The biomechanics of the knee has been the target of decades of scientific and clinical studies due to its significant role in locomotion. The joint exhibits high rates of injury and pathological conditions, e.g. osteoarthritis, a debilitating disease influencing more than 26 million only in the United States. As in any other musculoskeletal joint, the mechanical response of the joint, responsible for its function during activities of daily living, is the result of the complex anatomical construction, the mechanical properties of its tissue structures, and the mechanical interactions between these components. Computational modeling has been utilized broadly: in a descriptive fashion, to mine experimental data with the goal of understanding knee function; and in a predictive fashion, to design implants and assess surgical and therapeutic interventions. Nonetheless, high fidelity models, not only representative of the specimen-specific anatomy but also capable of reproducing specimen-specific joint response and specimen-specific tissue mechanical properties, do not exist. In addition, specimen-specific models, addressing differences in genders, ages, and pathologies, are not available. Development of robust and reliable knee joint models is a daunting task. In silico representations should be supported by elaborate mechanical testing at joint and tissue levels not only to build the models but also to establish confidence in them. In this collaboration with National Centers for Biomedical Computing, our goal is to establish a platform, supported by crowd-sourcing and cloud computing, to enable development of high fidelity knee models. Modeling efforts, while generally applicable to any musculoskeletal joint, will target at young, elderly, and osteoarthritic knees of different genders, supported by comprehensive anatomical and mechanical data acquired in a specimen-specific manner at multiple spatial scales. To accomplish this goal, we will characterize the joint kinetic-kinematic response, and the material properties of the joint's substructures. Anatomical reconstruction will be based on high resolution magnetic resonance imaging. For project management and also to allow community input, model development and dissemination efforts will be supported by the collaborative infrastructure provided by SimTk.org of Simbios, NIH Center for Biomedical Computation at Stanford. Finite element representations of the knee joint will be developed, with the analysis conducted by FEBio, finite elements for biomechanics. To give the community the opportunity to conduct simulations, a computation infrastructure will be provided by a gateway to XSEDE, Extreme Science and Engineering Discovery Environment. An advisory board of clinicians and knee modeling experts will routinely confirm the direction of the project. Adoption of open development practices, utilization of freely accessible software, and enabling cloud-based simulations will provide the opportunity for community-based development and testing of the models. Accessibility to experimentally confirmed comprehensive knee models will provide utmost reusability for the exploration of healthy and diseased knee mechanics and for establishing biomechanical management strategies to accommodate knee dysfunction.

Computational models provide the footing to understand normal and pathological mechanics of the knee joint and to guide simulation-based intervention design. If founded on comprehensive mechanical experimentation, i.e., acquired at joint and tissue levels from healthy and osteoarthritic knees of different genders and ages, confidence in model predictions, a necessity for clinical decision-making, can be established. Free and timely dissemination, supported by open development and accessible cloud-based simulation infrastructure, provides the opportunity to realize the scientific and translational value of such models by national and international research groups, clinical teams, and orthopedic industry.

The knee joint endures large mechanical forces during daily activities, exceeding multiples of body weights. Healthy mechanical response of the joint is necessary for normal locomotion and to provide stability during movements. Knee joint mechanics are an intricate function of its anatomy and the mechanical properties of the connective tissues, menisci, and cartilage. Influences of gender, age and disease on the mechanics of the knee joint have been studied extensively. Injuries to the substructures of the knee are high in prevalence, including but not limited to insults on cartilage, ligament damage, and meniscal tears [1]. Additionally, the highest prevalence and incident rates of osteoarthritis are seen in the knee [2]. It is not surprising that the study of knee mechanics as it relates to daily loads, and the understanding of individual and combined role of tissue structures in health and disease are still significant topics of basic and clinical research. A large number of experimental studies have established the fundamental knowledge of knee biomechanics. Computational modeling, on the other hand, provided the means to describe experiments and establish pathways for predictive investigations. As noted in the Interagency Modeling and Analysis Group Futures Report [3], integration of modeling in biomedical research is inescapable; and for the knee, computational models can provide the foundations for gender, age, and disease specific solutions to knee problems that can be virtually designed and tested. Nonetheless, robust models, founded on and confirmed against comprehensive experimental data, do not exist. Building such models however is a daunting task. It requires interdisciplinary interactions for ultimate reliability and utility.

Open science, while promising reproducibility, accountability, and reusability [4], has not been employed routinely, particularly in biomechanics research. For example, a PubMed search of finite element analysis of the knee joint (search string: “finite element” AND knee; conducted on January 24, 2011) results in 478 hits. However, to our knowledge, the only anatomically and mechanically realistic model of the knee (or any other musculoskeletal joint), developed in an open manner, or at least disseminated, is Open Knee, our own work [5]. Computational modeling and simulation, by its nature, is suitable for community-based development. It provides the opportunity to include any interested clinicians and investigators, and also to acquire and implement feedback from anyone during (not after) the research process. This capacity will likely to expedite reaching the scientific goals of knee biomechanics and the realization of simulation-based practice in the clinics; which in turn will maximize the utility of modeling and simulation efforts. This is certainly an advancement over the traditional knowledge dissemination, which is conducted through publications after the research is done.

The long term goal of this project is to establish experimentation, modeling, and simulation of musculoskeletal joints supported by community-driven science and cloud-based computing. Along this direction, this proposal specifically targets the knee joint with the following specific aims:

Specific Aim 1. To provide an open, freely available, and collaborative development, testing, simulation and dissemination platform for in silico exploration of the biomechanics of healthy and diseased knees.

Specific Aim 2. To develop in silico biomechanical models of healthy and diseased knee joints of different genders and ages, supported by specimen-specific joint and tissue level experimental mechanics.

This project will provide the opportunity for clinicians, researchers, industry, and the public not only to access and utilize knee models but also have a voice for the development of knee biomechanics research. The transparent platform, data, and models provided as part of this proposed activity will facilitate the understanding of the knee's mechanical response in health and disease, the evaluation of injury mechanisms, and the design of management strategies against pathological conditions.

This proposal uniquely fits to PAR-12-001 – Collaborations with National Centers for Biomedical Computing. For our group, collaboration with Simbios, NIH Center for Biomedical Computation at Stanford, will provide the infrastructure for development, dissemination and simulation through SimTk.org. While targeted at the knee, the tools will be applicable to any musculoskeletal joint. Experimentation to be conducted as part of the proposed activity can be an application driver for the analysis of joint and tissue level anatomical and mechanical data in the long term. This opportunity will promote the development of tools for experimental data parsing, post-processing of simulation results, and development of in silico representations of diarthrodial joints. Development of FEBio, an open source finite element analysis package for biomechanics [6], will also be supported. The project also has the potential to extend the biomedical realm of SimTk.org applications, where joint models can be coupled to musculoskeletal simulations of the lower extremity, to explore interactions between muscle function and joint & tissue mechanics. From an infrastructure perspective, this project aims to establish the link between the collaboration platform of Simbios and high performance computing resources, in parallel with the direction of Simbios geared towards the development of virtual machines to reproduce results of others [7].

