reuse is an emerging strategy to expedite innovation, enable scientific discovery, and facilitate clinical care[118]. As a result, the desire to conduct simulation cases, which the models are not necessarily developed for and validated against, is not uncommon. To emulate the anticipated use of the models after their dissemination, four simulation scenarios will evaluate relative predictive capacity of the models to quantify joint and tissue mechanics (Table 3). Group-specific predictions will be compared against each other (see C.7). These simulations will portray whether conclusions will be impacted for scientifically and clinically relevant use cases even when using the same data source for model creation. Note that specimen-specific experimental data for these cases are not necessarily available.

C.6.1. Passive flexion. This simulation will target performance of the model to predict knee joint kinematics-kinetics at low loads. Passive flexion is a joint motion that is guided through flexion while the remaining rotations and translations are free to find equilibrium. During passive flexion, coupling of tibiofemoral joint degrees of freedom to flexion angle is well documented[93]. Models of natural knees should therefore reproduce such behavior, which is an inherent property of knee mechanics due to the structural arrangement of the ligaments and the contact surface geometry of the tibiofemoral joint.

C.6.2. Pivot shift. Pivot shift is a clinical examination, which is commonly performed to understand the mechanical adequacy of the anterior cruciate ligament to stabilize the knee. During the exam, the physician flexes the knee while applying internal rotation and valgus torques. Similar to in vitro experimentation[119], in this simulation scenario the knee models will be loaded by prescribed flexion (from 0º to 90º) while simultaneously applying an internal rotation torque of 5.3 Nm and a valgus torque of 8.8 Nm. The loading case will be applied to the model with an intact anterior cruciate ligament and also after its removal. The goals are i) to understand relative performance of the models to predict an abrupt increase in anterior translation of the tibia due to the removal of the ligament (a joint level mechanical metric), and ii) for the intact case, to compare predictions of anterior cruciate ligament forces and principal stresses and strains (tissue level metrics). This clinically relevant simulation case will push the boundaries of models' predictive capacity at relatively high joint loads.

C.6.3. Weight-bearing x-ray. A weight-bearing, standing x-ray is a common clinical exam to understand the progression of osteoarthritis by evaluating joint space[120]. Simulations have provided insight for patient-specific assessment of cartilage health[6]. Similarly, this simulation case will predict cartilage contact stresses and meniscus deformations (tissue level mechanics), compartmental contact forces, and compression of the joint as an indicator of change in joint space due to loading (joint level mechanical metric). The boundary conditions of the model will represent the alignment of the femur and tibia as dictated by the exam (15º flexion[6]). A force of ½ body weight will be applied to the femur while the tibia will be held fixed and only the anterior-posterior movement of the femur will be constrained.

C.6.4. Activity of daily living (sit-to-stand). The functional biomechanics of the knee during activities of daily living will continue to be of interest for simulation-based investigations of natural and reconstructed knee behavior. Sit-to-stand offers practical relevance, which can be a demanding activity for the young and elderly[121]. The movement imposes challenges on the knee, both on the tibiofemoral and patellofemoral joints, as a weight-bearing task that requires large range of knee extension and imposes significant loading on the extensor mechanism. In this simulation scenario, the focus will be to explore the consistency of the models to

Table 3. In model reuse stage, four simulation scenarios will be used to compare models' predictions of joint and tissue level biomechanics (see section C.6 for details). BC: Boundary conditions; TF: tibiofemoral; PF: patellofemoral; ACL: anterior cruciate ligament. All the cases have scientific and clinical relevance to understand healthy and diseased knee function. While all the models will be based on the same data, variations as a result of analysts' preferences may result in discrepancies.

SIMULATIONS		CASE I	CASE II	CASE III	CASE IV
Scenario		passive flexion	pivot shift	weight-bearing x-ray (standing)	sit-to-stand
Biomechanics Metrics	*Joint*	kinematics (TF)	anterior tibia translation	joint compression (TF) contact force (TF)	kinematics (TF) patellar tracking contact forces (PF)
	Tissue	--	ACL force ACL stress ACL strain	cartilage contact pressure (TF) meniscus deformations	cartilage contact pressure (PF)
Loading & BCs		prescribed flexion no joint loading	prescribed flexion internal rotation torque valgus torque	prescribed flexion anterior constraint ½ body weight	prescribed flexion quadriceps loading lifelike forces & torques (TF)

predict tibiofemoral joint kinematics, patellar tracking (joint biomechanics metrics), and patellofemoral contact force and pressures (tissue level mechanics). Boundary conditions will be approximated based on previously predicted musculoskeletal loading[121]. Time history of quadriceps force will be prescribed along with tibiofemoral joint forces and torques (minus the contribution of extensor mechanism on tibiofemoral joint loading).

