PROJECT SUMMARY/ABSTRACT

BACKGROUND. Multi-layer tissue structures of musculoskeletal extremities are natural protective barriers, which are commonly exposed to injury during combat. High fidelity computational models, when and if available, can provide a framework to understand the mechanical interactions between tissues and to predict the deformation characteristics and haptic response of such tissue arrangements. Realistic simulations of surgery to train physicians and to design new techniques will be possible along with in silico explorations of injury mechanisms and virtual prototyping of protective gear. However, lack of fundamental data to build and evaluate computational models and the void of customizable and reliable models hinder the delivery of this premise.

OBJECTIVE/HYPOTHESIS. The goal of this study is to provide fundamental data, open and freely accessible databases of tissue mechanical and anatomical properties, models of multi-layer tissue structures of musculoskeletal extremities; all with proven utility in surgical simulations. Comparison of mechanically and anatomically detailed reference models (of varying degrees of specimen-specificity) against experimental data will establish the capacity to predict mechanics under different tissue arrangements and properties. Comparison of surrogate models (simplified for computational efficiency) against reference models and data will confirm their capacity to capture visual and haptic realism while interactions between tissue layers are considered.

RATIONALE. The aggregate mechanical response of bulk tissue covering the bones of the extremities is a function of the properties of underlying tissues (muscle, skin, and fat), their anatomical arrangement, and how they interact with each other. The knowledge of internal and external response of musculoskeletal limbs, and their representation in high fidelity computational models can lead into authentic simulations of extremities, realistically incorporating interactions between skin, fat, and muscle during surface manipulations such as indentation, retraction, cutting, and dissection.

SPECIFIC AIMS. (1) To establish an online platform to curate, distribute, and reuse data and models of multi-layer tissue regions of extremities. (2) To collect and disseminate anatomical and mechanical data for building and validating reference models of multi-layer tissue architectures of musculoskeletal extremities. (3) To build, validate, and disseminate mechanically advanced reference models representative of nonlinear material properties and realistic anatomy of multi-layer tissue architectures. (4) To build and evaluate fast and mechanically simplified yet visually and haptically realistic surrogate models to be used for surgical simulation.

STUDY DESIGN. A public project management website for data, models, computing, and dissemination will be provided. Tissue samples from cadaver specimens will be tested to provide material properties of muscle, skin, fat, and the interfaces in between. Anatomical imaging and mechanical testing of musculoskeletal extremity regions (of cadaver specimens and of human subjects) will provide supplemental information to build and validate models. High fidelity reference models will incorporate nonlinear physiology and anatomical realism for in-depth prediction of the role of multi-layer tissue arrangements on surface mechanics and on individual tissue interactions. Open source finite element analysis software will be used for this purpose. Models of varying degrees of specimen-specificity (complete representation for in vitro cases; partial representation for in vivo cases) will indicate the role of individualization on multi-layer tissue response. Simplified surrogate models will reflect dominant properties of multi-layer architectures and test the translational value of such representations in open source medical training and surgical simulation software.

RELEVANCE/IMPACT. Musculoskeletal extremity injuries comprise 50% of all combat wounds during latest operations of the United States Armed Forces. Computational models will provide the military the simulation capacity for surgical training and certification of field personnel. In addition, such models will support design of protective equipment to prevent damage on extremities. By providing fundamental mechanical and anatomical data, virtual representations of tissues and organs, and the tools to assemble data and models to build virtual representations of any desirable multi-layer tissue arrangement, the proposed activity uniquely fits to the Virtual Tissue Advancement Research Program. Along with advancement of science and engineering in virtual surgery, the data, models, and knowledge acquired from this activity can inform other research domains, e.g., of pressure ulcers, where mechanical response of multi-layer tissue structures has significant role in the etiology and prevention of debilitating conditions. The broader impacts on general public can extend further as these models can be utilized in industry for development of performance equipment and clothing, which interact with musculoskeletal extremity regions. All these will be enabled by adapting an open science approach.