A. Significance

A.1. Mechanical Function of Knee in Health and Disease. Mobility and load bearing capacity of the knee joint is an intricate result of the articulating surface geometries, the individual mechanical properties of ligaments, cartilage, and menisci, and their mechanical interactions with each other. The mechanical response of the joint is responsible for providing healthy locomotion and for enduring large forces during daily activities. Any dysfunction of the whole joint or its tissue components, may diminish the joint's mechanical capacity, which may limit performance, cause pain, and lead into disability. Unfortunately, insults and pathological conditions to the knee, chronic or traumatic, are very common. Problems associated with knee biomechanics were the most common reason for orthopedic surgeon visits, illustrated by ~19 million visits in 2003 [8]. In osteoarthritis, prevalence rates for the knee has been reported as high as 16%, the highest among other joints [2]. In the United States alone, ~27 million in total are affected by this debilitating disease [2]. Osteoarthritis of the knee has also been identified as one of the leading causes of disability among non-institutionalized adults, which frequently lead to joint replacement procedures [2]. Sports related injuries of the knee joint are also prevalent. Damage to anterior cruciate ligament and meniscal tears are commonly treated in the clinics [1]. Soft tissue injuries significantly influence the mechanics of knee joint and are known to preclude degeneration of the cartilage, likely as a result of the altered mechanical state [9]. For this reason, many tissue reconstruction techniques and rehabilitation protocols have been devised with the goal of bringing the joint back to its natural mechanical state [10]. Incidence rates between males and females can be significantly different, i.e., female athletes exhibit a two- to eight-fold higher rates of anterior cruciate ligament injury [11]. Occupational injuries of the knee are among the highest of work-related musculoskeletal injuries with meniscal tears, requiring surgery and physical therapy, leading these [12]. Complications of patellofemoral joint are also a major reason behind knee related clinical visits; as anterior knee pain is common among active young people.

Prevention of knee problems require a thorough understanding of the biomechanical function of the joint, its tissues, and their mechanical interactions. Management of knee problems may require surgical procedures, therapeutic interventions, and rehabilitative strategies with proven success rates. It is not surprising that fundamental research on the biomechanics of the knee, e.g. [13], and clinical trials to evaluate strategies for management of knee conditions, e.g. [14], are actively pursued by wide range of investigators.

A.2. Need for Dependable Computational Knee Models. Finite element analysis has become an important tool in knee biomechanics to explore joint and tissue function [15,16], to understand injury mechanisms [17], to study pathological joint mechanics [18] and to evaluate surgical performance [19]. Numerous models have been developed and used and in many cases, multiple models were constructed by independent research groups to investigate similar questions [20,21]. Explorations of cartilage mechanics are wide spread as a result of this tissue's importance for load bearing and its degeneration due to age, osteoarthritis, or injury. In that regard, many modeling and simulation studies targeted for translational use, evaluating mechanical interventions at the cartilage, i.e., osteochondral grafting [22]. Local stresses in healthy and/or diseased states were predicted as indicators of potential damage risk [23,24]. Exploratory investigations, such as those of joint malalignment [25], indicated the importance of joint level mechanical changes on cartilage stress.

Knee modeling approaches were not limited to cartilage, they were also utilized to understand mechanical role of other tissues, e.g. ligaments [26,27], menisci [16,28], on the overall joint response, and on the stress distribution within the knee. Examples included but were not limited to the studies of menisectomy [29], injury mechanisms of anterior cruciate ligament [30], biomechanics of the medial collateral ligament [31], and patellofemoral joint contact [32]. Computational models of the knee joint have significantly contributed to the the understanding of implant mechanics [33,34] and have been the tool of choice to evaluate performance of soft tissue reconstruction, i.e. of ligaments [35]. Recently, knee joint models have also been used to understand complicated multiscale interactions between joint mechanics, and tissue and cell biomechanics [36].

Ultimately, knee joint models will transform into clinical tools for patient assessment [18] and personalized care from their current role as research tools. Nonetheless, even as research tools (as described above), their capacity to provide fundamental knowledge on knee biomechanics, not even considering support for clinical-decision making, is highly hindered due to missing data to establish model parameters, lack of representation of different populations, and the void for a systematic approach to establish confidence in model predictions. The typical process for generating a validated, specimen-specific finite element representation of the knee involves: anatomical imaging data; kinetic and kinematic data for the intact joint; material testing of the substructures;

reconstruction of anatomical geometry; mesh generation; constitutive modeling of tissues; definition of boundary conditions, loads, and constraints; mesh convergence analysis; and validation and sensitivity analysis. The entire process is a laborious task and it is not necessarily achievable in vivo. Yet, it is possible to develop dependable models of cadaver specimens where we can establish our error bounds for prospective patient-specific analysis. It is unfortunate that such elaborate studies do not exist. These models will be indispensable tools, which can be used in a descriptive fashion, to document joint and tissue function, and in exploratory studies, targeted at design of novel interventions. If, in the long term, we want knee joint models as virtual prototyping test beds and as tools to support regulatory process, we need to build new knee joint models that rely on large sets of specimen-specific data (for development and evaluation) and sound engineering principles to represent lifelike response in a usable form. Only after this, stringent evaluation criteria (such as those of the Food and Drug Administration) for using knee joint models as medical tools may be met.

A.3. Citizen Science for Knee Biomechanics. Dissemination of scientific research, and in the particular case of knee biomechanics, experimental data and models, will have utmost impact on users. Scientists, engineers, and clinicians need dependable information to develop new technologies for prevention of knee injuries and for the design of rehabilitative, therapeutic, and surgical interventions to treat knee problems. If the community is involved at the beginning of and during knee biomechanics research (rather than at the end), the scientific goals of understanding healthy and diseased function of the knee and providing a virtual test-bed for simulation-based knee care can be expedited. Open science approaches have been successful for research on drugs [4] and there is no reason not to reproduce this success for biomechanics. Citizen science, allowing everyone to criticize and contribute as the work goes on, is transparent and adaptable [4]. It continuously goes through a stringent peer-review process. An open source approach also gives the opportunity for anyone to pick up the work to continue progress or to steer it other directions, and it is especially valuable when investigators leave the project. Open development and community involvement has a proven track-record for delivering highly successful free and open source software projects [37]. Development of musculoskeletal joint models can certainly benefit from similar approaches. As phrased by Woelfle et al. [4], none of us is likely to be as smart as all of us. The research team not only seeks to provide computational models which can be extended and modified to meet a particular researcher's need, but also to benefit from the expertise of numerous investigators (or any interested party as a matter of fact) who may want to use these models, provide feedback during their development, and contribute to their construction. In return, model quality will be enhanced by wide-spread suggestion and criticism.

A.4. Broader Implications for Simbios and Biomechanics Community. While biomechanical simulation software, for musculoskeletal modeling [38] and for finite element analysis [39], are freely available, accessible models that leverage their functionality to directly address research and clinical problems are scarce. Virtual representations of the knee will provide scientists, engineers, and clinicians, the ability to directly utilize simulation software without the burden of model development efforts. If computation platforms are accessible as well, the usability and translational value of such models will dramatically increase. Models of the knee joint will also extend the capabilities of Simbios. First, tools developed for the proposed knee models can be applied to any other musculoskeletal joint due to the generalized approach for finite element representation of the joint. It is also possible to couple joint models with musculoskeletal movement simulations to understand feedforward and feedback relationships between mechanically realistic joint and tissue function, and movement control [40]. For example, finding adaptive movement strategies to prevent hazardous loading of the knee joint, which may induce tissue damage, may be possible. Examples of such simulations, yet for other organs, exist [41]. Prospective integration of anatomically and mechanically realistic representations of the knee in movement simulations will increase our capabilities to address relationships between healthy and pathological locomotion, muscle function, and joint and tissue mechanics. An open development approach, and timely dissemination of data and models give biomechanics researchers (established and emerging investigators, students, etc) the opportunity to learn (or teach) principles of biomechanical experimentation, and modeling and simulation. It is likely that greater access to documented and comprehensive data and models will foster new research venues in musculoskeletal joint biomechanics.