C.7. Comparative analysis. Performance of the models will be assessed based on their predictive capacity, by comparing the model components, by evaluating computational cost and resource requirements, and through their compliance to proposed standards and formats in the biomechanics community. Predictive performance will indicate accuracy and precision of simulations, a fundamental concern for the scientific and clinical utility of the models. Differences in knee model components may indicate the source of prediction discrepancies; therefore they need to be documented. Modeling expenses should also be evaluated as they can be prohibitive; preventing adoption of models for routine use. Evaluation of the workflows, in terms of how they utilize widely available tools, data and model formats and how they conform to existing standards, is imperative when exchange of data, models, and simulation results is anticipated. The modeling teams will rely on colleagues at the U.S. FDA to act as an external and independent authority to evaluate individual modeling and simulation outcomes at each stage (development, calibration, benchmarking, reuse) and to provide an unbiased comparison (see letter of support). Upon finalization of each modeling stage, each group will prepare a report of the activity (detailing their modeling and simulation choices) and outcome data, e.g., simulation predictions. These reports will be prepared based on guidance from the biomechanics community[58] and the U.S. FDA[122], and submitted to colleagues at the U.S. FDA for review.

C.7.1. Predictive capacity. Comparative analysis to evaluate predictive performance of models requires extraction of joint and tissue metrics. These were detailed for each simulation case (C.4-C.6, also Table 3). Raw simulation results include vast information, i.e., rigid body dynamics, reaction loads, and tissue mechanics defined by strain and stress distributions. Post-processing of simulation results will likely be required, i.e., joint loading and kinematics need to be represented in a clinically relevant manner[89] and consistently among the teams. Tissue mechanics outcomes will be processed to obtain summary metrics, such as peak contact pressures, principal stresses and strains, etc. Averaged or cumulative quantities will also be calculated for tissues, e.g., total contact force. In theory, multiple models relying on the same source data and simulation case should provide the same predictions. On the other hand, variations in model development may result in mismatches. When experimental data on biomechanical metrics exist, an absolute reference can be established to rank the predictive capacity of the models, i.e., as a fit error (see section C.4 on calibration) or as a deviation from a benchmark (see section C.5). When such information is not available, a relative ranking needs to be performed to understand predictive capacity in relation to each other (as for cases described in section C.6). Simulation results are information rich, e.g., scalar biomechanical metrics such as joint reaction force, vector biomechanical metrics such as ligament force, field variables such as cartilage contact pressure and temporal metrics such as joint kinematics. For a given simulation case, the predictive performance of a model can be assessed by calculating a difference metric from an experimental benchmark (absolute predictive capacity) of from other models (relative predictive capacity). For scalar and vector metrics this can be in the form of a Euclidian norm; for field and temporal metrics, root-mean-square differences can be calculated. These difference measures can be calculated for each model against the results of experiments, i.e., for the benchmarking case (C.5) or of the other models, i.e., one against four (for simulations of C.6). This simplified analysis provides a pragmatic approach to rank the models. It illustrates which model is close to an experimental benchmark or to other models (lowest mean of differences) and how far apart the models are (based on the interpretation of mean and standard deviation of differences). Predictions of models will also be aggregated and compared to benchmark data and to each other through a generalized Bland-Altman analysis to provide limits of agreement among multiple methods[123]. It is possible to use more sophisticated strategies for model selection based on information theory[124] and examples exist in biomechanics literature[125]. In summary, the absolute performance of a model against experimental data and relative performance of a model among a group of models, across varying simulations cases and for different descriptors of joint and tissue biomechanics, will be quantified. Practical implications of the magnitudes of differences will be open to interpretation. These would depend on the simulation case and metric under consideration. It is therefore imperative that the collaborating teams seek for external and independent review (in this case U.S. FDA) and will have follow up discussions to answer the question "How good is good enough?"