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STATEMENT OF WORK

High incident rates of combat injuries to the musculoskeletal extremities dictate the immediate need to understand and simulate contact mechanics and internal mechanical interactions of layered tissue organization of these body regions. The mechanical response of multi-layer tissue structures around the legs and arms is a function of the underlying muscle, skin, and fat tissues and the junctions in between. With the knowledge of individual tissue material properties, layered anatomy, and the mechanical capacity of tissue interfaces, it will be possible to develop computational models to conduct descriptive and predictive simulations. Such in silico analyses have utmost importance to develop and evaluate diagnostic strategies, surgical interventions, and protective equipment. The overall goal of this study is to establish the founding knowledge, data and models for the mechanics of multi-layer tissue structures of the limbs, particularly of the lower and upper legs and arms. By delivering this lacking information, the activity will promote scientific research in layered tissue structures and allow reliable virtual surgery simulations for clinical training and certification. Below is a list of project milestones, which correspond to the specific objectives of the project. All data and models will be provided in an open and freely available manner to maximize outreach of this information.

YEAR 1	***Milestone.*** Web-based interfaces for data curation, queryable data and model databases. *Tasks.* Web design and programming to incorporate new features in online collaboration infrastructure. *Deliverables.* Prototype of web-based tools for data curation and analysis, model assembly, simulation, and post-processing.
YEAR 1	***Milestone.*** In vivo multi-layer tissue anatomy and indentation mechanics. *Tasks.* Recruitment of human subjects, acquisition of demographics, anthropometric measurements, ultrasound measurements of layered tissue thicknesses of legs and arms, indentation with ultrasound. *Deliverables.* Data on gross anatomy and indentation mechanics of lower and upper legs and arms of 100 human subjects.
YEARS 1-2	***Milestone.*** In vitro multi-layer tissue anatomy, mechanical properties, and indentation mechanics. *Tasks.* Acquisition of cadaver specimens, magnetic resonance imaging of cadaver legs and arms, indentation with ultrasound, sampling of skin, muscle, fat tissues and junctions, mechanical testing of tissues and junctions. *Deliverables.* Data on detailed anatomy, tissue and tissue-interface properties, and indentation mechanics of cadaver lower and upper legs and arms (10 specimens for each region).
YEAR 2	***Milestone.*** In vitro quantification of tool forces during surgery of multi-layer tissue structures. *Tasks.* Acquisition of cadaver upper leg specimens, mechanical manipulations using instrumented tools, magnetic resonance imaging, sampling and testing of skin, muscle, fat and their junctions. *Deliverables.* Data on mechanical and haptic responses of 10 cadaver upper leg specimens during surgical procedures.
YEAR 2	***Milestone.*** Physiologically realistic, fully specimen-specific, nonlinear reference models. *Tasks.* Finite element analysis of non-linear mechanics of cadaver specimens. *Deliverables.* Specimen- and region-specific reference models of upper and lower legs and arms confirmed against indentation data (8 models - 4 regions, 1 male and 1 female representative donors).
YEAR 2	***Milestone.*** Physiologically realistic, partially subject-specific, nonlinear reference models. *Tasks.* Finite element analysis of non-linear mechanics of multi-layer tissue regions of human subjects. *Deliverables.* Partially subject- and region-specific reference models of upper and lower legs and arms confirmed against indentation data (8 models - 4 regions, 1 male and 1 female representative subjects).
YEAR 3	***Milestone.*** Computationally efficient surrogate models for multi-layer tissue structures. *Tasks.* Model reduction and simplification to develop cost-effective models of surface manipulation of multi-layer tissues. *Deliverables.* Specimen- (or subject) and region-specific surrogate models of upper and lower legs and arms confirmed against indentation data and reference models (16 models - 4 regions, 2 male and 2 female representatives).
YEAR 3	***Milestone.*** Demonstration of efficient surrogate models of multi-layer tissue structures. *Tasks.* Model reduction and simplification to develop cost-effective models of surgical manipulation. *Deliverables.* Specimen-specific surrogate models of upper legs confirmed against data from lifelike manipulations of surgical procedures (2 models - 1 male and 1 female representative donors).
YEARS 1-3	***Milestone.*** Population and dissemination of data and models. *Tasks.* Routine utilization of web-based interfaces to curate data, populate databases, and disseminate models. *Deliverables.* Free and open access to all deliverables of the project.