B. Innovation

B.1. Anatomically & Mechanically Founded Knee Models. Many models of the knee have knee-specific anatomy, acquired from a subject's knee [25] or from a cadaver specimen [42]. However, the material properties of the tissues, that dictate joint and tissue mechanics along with joint geometry, are not specific to the same knee. The tissue properties commonly rely on values found in literature or fits to data available from tissue samples obtained from other resources [15,26,42,43]. In many cases, these properties do not represent the age, gender, and or disease state of the subject or donor, which may result in an erroneous representation of the alter material level tissue response. This mismatch of anatomy and tissue mechanical properties is a source of uncertainty. For modeling of the in vivo joint, acquisition of tissue properties will likely require elaborate experimentation [44] and inverse analysis techniques [45–47], yet it may not even be possible for the knee. For modeling of cadaver specimens, acquisition of tissue mechanical properties along with joint and tissue anatomy is possible [48] but due to the amount of experimentation, it requires strategic planning. A primary novelty in this proposed activity is to develop models of knee joints not only based on specimen-specific anatomy but also including specimen-specific properties of ligaments, cartilage, and menisci.

The capacity of knee models to reproduce the actual mechanical function of the joint needs to be evaluated at multiple levels, and ideally in a specimen-specific manner. For example, a tibiofemoral joint model needs to represent experimental joint level kinematics and kinetics. Current literature in knee modeling commonly lacks an elaborate model confirmation approach, where the “validity” of the model is based on simplified loading conditions that may or may not recruit all the underlying tissues of interest[42]; and sometimes it was not specific to the modeled joint[16]. In addition, “validity” is commonly implied, not directly established. It is unfortunate that there is not a single intact knee model that has a joint mechanics response confirmed against a large set of simple and combined joint loads. As a significant novelty, this proposal will incorporate comprehensive joint testing along with a matching simulation test-bed to fill in this gap. This will indicate the quality of models' joint level functionality as a result of the combined effects of articulating geometry, menisci, and ligaments.

B.2. Diversity in Virtual Representations of the Knee. The mechanical functions of the knee joint and its tissue structures are influenced by gender related differences [49], aging [50], and through the progression of osteoarthritis. For example, the female knee joint may be more prone to anterior cruciate ligament injuries due to its anatomical construction, e.g. larger Q-angles and smaller intercondylar notch [51]. Anatomical and mechanical properties of the knee joint are different in the elderly, i.e. cartilage gets thinner, tissue structures become stiffer [50]. Osteoarthritis significantly affects joint properties, sometimes differently in males and females [52]. If one needs to explore such mechanical differences in joint and tissue function in health and disease, and prototype interventions for management of knee joint problems in specific populations, diverse biomechanical representations of the knee are indispensable. In knee modeling, a plethora of models exist, yet modeling of diseased states commonly relied on adaptation of “healthy” knee models using guidelines from other investigations [23,53]. As described in section B.1, many of these models lack full specimen-specific representation including anatomy and mechanical properties. To accommodate explorations of knee mechanics as a function of gender, age, and osteoarthritis, this proposal aims to establish a diverse set of computational knee models, based on systematic anatomical and mechanical characterization. This is an innovative step for the science of knee biomechanics, and in modeling and simulation of musculoskeletal joints.

B.3. Open Development Approach. A significant novelty of the proposed activity is the implementation of an open development practice (see sections C.2.3 & C2.4). This is not necessarily limited to viewing the progress of research but also provides mechanism for feedback and contribution. This is a significant step, which moves beyond free and open dissemination towards the realization of citizen science in biomechanics. Examples of this approach can be seen in drug development [4] and we have already initiated open modeling and simulation as evidenced by our preliminary work on knee biomechanics [5]. This culturally novel approach to perform experimentation of musculoskeletal joints and develop their virtual representations will likely enhance the quality of data and models available for the exploration of knee biomechanics. Relevant to open development, another novelty proposed by this project is the incorporation of a web-based computing infrastructure to allow users and developers of knee models to conduct simulations on the cloud (see section C.3.2). This will help investigators with limited resources to be able to run loading scenarios that may require significant computational cost. It will provide the opportunity for in silico discovery of knowledge for understanding of the knee biomechanics and treatment of its disorders. Similar interfaces has been developed for protein folding [54] but not in the discipline of biomechanics.

C. Approach

C.1. Qualification of Investigators. The proposed study will incorporate a diverse group of personnel including biomechanics researchers, clinicians, software developers, system administrators, and web designers. The activities will be led by Dr. Erdemir, Principal Investigator, and his research team, who have the necessary expertise in and resources for computational modeling [40,41,47,55–57] and experimentation of musculoskeletal joints [44,58,59]. The infrastructure for heterogeneous collaboration, biomedical computing and cloud-based simulations will be supported by Simbios, NIH Center for Biomedical Computation at Stanford, simulation software developers at the University of Utah, and computing and web site deployment services at the Cleveland Clinic. Dr. Delp and Dr. Ku at the Stanford University bring significant expertise in open source biomedical software [38] and infrastructure development [7]. Dr. Weiss at the University of Utah is the lead developer of FEBio, finite elements for biomechanics [39], and is an expert is experimental and computational mechanics of joints and tissues [60–64]. Dr. Erdemir has a long history of collaborations with the teams at the Stanford University [65] and the University of Utah [65,66]. Mechanical testing of joints and tissues will be supported by the BioRobotics and Mechanical Testing Core, who has illustrated leadership in cadaver simulations of musculoskeletal joints and characterization of tissues [67–69]. Anatomical imaging of knee joints will be provided by the Case Center for Imaging Research. Both these facilities have been previously utilized by Dr. Erdemir; his team and members of these groups have collaborated for testing of organs, joints, and tissues [48,58,70] and imaging of knee joints [48]. Ongoing work of the team will be appraised by an Advisory Board; a group of clinicians (Drs. Andrish, Jones, Saluan) and scientists (Drs. Dhaher, Guess, Korhonen), experienced professionals of clinical care of the knee joint [71–73] and computational mechanics of the knee [26,53,74–77], respectively.

C.2. Approach for Community Supported Modeling & Simulation. The overall approach for modeling and simulation of joint mechanics incorporating community input will require multiple components: leadership of the project, facilities for experimentation and modeling, and online infrastructures enabling timely dissemination, community input, and computing (Figure 1). In the proposed activity, these components will be provided for the experimentation, modeling, and simulation of the knee joint, yet they can be adapted for general modeling and simulation practice of musculoskeletal joints. A tentative timeline, to implement the community-supported cloud-based modeling and simulation of knee joints, can be found in Table 1.

C.2.1. Project Steering. Dr. Erdemir, Principal Investigator, and his team will lead the daily operations of the project, including the development of platforms to facilitate online collaborations and simulations and the execution of experimentation and the majority of model development. He will be the liaison between core facilities within the Cleveland Clinic, external collaborating institutions, the Advisory Board, and contributors from the community. Dr. Erdemir leads the Computational Biomodeling (CoBi) Core at the Cleveland Clinic. He has managed many projects of this size [65,66]. His team has substantial experience in collaborative work with fellow investigators (internal or external), clinicians, and volunteers [55,57,78–81].