C.7.2. Model components. Model components rely on processing of raw data to bring it into a form that can be directly incorporated in the virtual representation of the knee. At the fundamental level, these derivative data include geometries, tissue material properties, and representations of loading. For a single tissue, it also includes the combination of anatomical and constitutive representation to represent the mechanics of a single component of the whole knee model. Topological similarities and differences between geometric representations can be acknowledged using metrics such as the Hausdorff distance[126]. Mechanics of individual tissue components, at the material level (based on constitutive parameters) and at the structural level (based on the simulation of the tissue standalone) can be compared and ranked among different knee models.

C.7.3. Cost. Total burden of modeling and simulation emerges from computational cost, resource needs, and labor. Computational cost (CPU time and wall clock time) will be reported for all simulations along with the utilized computing power. Computing software and hardware will be documented as part of the modeling and simulation specifications (see C. Approach). The cost of software and hardware can be estimated from vendor pricing. The cost of labor, while difficult to pinpoint, can be evaluated from documentation of activities (see C. Approach), i.e., standard operating procedures adopted by the modeling teams. Both computational cost and total monetary cost will then be compared and ranked among different approaches.

C.7.4. Compliance. Modeling teams are free to utilize any workflow or tool that best suits their needs and background, and the requirements of the modeling stages. This is a pragmatic approach in response to the low traction in the adoption of standards for modeling and simulation worfklows and of general purpose formats for model and data exchange in the biomechanics community. This situation is primarily driven by the availability of and expertise in resources, capabilities of tools, time constraints, and incompatibility of proposed formats to completely encapsulate information. Nonetheless, the teams, in good faith, are committed to follow guidance and formats on management of workflows[21,127], ontologies[128], reporting[58,129], verification and validation[130], and model exchange[62]. Public documentation of detailed modeling and simulation specifications (see C. Approach) will provide the opportunity to establish the level of correspondence between individualized worfklows against idealized representations of standardization and unification efforts.

C.8. Outreach. The proposed activity will have a significant impact on the appropriate use of computational modeling for scientific studies of knee biomechanics and for clinical management of knee pathologies. An important potential outcome of the project will be the confirmation of reproducibility potential of modeling and simulation workflows for the exploration of biomechanical systems. This knowledge base will also inform the broad credibility problem in modeling and simulation in healthcare. Therefore, it is of utmost importance to reach out to specific communities and the general population, not only via traditional scholarly publishing but also by an aggressive dissemination strategy and through proactive communication platforms.

C.8.1. Dissemination. The contributing teams will engage with the community through a project website, which was recently launched at SimTK[131]. The project site provides a collaborative infrastructure for dissemination of data, models, documents, publications, discussion platforms such as forums, and development tools including a wiki for ongoing documentation and a source code repository to keep developing scripts and models under version control. The project will result in detailed documentation of model development and simulation workflows (know-how) and virtual anatomical and mechanical representations of the knees (models from each contributing team), and potentially model and data exchange scripts and code for comparison of model components and simulation results. When possible, the distributed material will be licensed under liberal terms, e.g., Creative Commons Attribution[132], to allow non-restrictive adaptation, reuse, and further dissemination. The research teams have significant experience in and commitment to open science and data and model sharing, e.g., illustrated by the open development philosophy of the Open Knee(s)[13,18], the data dissemination efforts of the University of Denver group[12], and the Musculoskeletal Atlas Project from the Auckland Bioengineering Institute[133].

C.8.2. Assemblies in conferences. The research teams will meet at national and international conferences targeted for biomechanics, engineering, and clinical audiences. The goals of these assemblies will be multiple. First, the teams will discuss progress. Second, through organizations of workshops and/or sessions, the contributing team members will promote the use of modeling, simulation, and associated training, especially for those developed here. As a result, an active engagement with the community will be possible. These assemblies will be held annually at a minimum. Target conferences include but are not limited to (focus areas in parenthesis): American Society of Biomechanics and International Society of Biomechanics (broad biomechanics research), symposia on Computer Methods in Biomechanics and Biomedical Engineering (applications and research in modeling and simulation - biomechanics focus), Multiscale Modeling Consortium meeting (clinical and scientific multiscale modeling, credibility issues), annual meetings of the Orthopaedic Research Society (clinical research) and American Academy of Orthopaedic Surgeons (clinical practice). The team leads have organized many sessions and workshops in such meetings in the past years.