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BODY OF APPLICATION

1. Background

1.1. Multi-Layer Tissue Structures of Musculoskeletal Extremities. Musculoskeletal limbs are surrounded by layers of skin, fat, and muscle stacked on the bones (Figure 1). While the fundamental function of the musculoskeletal system is enabling the mobility of the body, the multi-layer tissue structures of the legs and arms protect the underlying skeleton and bear mechanical loads of the environment. Injuries to multi-layer tissue structures are common; the intensity of damage ranges from minor bruises of civil life to major clinical complications associated with pressure ulcers[1] to drastic blast injuries and gun-shot wounds of combat[2,3] (Figure 2). Extremities of the body, specifically legs and arms are major wound sites in warfare; almost half of the injuries affect musculoskeletal limbs[4]. With advances in body armor technology, survival chances increase but these unprotected regions of the body commonly require surgical reconstruction to restore musculoskeletal function[5] (Figure 2). Knowledge on the biomechanical behavior of multi-layer tissue components can guide the development of novel strategies for surgical, therapeutic, and rehabilitative care of these regions. Dependable computational models of skin, fat, and muscle, when predictive of their aggregated response at the body surface and of the individual layer mechanics, can facilitate teaching structure-function relationships among tissues and increase the effectiveness of physician training to tackle challenging interventions prescribed on these tissue layers.

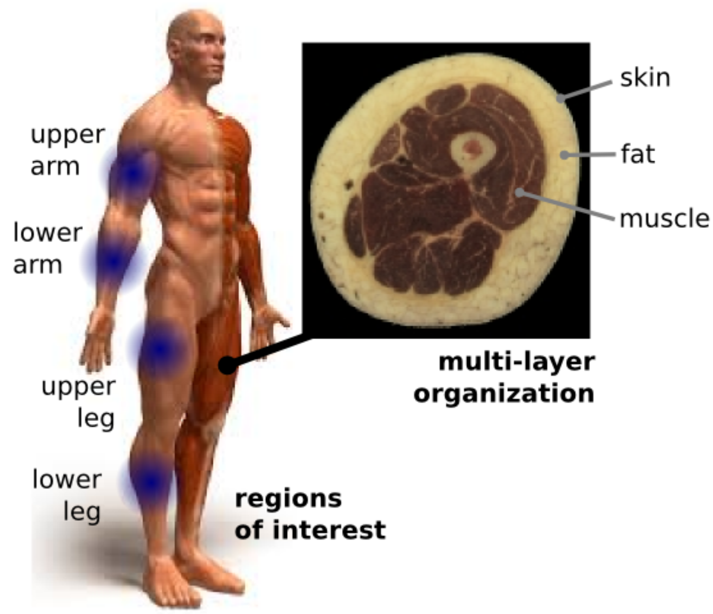

Figure 1. For the project, the target regions of interest in the body are musculoskeletal extremities, in particular upper and lower legs and arms. These regions are surrounded by a multi-layer tissue structure; an aggregate of skin, fat, and muscle. The mechanics of these tissues and their interactions serve as a protective barrier to the skeleton. The multi-layer tissue structures of musculoskeletal extremities are major sites of combat related injury.

1.2. Finite Element Analysis of Multi-Layer Tissue Structures. In finite element analysis, geometry, tissue constitutive response, and interactions between tissue components can be modeled to predict deformation and stress fields under complicated loading and boundary conditions[6]. Faithful to anatomical details and physiological tissue properties, e.g., anisotropic, heterogeneous, nonlinearly elastic, finite element analysis has become de facto standard to evaluate nonlinear behavior of biomechanical structures as they interact with their functional environment[6,7]. In relevance to multi-layer tissue structures, individual computational models of skin[8], fat[9], and muscle[10] exist. Models of multi-layer tissue composites can also be seen in literature. For example, a plethora of studies explored mechanics of skin and subcutaneous tissue[11]. Other examples of in silico work, which focused on multi-layer mechanics, includes models of the facial tissue[12], the arm[13] and the foot[14]. Most predominantly, layered representations of tissue at bony prominences have been wide-spread in pressure ulcer literature. Contact mechanics and internal deformations of skin, fat, and muscle layers have been explored[15] as the mechanical environment was found to be a significant factor for pressure ulcer development[1,16]. The contributions of the aforementioned modeling studies for the advancement of knowledge in multi-layer tissue biomechanics should not be overlooked. Nonetheless, new generation of multi-layer tissue models founded on comprehensive data, particularly for musculoskeletal limbs, is an emerging need.