C.2.2. Advisory Board. The proposed activity will have an Advisory Board that will evaluate the progress of the project biannually, from clinical and scientific perspectives and also in regards to the involvement of the biomechanics community. The Advisory Board will have three clinical and three scientific members to accomplish this goal. Drs. Andrish, Jones, and Saluan, all from the Cleveland Clinic, will serve as clinical members. These orthopedic surgeons commonly manage disorders of the knee in their clinical practice and have a significant interest and active involvement in knee

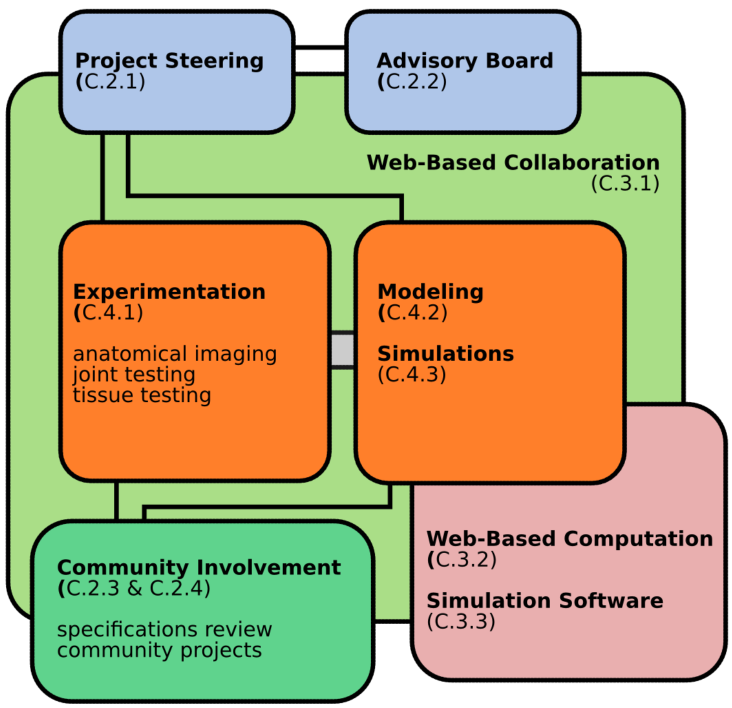

Figure 1. Organization of the proposed activity. Project Steering will be conducted by Dr. Erdemir and his research team supported by an Advisory Board of clinicians and researchers in knee biomechanics. Concurrent experimentation and modeling efforts will be strengthened through community involvement. Web-based collaboration and computation interfaces will enhance development of virtual representations of the knee through an open science practice. For each component, relevant sections in the text are referred.

related biomechanics research [73,82–85]. Dr. Dhaher, from the Rehabilitation Institute of Chicago, Dr. Guess, of the University of Missouri – Kansas City, and Dr. Korhonen, from the University of Eastern Finland, will act in the Advisory Board as scientific members. All of them have significant research programs focusing on the knee joint mechanics, i.e. Dr. Guess in musculoskeletal biomechanics of the knee [75,76,86], Dr. Dhaher in joint and tissue mechanics of the knee [26,74,87,88], and Dr. Korhonen in multiscale cartilage mechanics at joint, tissue, and cell levels [53,77,89]. The group brings vast expertise in modeling and simulation of this musculoskeletal joint. Biannually, Dr. Erdemir will prepare a progress report that will detail past 6 months' scientific achievements and bottlenecks, community involvement, and planned activities for the following 6 months. He will also give a presentation, as a webinar and through a conference call (to accommodate all members to attend remotely), which will summarize progress. Each member of the Advisory Board will be responsible to review and provide feedback on the progress. They will also vote on any items that are proposed as planned activities.

C.2.3. Open Development. The project will adapt an open development approach where access to ongoing work by the research team, the biomechanics community, and public will be available, not only for viewing but also for active contributions. We have utilized this approach in our preliminary work, Open Knee [5] (Figure 2, Table 2). Any interested party was able to freely download release versions of the models and also had access to the developing source code. For those who wanted to contribute actively, mechanisms were implemented, where a request to be added as a team member need to be submitted with a brief description on the reason of their interest in the project and their planned contributions. This approach successfully enabled a volunteer investigator to upgrade model development scripts, which was provided as a result of his appreciation for being able to use Open Knee freely for his research (Table 2). The proposed open development activities will implement similar practices. Additionally, initial specifications for experimentation and modeling (see section C.4) will be posted on project site (see section C.3.1) for others to review and provide their recommendations before starting the actual work (Table 1). To encourage contributions, a community projects program will be initiated for rewarding involvement (see section C.2.4). A necessity of open model development is that any computational tool used for relevant work need to be accessible. All supporting model development, and analysis scripts will be written in Python programming language [90], which is free to use for any entity. Finite element analysis will be conducted using FEBio[6] (see section C.3.3). It should also be noted that users and developers may need to access high performance computing resources, and for this reason, a web-based gateway to such an infrastructure is planned (see section C.3.2). To promote community involvement, activities of the project will be posted at Biomch-L [91], a community of more than 10,000 people conducting biomechanics research, and will be publicized in national and international conferences.

Table 1. Tentative timeline for the proposed research activities. Each item signifies a milestone in the project. S1-6: Specimen 1-6. AS: Additional specimens (if necessary). R: Community review of specifications and work in progress.

Activity	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
Specific Aim 1																
Web collaboration infrastructure (C.3.1)																
Web computation infrastructure (C.3.2)																
Simulation software improvements (C.3.3)																
Specific Aim 2																
Experimentation (C.4.1)		R		S1	R	S2	S3	S4	R	S5	S6	AS				
Modeling (C.4.2)			R		S1	R	S2	S3	S4	R	S5	S6	AS			
Simulations (C.4.3)			R		S1	R	S2	S3	S4	R	S5	S6	AS			
Advisory Board review (C.2.2)																
Community projects program (C.2.4)																
Dissemination (release versions) (C.6)																
Publications																

C.2.4. Crowd-Sourcing. The project will include many subprojects: analysis of experimental data for model development, individual components of model generation, and simulations for verification and validation. Many of these subprojects will be incorporated into a community projects program similar to the Google Summer of Code [92]. Each of these projects will be designed by the research team to fit into a work load equivalent of the traditional summer student research. The projects will be summarized and listed at the project site (see section C.3.1). Applications from the members of the biomechanics community (students, post-docs, any interested party) to complete such projects will be accepted by the research team. Review of applications will be conducted by the research team and the Advisory Board. Selected members will become part of the development team and they will be rewarded through a fee-for-service mechanism, in concert with the review of their work.

Specific Aim 1. To provide an open, freely available, and collaborative development, testing, simulation and dissemination platform for in silico exploration of the biomechanics of healthy and diseased knees.

C.3. Infrastructure for Community Supported Modeling & Simulation. A transparent and freely accessible web-based infrastructure that supports collaboration and computation will be developed (Figure 1).