C.9. Qualifications of investigators. The participating investigators account for more than 100 studies in knee biomechanics, including modeling and simulation and experimentation (a total of 117 based on a PubMed search conducted on June 15, 2017 with the search term “knee AND (Erdemir A OR Laz PJ OR Shelburne KB OR Besier TF OR Halloran JP OR Imhauser CW)”. Highlights from mostly recent scientifically and clinically relevant work include: Open Knee(s) project by Dr. Erdemir[18] and his simulation-based explorations of cartilage mechanics at joint, tissue, and cell scales[50]; statistical modeling of knee shape and alignment by Dr. Laz[134,135]; Dr. Shelburne’s studies on subject specific knee modeling[67] and on contact mechanics of implants under musculoskeletal loading[48]; patellofemoral joint biomechanics led by Dr. Besier[33,136]; Dr. Halloran’s seminal work on mechanics of knee implants using explicit finite element analysis[38,137]; Dr. Imhauser’s robotics experimentation to characterize in vitro knee joint mechanics[138] and multibody modeling to investigate knee dynamics[106]. In the past, the investigators interacted with each other at multiple occasions, which resulted in meaningful knee related scientific contributions[41,139,140] (Drs. Erdemir and Halloran) and for understanding the impact of modeling uncertainties through probabilistic approaches [95,141] (Drs. Laz, Shelburne and Halloran).

Experiences of the investigators to enhance quality of and access to computational modeling are relevant to the proposed project. The project has enthusiastic support from Dr. Morrison (Deputy Director at the U.S. FDA in the Division of Applied Mechanics in the Office of Science and Engineering Laboratories). She has a vested interest in understanding the biomechanical environment of organs, musculoskeletal joints, and tissues for medical device regulation[142]. Ahmet Erdemir (Principal Investigator) is the co-chair of the Committee on Credible Practice of Modeling & Simulation in Healthcare[143]. Dr. Morrison is a member of this committee and also chairs the ASME V&V40 committee on verification and validation in computational modeling of medical devices[130]. Drs. Erdemir, Halloran, and Morrison previously outlined good practices for reporting finite element analysis studies[58]. Most recently, Drs. Erdemir and Halloran collaborated to understand the requirements of integrating model sharing and reproducibility analysis to publication workflow[71].

C.10. Limitations and alternative strategies. As any research study, the proposed activity has limitations. First, the number of contributing teams may appear small. This is partly due to the logistics of mobilizing multiple groups in a timely fashion within the financial constraints of funding. Nonetheless, given the open nature of data sources, any external team interested in participating will be encouraged to do so. While the utilized data sets have been previously used for computational modeling for knee biomechanics[67], issues may arise due to the diverse modeling and simulation workflows. As new data become publicly available, or issues surface, the teams may consider alternative methods and sources of data or may collect new data. Due to the public availability of source data, it will not be possible to conduct a blinded evaluation. Nonetheless, involvement of U.S. FDA for external and independent review will provide an objective means for assessment of the performance of models. In addition, this approach will help justify, design, and subsequently create blinded data sets for future community wide benchmarking activities. Across group comparisons will provide relative uncertainty introduced by variations in modeling and simulation workflow. Such situations are becoming common with the pressing need for model reuse in research and clinical care[118]. In addition, the model calibration and benchmarking steps (sections C.4 and C.5) will likely provide pathways to establish indicators of each models’ predictive capacity in an absolute manner. If needed, the teams may decide to add other simulation cases. Finally, predictions across the groups may deviate largely. Such discrepancies are not necessarily expected for joint level biomechanical metrics, yet may be apparent in tissue level biomechanical outcomes. Comparisons of derivative data, which are generated as part of model development, are proposed to identify potential sources of such discrepancies (section C.7.2). Following such analyses, the teams may want to swap anatomical and mechanical representations of tissues with each other to develop the next generation of improved models.