1.3. Surgical Simulations of Multi-Layer Tissue Structures. When providing visual and haptic realism, modeling and simulation can have utmost utility for virtual surgery and medical training[17]. To accommodate the constraints associated with the desire for real time simulation, mechanical fidelity of the models are lowered; yet with advanced computing strategies, e.g. using graphics processing units[18], models with increasing levels of physiological realism are emerging[19]. Of particular interest to this project are recent virtual surgery models of heterogeneous tissue. Using SOFA, simulation open framework architecture[20], contact and cutting of heterogeneous (in some cases layered) tissue structures have been simulated in real-time for cataract surgery, laparoscopic hepatectomy, and tumor surgery[21]. Similar techniques have been utilized to model embedded structures, e.g. vascular system in the liver[22]. Directly relevant to multi-layer composites of skin, fat, and muscle, craniofacial surgery simulations accommodating layered mediums have been performed[23,24]. All these recent developments indicate that computational technology has evolved to a level where authentic simulations of multi-layer tissue structures for virtual surgery and medical training can be conducted. Such simulations still introduce varying levels of simplifications for feasible computations yet have the capacity to provide comparable predictions of gross mechanical response in reference to nonlinear finite element analysis[21,22]. However, comprehensive data and reliable reference models to base the representations of multi-layer tissue structures for virtual surgery and medical training are lacking.

Figure 2. Use of body armor protects the trunk of the body. Injuries to musculoskeletal extremities are common in service personnel surviving blasts. Figure adapted from O'Brien and Cox[5].

1.4. Need for Data and Models for Multi-Layer Tissue Biomechanics. Experimentation on multi-layer tissue structures should allow development of reliable models, by minimizing any source of uncertainties, e.g., by quantification of specimen-specific anatomical and material properties of tissue layers. In addition, adequate data on the mechanical response of tissue layers should be acquired to evaluate models in a specimen-specific manner. Acquisition of this missing information will provide the necessary grounding for any modeling attempt of skin, muscle, and fat layers of musculoskeletal extremities. Many separate studies have characterized the mechanical properties of skin[25], fat[26], and muscle[27]. Nonetheless, properties of these different tissue types were not determined for samples acquired from the same donor, permitting delineation of any correlations in between. In addition, a firm understanding of the mechanics of tissue junctions, e.g. fat-muscle, muscle-muscle, muscle fascia, is missing. An exception to this is the existing knowledge on the mechanical coupling between skin and subcutaneous tissue[28]. When grounded in data from individuals from a diverse population, computational models can represent actual anatomical and mechanical variations in multi-layer tissue structures. As such, appropriate prediction of the surface and internal mechanics for the limbs of individuals with specific demographic characteristics (military or civilian) can be accomplished.

1.5. Leveraging Open Science for Multi-Layer Tissue Biomechanics. Open science approach, i.e., open development and public dissemination, had significant success for research on drugs[29] and has been recently adapted in computational biomechanics for investigations of musculoskeletal joint mechanics[30]. Public dissemination of data and models relevant to multi-layer tissue mechanics will have utmost impact on scientists, engineers and clinicians who are in need of dependable information to understand multi-layer tissue function. Barriers to entry to the research field can be minimized, as the community can focus on answering the scientific and/or clinical question rather than on the laborious activities to acquire data and build models. Computational models can be reused to expedite explorations utilizing virtual surgeries, implementation of simulation-based medical training systems, and launching of novel interventions to prevent and manage injuries. Apart from dissemination, open science introduces open development as an added value. When the community is given the opportunity to be involved at the beginning of and during multi-layer tissue biomechanics research, the objectives of acquiring dependable data, establishing useful tissue property databases, and developing reusable computational models can be expedited. Everyone can criticize and contribute as the activities move on. Upon project completion, the open development approach gives the opportunity for anyone to pick up the work to continue progress or to steer it to other directions. Such approaches have a proven track-record for delivering highly successful free and open source software projects[31].