C.3.1. Web-Based Collaboration. Simbios will provide the infrastructure for collaboration via SimTk.org, a web-based platform for software development and dissemination [7,93]. Communication between investigators and other collaborative model developers will be facilitated by a project web site at SimTk.org. Our research group already has a site on knee modeling that can be utilized for this purpose (Figure 2). For development, the project site includes a wiki and a source code repository, all under version control with the capacity to track contributions. Additional features such as mailing lists and forums will also facilitate communications between developers. The project site will also be the hub for dissemination of documentation, data, models, and scripts (see section C.6). SimTk.org infrastructure provides full backup, captures usage statistics, and facilitates full control of what information is publicly accessible. During the research timeline, the developer areas, e.g. source code and wiki, will be given read access to the public as the individual components mature. In addition, interested parties will be provided write access in order to contribute (see section C.2.3). On a need basis, Simbios team has agreed to implement new features to support crowd-sourced model development and cloud-based simulations of biomechanical joints. These modifications will likely include enhancements for easier sharing of models, experimental data, and simulation results, addition of mechanisms to better assess and increase community involvement in the project, and features to allow the project to take advantage of cloud computing resources. In particular to community involvement, Simbios personnel will create formal documents and examples to demonstrate best practices for using this collaborative environment. In addition, a ratings and/or a rewards system can be implemented to assess and increase contributions. The Simbios team will also work closely with the research team to identify how data and software hosted on SimTk.org can best be integrated with cloud computing services. Specifically, online communication between collaboration and computing environments will be established to enable automated update of models at the web-based gateway for simulations (see section C. 3.2). Dr. Delp, Co-Principal Investigator of Simbios, and Dr. Ku are leaders in open source development of biomechanical software and relevant dissemination [7,38]. Dr. Erdemir has previously worked with the Stanford University team in another collaboration with Simbios [65]. From an infrastructure point of view, this previous collaboration resulted in the implementation of the wiki feature at SimTk.org.

Figure 2. Project website at SimTk.org, web-based collaboration infrastructure of Simbios. The site was created as part of our preliminary work on open development of a three-dimensional finite element representation of the knee joint, Open Knee, https://simtk.org/home/openknee. The site provides "Downloads" and "Documents" sections for release versions of data, models, scripts, and relevant documentation. Interactions between collaborators and community are conducted through the "Wiki", "News", and "Forums". Development is supported by feature requests, bug tracking and a source code repository under the "Advanced" section. Both the wiki and source code repository provide version control systems to track activities of developers and facilitate collaborative work. Visitor, user, and developer statistics are also available.

C.3.2. Web-Based Computation. Free availability of the simulation software (see section C.3.3) provides the capacity for anyone to be able to develop models and run simulations on their own computers. Nonetheless, necessity to perform nonlinear biomechanical analysis of

Table 2. Statistics from the preliminary work of the research team on open development and dissemination of a finite element representation of the knee joint (also see Figure 2). Even at a preliminary stage, the impact of this approach on other biomechanics investigators and trainees can be inferred from web statistics provided by SimTk.org, which is provided by Simbios.

Open Knee Statistics (January 30, 2012)	
Project site	https://simtk.org/home/openknee
Project launch date	February 18, 2010
Page hits	19525 (past 180 days)
Unique visitors	902 (past 180 days)
Team members	8 total 3 active 2 original, 1 from community
Documentation	1 user's guide 3 conference abstracts
Development	248 repository commits
Releases	v.1.0.0.199 (major) December 17, 2010 v.1.0.1.202 (minor)
Release downloads	207 total 162 unique
Expected use of downloads (feedback provided by users)	56 research 54 training 24 reference for other models 14 evaluation 9 anterior cruciate ligament 9 instrumentation/implants/ orthotics/prosthetics 6 cartilage/osteoarthritis 5 potential contributions 4 impact biomechanics 4 knee loads 2 knee movements 2 knee geometry 1 meniscal injury 1 femur biomechanics Rest unspecified/unsure

knee function may dictate the users and developers to have access to high performance computing resources. To enable a web-based simulation interface for the community, the proposed activity will target at the development of a science gateway using XSEDE, Extreme Science and Engineering Discovery Environment [94]. XSEDE is a federally funded project unifying computing resources in the nation to provide a single virtual system that scientists can use to interactively share computing resources, data, and expertise. The proposed gateway will provide an online site, where knee joint models under development or released as part of the project timeline, will be available for simulations on the cloud using computing resources of XSEDE and the simulation software (see section C.3.3). The site will also include workflow tools, job submission modules, and tutorials for configuring and running biomechanical simulations of the knee. The research team will apply for XSEDE allocation to accommodate development and use of the gateway. To build the web-based portal, a web-server on a virtual machine, hosted by XSEDE, will be developed. The gateway site will provide secure access utilizing commodity web site development software and open standards. The system will provide routine backups, institute a user registry, track usage and job load, and collect account statistics to summarize community involvement. This portal will provide behind scenes connection of XSEDE computing resources and models at the project site, eliminating the need for the users and developers of models worry about the cyberinfrastructure needed to conduct simulations. Development of the gateway will be conducted by the web development and system administration personnel of the Computing Services at the Cleveland Clinic. Simbios web development team and simulation software developers at the University of Utah will support these efforts.

C.3.3. Simulation Software. Simulations of knee joint models will rely on finite element analysis. Specifically, FEBio [6], a free and open source finite element analysis software, will be utilized. FEBio is developed by our collaborators at the University of Utah, led by Dr. Weiss. The software provides a nonlinear implicit finite element analysis framework specifically designed for computational solid biomechanics, i.e large deformations, contact of solid and biphasic materials [39]. FEBio offers a wide variety of constitutive models, loading and boundary conditions, and interaction definitions, e.g. contact, relevant to simulation of lifelike scenarios for joint and tissue mechanics [95]. The software utilizes object-oriented C++ code for extensibility, and incorporates analysis algorithms tuned for scalar and parallel performance. The package is supported by a large verification suite; and pre- and post-processing software, PreView and PostView, respectively. For the proposed project, FEBio developers will implement a variety of new features targeted at the investigation of joint mechanics. New loading and boundary condition definition scenarios will be added to prescribe rigid body kinematics and kinetics. To accommodate realistic ligament behavior, definition of in situ material strain will be incorporated (also see C.4.2). The University of Utah team will also help in porting of the software on high-performance computing architectures and conduct necessary performance optimizations on such systems. Dr. Erdemir and his team has previously partnered with the University of Utah group for two federally funded projects[65,66] and also in the early versions of Open Knee [96] (Figure 2). These partnerships have resulted in continuous testing and evaluation of FEBio by our team [39] and also in the implementation of a variety of new features, e.g. the capacity for computational homogenization [95].

C.3.4. Evaluation of Community Involvement. The web-based collaboration infrastructure (see section C.3.2) will provide statistical data on the use of the site. Not only access statistics for the site is available, i.e. number of visits, geography of use, etc; specific information on number of downloads (with expected use) is also provided (Table 2). For active contributions, the source repository and the wiki is under version control, which will provide a log of work conducted by the research team and contributors from the community. Statistics from public forums will also provide a quantification of community involvement, i.e. for public review of experimentation and modeling specifications (see section C.4). The web-based computing infrastructure will also record statistics of simulations (number of simulations, computing time, etc) conducted by users, the proposed team, and community developers, in addition to a summary of simulation results, abbreviated through automated post-processing[36]. Application statistics (number of applications, their geographical location) of the community projects program (see section C.2.4) and success rate (as defined by being able to meet subproject specifications) will also be collected. All this information will be summarized by Dr. Erdemir for review by the Advisory Board in order to evaluate progress in community involvement. The aforementioned statistical information has been used to quantify community involvement in our preliminary work on knee joint model development (Figure 2, Table 2).

Specific Aim 2. To develop in silico biomechanical models of healthy and diseased knee joints of different genders and ages, supported by specimen-specific joint and tissue level experimental mechanics.