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This is a resubmission of *Reproducibility in Simulation-Based Prediction of Natural Knee Mechanics* to the parent R01 program. The original submission was reviewed by the Modeling and Analysis of Biological Systems study section (Impact Score: 44; Percentile: 24). Based on the summary statement, our impression of the reviewers' and the panel's enthusiasm is that the significance and innovation were outstanding (if not exceptional) but the categorical scores and the overall impact score were dampened by the *"lack of an external standard to benchmark modeling"* and some other minor weaknesses in the approach. The summary of discussion and the reviewers' comments strongly emphasized potential impact and novelty, e.g., *"The reviewers considered the proposed focus on "human decisions" in biomechanical modeling to be innovative and to address a recognized, but previously unexamined source of irreproducibility in the field." "This issue is the 10,000 lb. gorilla in the modeling community, and answering this question, even for the knee biomechanics community, could have broad significance to the broader modeling community." "There is no doubt that this study will have high visibility and shape the field of biomechanics modeling." "... this is an outstanding proposal that addresses a critical road block ..." "... unconventional proposal ..." "There is tremendous innovation in seeking to document and understand the uncertainties that underlie a modeler's decisions ..." "There are currently no comprehensive standards for model exchange in the biomechanics community, and this proposal will be the first to develop those." "This may be the first effort of its kind to assess systematic differences in modeling workflows with an emphasis on modeler decision-making."*. Investigator(s) and environment were recognized as exceptional, e.g., *"The principal investigator was considered highly qualified to direct the proposed studies, and to have assembled an excellent set of collaborative teams to perform the individual modeling exercises." "The environment at all five sites is uniquely positioned to support the proposed study."* Our strategies to resolve the concern on model benchmarking and minor weaknesses in approach are summarized below. Significant text changes in the proposal are highlighted by vertical lines in page borders.

While the Approach was found to be well structured, well reasoned, and rigorously designed, the reviewers and the panel raised *"mixed levels of concern that there was no external standard for benchmarking"*. In the resubmission, we specifically break down the modeling and simulation workflow to model development, model calibration, model benchmarking, and model reuse to closely resemble the anticipated lifecycle of the models. Within each dataset, the joint kinematics-kinetics data are now strictly divided into two groups; one for model calibration (see C.4), i.e., to inform the assignment of specimen-specific model parameters to match specimen-specific response, and one for model benchmarking (see C.5), i.e., to provide an absolute metric of predictive capacity (rather than consensus results) in a manner based on specimen-specific data, which will be prohibited for use in model development or calibration. Activities for model reuse will still indicate relative performance of models in situations where they will be utilized for scientifically and clinically relevant cases that they have not necessarily been validated for. Our colleagues at the U.S. FDA are also enthusiastic to have a more hands-on role in the project, i.e., to essentially act as independent reviewers of the models and simulation results at model development, calibration, benchmarking, and reuse stages (see letter of support and C.7).

Minor weaknesses in the approach were acknowledged by the reviewers as *"unavoidable limitations",* which *"the PI is well aware of".* For example, one reviewer indicated *"broadening the scope beyond knee simulations"*. The resubmission elected to keep the application focus on the knee. Yet, both this reviewer and others already recognized that *"physics-based computational modeling of the knee joint biomechanics is an ideal exemplar that should also be informative to other areas of computational biomedicine and biomechanics"*. One reviewer recommended the proposal to take advantage of *"developments in model sharing and computer science communities"*. We are well aware of the ontologies, resources, and efforts for standardization of modeling and simulation workflows and model representation and exchange in the broad biomedical community. However, in the biomechanics community, there are no comprehensive standards (as also indicated by another reviewer) and simulation platforms are largely fragmented. In the resubmission, we clarify our unique position to understand the correspondence of existing but *"admittedly incomplete"* community efforts for standardization (an ideal scenario) and our individualized modeling approaches (a pragmatic response) (see C.7.4). This knowledge will emerge from the detailed documentation of the modeling and simulation workflows and of the computational tools for data and model representation and exchange. To clarify the plan for keeping track of each modeler's decisions during the model building process, the resubmission proposes a process for the individual teams to submit specifications for model development, calibration, benchmarking, and reuse at the project website before executing the steps necessary to accomplish these (see C. Approach introduction). Similarly, protocol deviations from the original specifications will be submitted and recorded at the project site. This strategy also aims for collection of information to document prerequisite computational tools and formats (see C.7.4), and to determine the cost of modeling, both in terms of simulation costs and in terms other resource expenses such as man-hours (see C.7.3).