C.4. Virtual Representations of the Knee. Models of musculoskeletal joints extend the capabilities of simulation software (similar to plug-ins) to directly address problems relevant to biomechanics research and potentially clinical care. In the proposed activity, virtual representations of the knee joint will be developed through a pipeline of modeling procedures based on comprehensive experimentation. A total of six models are planned: young-healthy-male, young-healthy-female, elderly-healthy-male, elderly-healthy-female, elderly-osteoarthritic-male, elderly-osteoarthritic-female. Cadaver specimens that will be the basis for these models will be acquired from various suppliers, e.g. National Disease Research Exchange. Donor age for young specimens will be targeted to be below 35 years old and for old specimens above 65 years old. For osteoarthritic representations, specimens with moderate to severe osteoarthritis of the tibiofemoral joint (Grade II and above based on Kellgren-Lawrence grading [97]) will be acquired. Before conducting any work, orthopedic knee surgeons will evaluate the conditions of each knee to ensure their fit to the desired specifications.

C.4.1. Experimentation. Anatomical imaging and mechanical testing of each cadaver knee joint will be conducted in three stages: magnetic resonance imaging for anatomy, robotics testing for joint mechanical response, and mechanical testing of tissue samples for characterization of tissue properties.

Each specimen will be prepared by an orthopedic surgeon so that only the salient structures of the tibiofemoral and patellofemoral joints to be included in a prospective computational model remain intact (bones, ligaments, cartilage, menisci, capsule). The orthopedic surgeon will also conduct a gross evaluation of the specimen to ensure that it matches the desired specimen specifics, including preliminary assessment using magnetic resonance images. To match the image (potentially defining the model) and mechanical testing coordinate systems, registration marker sets (three radius hollow plastic spheres filled with water based gel) will be placed on the femur, tibia, and patella using plastic screws. This registration setup has a relative accuracy within 1% for measuring the distance between two markers. For imaging, the specimen will be fixed to a non-magnetic holder designed to keep the joint at a neutral state while also preventing any relative movement of the joint. Magnetic resonance images will be acquired at the Case Center for Imaging Research, using a 4 Tesla scanner (using T1 Turbo Spin Echo, no fat suppression, 0.3125 mm pixel size, 1.5 mm slice thickness; Medspec, Bruker Biospin Corp., Billerica, MA) (Figure 3). Registration markers will be digitized on MR images to establish the relationship between mechanical testing and imaging coordinate systems. For this purpose, following the mounting of the specimen on the mechanical testing setup, a three-dimensional digitizer (MicroScribe G2L, Immersion Corp., San Jose, CA) will be used to capture points on the outer surface of each spherical marker. A sphere fit will be performed for each set of points to locate the center. The described imaging modality and registration protocol has been used in our laboratory successfully for development of knee joint models and to establish relationship between imaging and testing coordinate systems (Figure 3).

The BioRobotics and Mechanical Testing facility will be used for mechanical testing of the knee specimens [69]. Testing of tibiofemoral joints will be conducted on a six degrees of freedom motion control robot (Rotopod

R-2000, Parallel Robotic Systems Corp., Hampton, NH, USA). The knee will be placed in a fixture designed for knee joint testing, which can prescribe high flexion angles (Figure 3). A spatial load transducer (Theta, ATI Inc., Apex, NC) will record joint kinetics (three forces, three moments). A joint coordinate system will be established between the femur and tibia and related to the coordinate systems of the load cell, robot, and registration markers. Laxity and combined loading tests will be performed for flexion angles ranging from 0 to 90 degrees in 30 degree increments. Laxity tests will be conducted independently for the three degrees of freedom under the following loading conditions: (1) internal-external rotation moments from 0 to ± 5 Nm in increments of 1 Nm; (2) varus-valgus moments from 0 to ± 10 Nm in increments of 2.5 Nm; (3) anterior-posterior forces from 0 to ± 100 N in increments of 10 N. Off-axis loads will be minimized during these test conditions. A combined loading test will consist of internal-external rotation moments ranging from 0 to ±5 Nm and varus-valgus moments ranging from 0 to ± 10 Nm while under an anterior or a posterior drawer force of 100N. A randomly selected laxity test will be performed at the end of mechanical testing to assess the repeatability of the procedure and to rule out any damage to the specimen. The testing protocol was adapted from previous studies[98] and has successfully been utilized in our laboratory to characterize tibiofemoral joint response[48] (Figure 3). In another testing session, a quasi-static testing protocol, similar to our previously established procedures [70,99]. A pressure sensor (K-Scan sensor 5051, Tekscan Inc., MA) will be placed between the cartilage surfaces of the patella and femur to measure the contact pressure distribution. To quantify joint kinematics, Optotrak (NDI Corp., Ontario, Canada) infrared emitting diode (IRED) marker clusters will be attached to each bone. Patellofemoral joint loading will be performed at a range of expected tibiofemoral flexion angles during gait; at 0°, 15°, 30°, 45°, and 60°. Each tibiofemoral joint configuration will be achieved through passive flexion, during which tibiofemoral joint loads will be minimized, the configuration will be locked subsequently, followed by quadriceps loading. At each angle, a nominal quadriceps loads from 100 N up to 600 N will be applied in 100 N increments. Quadriceps tendon forces will be applied through a linear actuator attached to the tendon using a freeze clamp [99]. At each increment, relative bone positions and patellofemoral contact pressures will be recorded.

Mechanical tissue testing will be conducted by Dr. Erdemir's research team in collaboration with the BioRobotics and Mechanical Testing Core. The Core has the expertise in standardized testing of tissue specimens for mechanical characterization. Professional services of the Core include using off-the-shelf mechanical testing equipment, custom designed fixtures, and de facto standard sample preparation for identification of the stress-strain response of samples under uniaxial loading

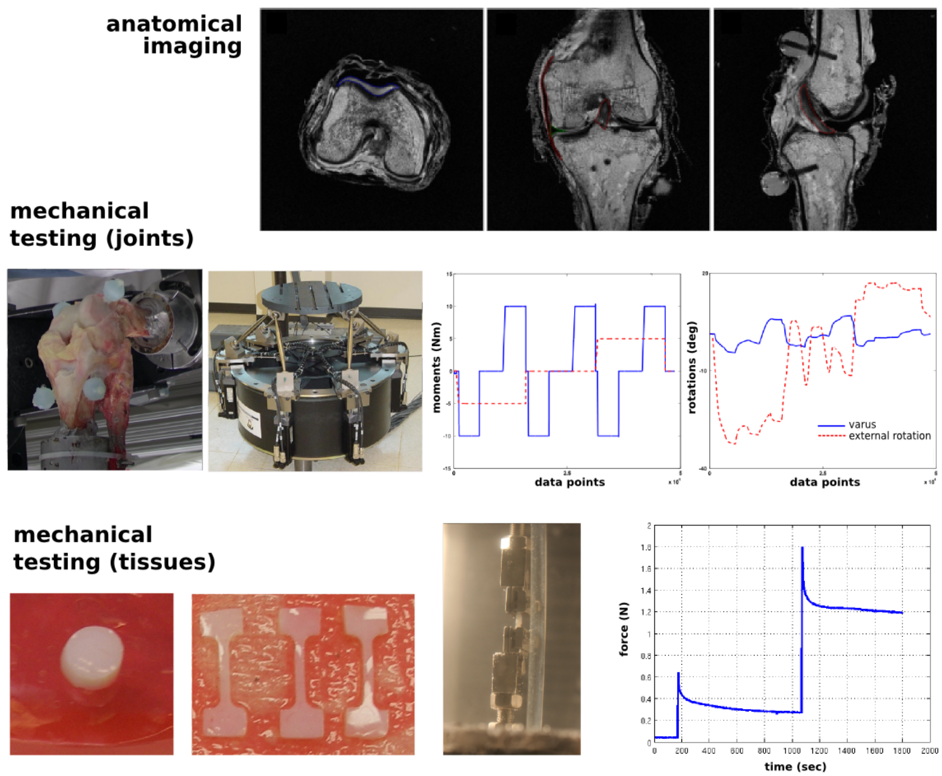

Figure 3. Dr. Erdemir's team has previously established collaborations with Case Center for Imaging Research and BioRobotics and Mechanical Testing Core for anatomical imaging and mechanical testing, respectively. Magnetic resonance imaging will provide the anatomy of joint models, as illustrated by the transverse, coronal, and sagittal scans of the tibiofemoral joint. A variety of tissue components are delineated in these images (highlighted contours). The team has also conducted robotics testing of the tibiofemoral joint (shown with registration markers). The robot can apply simplified and/or combined joint loading trajectories. For example, during a test a combination of applied varus and external moments are shown. The resulting joint rotations are also illustrated. Our established protocols for tissue testing will provide the necessary mechanical data for characterization of tissue material properties. The team has experience in obtaining and testing of uniformly shaped tissue samples, in particular cartilage, menisci, and ligaments. The team has also applied similar protocols for the experimentation of the patellofemoral joint.

(tension/compression, creep, relaxation tests). The capabilities extend to biaxial testing to quantify multimode loading response of the specimens. Upon completion of joint testing, uniformly shaped samples will be extracted from the ligaments, cartilage and menisci of the knee (Figure 3). From each ligament (anterior and posterior cruciate, medial and lateral collateral, and patellar ligaments), multiple samples will be extracted. Cartilage samples will be collected from each of the articulating regions of the femoral condyle and tibial plateau, femoral grove and patella. Meniscal samples will be acquired from each meniscal component (medial and lateral). Ligament samples will be tested in uniaxial tension to establish their stress-strain response. Mechanical testing devices, e.g. Model 5543, Instron, Norwood, MA, in the BioRobotics and Mechanical Testing Core will be used for this purpose. Cartilage response will be measured for uniaxial compression (confined and unconfined). Meniscus samples will be tested under compression and also for tension (for characterization of circumferential and radial properties). Each loading modality will include a stress-relaxation test to illustrate rate dependent behavior of tissues. Our research team has successfully implemented these protocols for testing of man made materials [100] and tissue samples [48] (Figure 3).

C.4.2. Model Development. For each knee specimen, a computational model will be developed based on finite element representation. The geometry of the knee will rely on the magnetic resonance images of the specimen. Image segmentation will establish the three-dimensional reconstruction of the tibiofemoral and patellofemoral joint components; predominantly the femur, tibia, and patella; femoral, tibial, and patellar cartilage; medial and lateral collateral ligaments, anterior and posterior cruciate ligaments, and patellar ligament; menisci; and other passive components of the capsule that may be deemed necessary for the investigation of tibiofemoral and patellofemoral joint mechanics. Each tissue geometry will be meshed using TrueGrid (XYZ Scientific Inc., Livermore, CA) to obtain a high quality hexahedral mesh (Figure 4). Each tissue will be assigned appropriate density to allow accurate nonlinear dynamics simulations. The bones will be assumed to be rigid based on their relatively high stiffness when compared to other soft tissue structures [101]. Constitutive relationships representative of typical nonlinear stress-strain behavior of the other underlying tissue structures will rely on well-established literature available for ligaments [102], cartilage [103], and meniscus [104]. Coefficients of these constitutive relationships, which describe tissue material properties, will be obtained in a specimen-specific manner based on fit to specimen-specific tissue stress-strain data obtained from tissue level experimentation described above. Ligament representation will incorporate in situ ligament strains [64]. Ligament-to-bone wrapping, ligament-to-ligament wrapping, and contact interactions in between cartilage and in between cartilage and menisci will be defined. Contact between components will be modeled as frictionless based on the low friction in synovial joints [105]. Loading and boundary condition specifications will allow prescription of the tibiofemoral and patellofemoral loads (forces and moments) or kinematics (rotations and translations) or a combination of those. In return, the model will output unspecified kinetic variables or degrees of freedom. Complete stress-strain state for the tissues will also be calculated as part of the solution process. For finite element analysis, FEBio (see section C.3.3) will be utilized to conduct nonlinear dynamics analysis utilizing an

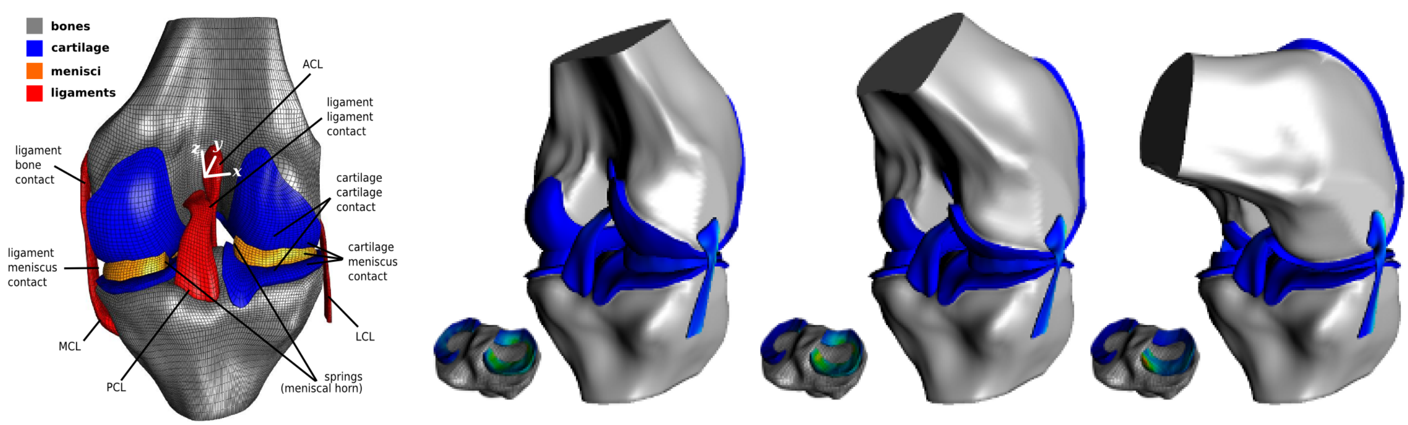

Figure 4. A tibiofemoral joint model developed by the research team lead by Dr. Erdemir is shown on the left. The team can generate high quality hexahedral meshes of bones, ligaments, cartilage, and menisci. The shown model incorporated nonlinearly elastic tissue properties and contact definitions between relevant articulating surfaces. Simulation results for passive knee flexion are displayed along with meniscal strain contours. FEBio, finite element analysis software developed by collaborators at the University of Utah, was used for the analysis. With this model, the team illustrates their capacity to model nonlinear mechanics of the knee joint and its underlying tissue structures.

implicit solution algorithm [39]. This modeling approach will provide knee representations not only specific to the specimen's anatomy but also specific to the tissue properties of the same specimen. Also important to note is the digitization of the registration phantoms from the images, which will establish the necessary transformations between bone segments to relate joint experimentation coordinates systems with those of the model coordinate system (see above).

All modeling efforts will be led by Dr. Erdemir's team with anticipated community involvement. Dr. Erdemir's team has built similar tibiofemoral joint models as part of the Open Knee initiative [5] (Figure 4) , and utilized these models in multiscale simulations [36]. The team has also developed patellofemoral joint models and utilized them for understanding the effect of surgical conditions on patellofemoral contact pressures [70,106]. To facilitate model generation, our custom-developed Python scripts will be updated [36,107]. These scripts allow quick generation of FEBio model files, starting with a mesh file and a model configuration file [107]. Changing tissue material properties, and/or time history of loading and boundary conditions becomes trivial with the use of such scripts.

Finite element analysis is the preferred modeling and simulation tool for the proposed project due to its capacity to provide predictions of joint mechanics (knee kinematic-kinetic response) and tissue mechanics (ligament, cartilage, menisci stress-strain state). Based on the research question (and supported by the proposed experimental data), abstractions (anatomical and material) both at the joint and tissue level can be changed easily to balance the accuracy, needed to address the scientific (or clinical) question, and the cost required for the analysis. For example ligaments can be modeled simply as spring elements [15], a rigid-body based modeling approach can be elected to replace finite element analysis [75], or to evaluate the poroelastic behavior of the cartilage, a nonlinear biphasic analysis can be conducted [43]. All of these will be possible branches based on the proposed activity. It will also be possible to couple these joint models to musculoskeletal models of the lower extremity [40]. Using muscle or joint level information calculated as part of musculoskeletal movement simulations [56], a concurrent or a post-processing based data flow can be established which will drive these joint models with muscle forces, joint loads, or joint kinematics.

C.4.3. Simulations. The knee joint models will be used to simulate loading and boundary conditions of joint mechanics experimentations (see section C.4.1). These simulations will serve for two purposes. First, they will establish a confidence level in the models' capacity to reproduce specimen-specific joint kinematic-kinetic response (practically the passive joint properties dictated by the combined mechanical function of soft tissues and articulating geometry). Second, the results of these simulations will expand upon the experimental joint mechanics description by providing specimen-specific mechanical state of individual tissue components as a function of joint loading.

We need to emphasize that the models will be based on specimen-specific anatomy and tissue properties, acquired from imaging data and tissue testing, respectively. Experimental joint movements and loads will be used as an independent dataset for confirmation of model predictions. Specification of experimental joint loads to drive model will result in model predictions of joint movements, which can be compared against experimental joint movements. Since a fully specimen-specific modeling scheme will be utilized, the discrepancies in model predictions and experimental data should not be larger than the combination of data collection errors and estimated uncertainties for modeling. Any discrepancy beyond these estimated errors may indicate issues related to modeling assumptions that may need to be revisited. As a less stringent model confirmation metrics, we will also explore the linear correlation between model predictions and experimental data rather than a direct magnitude comparison. This has been a promoted approach for verification and validation of biomechanical models [63,108].

Identification of the mechanical environment of cartilage, ligaments, and menisci for knees of different ages, genders, and disease states has implications on the individual mechanical function of these structures under simplified and/or combined joint loadings. Post-processing of the results of the previously mentioned knee joint simulations can provide tissue level mechanical variables, e.g. cartilage contact stress, anterior cruciate ligament strain, which may be utilized for generation of hypothesis, driving future studies. For example, one may quantify the change in cartilage mechanics with age and disease, and how the role of anterior cruciate ligament and menisci varies between genders. The proposed activity will use data-driven joint simulations to identify such hypotheses to advance the biomechanics of the healthy and osteoarthritic knee.

C.5. Limitations & Alternative Strategies. It is certainly possible that the proposed activity may need alternative strategies to overcome potential hurdles related to infrastructure development, experimentation, and modeling. While the collaborative infrastructure has been used successfully by the research team, the web-based computation platform is a novelty for biomechanics research, as is community-supported development. Other biomedical researchers have successfully deployed science gateways for simulations [54]. We will benefit from their experience. If the design and deployment of an easy-to-use interface for web-based configuration of models and their simulation becomes a bottleneck, we will fall back to a more traditional high-performance computing approach where users prepare model files on their local computers and submit jobs to high performance computing queues. We have experience in using high-performance computing [36,109] and will deploy this mechanism on the proposed computing resources or elsewhere, e.g. the Ohio Supercomputer Center [110]. Active involvement of the community will definitely strengthen the progress and the impact of musculoskeletal joint modeling. Our planned activities, e.g. community projects program, to engage the community may not be at a desirable level. We will support community involvement by the addition of training programs. We will use our network of biomechanics researchers and teachers to encourage involvement of their students as part of their curriculum in experimentation, modeling, and simulation of joint and tissue mechanics. The expected use of Open Knee, our preliminary work, illustrates the significant interest in the use of knee models for training (Table 2). Experimentation of the same specimen for acquisition of information on its anatomy, and joint and tissue mechanics can be a logistical problem. While we have been successful at that level of experimentation previously, there is the likelihood of loosing information on some specimens due to failure in mechanical tests. We will attempt to test more than the required six knee specimens as a backup (Table 1). This approach will also account for the potential difficulties in the acquisition of specimens representative of desired demographics. For the sake of cost-effectiveness, we will acquire specimens based on an a-priori selection criteria, rather than scanning and testing cadaver specimens of the same population, e.g. young-healthy-male, and using a representative one for modeling. Orthopedic surgeons will assess the suitability of the specimens for given population specifics. If necessary, we will also evaluate the anatomical features, and joint and tissue mechanics of a selected specimen against literature and or databases available for the population, e.g. Osteoarthritis Initiative. The modeling approach will certainly rely on some simplifications. Certain variables, e.g. in situ strains, will be based on literature [16,26]. Regardless, the model parameters will be easy to change, from geometrical representations, to tissue properties, to loading and boundary conditions. They can be even optimized such that model predictions match a subset of joint mechanics, i.e. the response during laxity tests. We have conducted such studies, aka inverse finite element analysis, for other organs and tissues [47]. It will also be possible to conduct detailed sensitivity analysis [26], particularly through the involvement of community for testing and evaluation. The potential of open science for successful research should not be underestimated. Providing the opportunity for others to review the experimentation and modeling procedures a-priori will help identify potential problems and explore alternatives as a community, which will likely minimize risk of failure.

C.6. Data & Software Sharing. The project will employ an open science approach, providing completed work and those in progress in a free and transparent manner (see section C.2.3). As described previously, a project site at SimTk.org will be used for this purpose. A multitude of improvements on existing infrastructure and software, data, analysis scripts, models, and simulation results will be generated. Improvements on web-based collaboration infrastructure (see section C.3.1) will be accessible to other users utilizing the resources provided by Simbios. Any custom-developed code for running the web-based computation infrastructure (see section C. 3.2) will be made available at the project site. New features, implemented in the finite element analysis package FEBio (see section C.3.3), will be incorporated in upcoming release versions of this software. Experimental data (see section C.4.1), developed models (see section C.4.2), and simulation results (see section C.4.3) will be disseminated at the project web site. Analysis scripts to parse experimental data, to configure and automatically generate models, and to post-process simulation results for summarization will be provided as well. All data, models, scripts, etc. will be supported by white papers describing their specifications and also by user manuals. All information will be provided in accessible (potentially open) formats, e.g. XML files for models, HDF files for data. Open access to data, models, and related documentation will permit future utilization, in the event of its abandonment by the contributors and their relevant institutions. After finalization of the project, the project site is anticipated to have continuing support through our related research and from the SimTk.org community through the user forums and the wiki site. The Principal Investigator has successfully implemented this approach in projects funded by the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health [65,66].

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