2. Hypotheses

The hypotheses to be tested in this activity have relevance to (i) the importance of tissue layer anatomy and mechanical properties on emerging mechanical behavior at the surface of multi-layer tissue regions of the musculoskeletal extremities and on individual tissue layer deformations, (ii) the capability of physiologically realistic models (reference models) capturing the nonlinear mechanical behavior of multi-layer tissue response at the surface and within layers, (iii) the possibility to develop computationally efficient models (surrogate models) fast enough for surgical simulations and adequate enough to capture visual and haptic realism of mechanical manipulations of multi-layer tissue structures at the surface and across layers. All these hypotheses are provided below, along with the expected results:

Hypothesis 1. In vivo indentation stiffness, an aggregate mechanical behavior of multi-layer tissue regions, is related to thickness of skin, fat, and muscle comprising the layered tissue architecture.

It is certainly predictable that the structural response of the legs and arms covered by layers of skin, fat, and muscle will indeed be a function of the anatomy of these individual layers. It is therefore expected that the data will support this hypothesis. More importantly, the explorations will establish the individual role of skin, muscle, fat tissues and their interactions on the emerging mechanical response at the extremity surfaces of live subjects.

Hypothesis 2. In vivo deformation of individual layers of multi-layer tissue regions during indentation, a mechanical manipulation at the surface, is related to thickness of skin, fat, and muscle comprising the layered tissue architecture.

The influence of tissue thickness on its (and on neighboring tissues') deformations is expected. Testing of this hypothesis will support the relative roles of individual layer thicknesses and the potential interactions in between.

Hypothesis 3. In vitro indentation stiffness, an aggregate mechanical behavior of multi-layer tissue regions, is related to material properties of skin, fat, and muscle comprising the layered tissue architecture.

Testing of this hypothesis will explain the variability on describing multi-layer tissue response unaccounted by solely examining tissue thickness (as can be done for human subjects in Hypothesis 1). Augmenting the analysis by quantifying anatomical and mechanical properties of tissues on cadaver specimens, the role of skin, muscle, and fat properties on the surface mechanics of multi-layer tissue structures will be explained.

Hypothesis 4. In vitro deformation of individual layers of multi-layer tissue regions during indentation, a mechanical manipulation at the surface, is related to material properties of skin, fat, and muscle comprising the layered tissue architecture.

The influence of tissue mechanical properties on its (and on neighboring tissues') deformations is expected. Testing of this hypothesis will support the relative role of material properties of multiple tissue layers and the potential interactions in between.

Hypothesis 5. Physiologically realistic computational models of multi-layer tissue regions (reference models), incorporating full specimen-specificity (detailed anatomy and nonlinear tissue properties), can predict indentation stiffness and deformation of skin, fat, and muscle layers.

With detailed anatomy acquired from multi-layer tissue structures of cadaver specimens and with nonlinear, heterogeneous, and anisotropic material properties of tissue layers (and junctions) acquired from the same specimens, complete specimen-specific models can be developed using finite element analysis. By accounting for specimen-specificity for all model parameters, this modeling approach minimizes any sources of uncertainty. Model predictions of indentation response (force-displacement) and deformations of tissue layers are therefore expected to match data collected on the same specimens.

Hypothesis 6. Physiologically realistic computational models of multi-layer tissue regions (reference models), incorporating partial subject-specificity (approximated anatomy and generic nonlinear tissue properties), can predict indentation stiffness and deformation of skin, fat, and muscle layers.

Acquisition of data from human subjects, to build fully subject-specific models of multi-layer tissue structures, may not be feasible. Using imaging modalities compatible with the field operations, e.g., ultrasound, geometry of the models can be approximated by thickness measurements of tissue layers of the musculoskeletal extremity. The material properties will need to be estimated from literature or from relevant databases (see Hypothesis 5). Despite these limitations, model predictions of indentation response (force-displacement) and deformations of tissue layers are expected to match data collected on human subjects, albeit with decreased accuracy due to lack of pure specificity.

Hypothesis 7. Mechanical representation of multi-layer tissues and their interactions in physiologically realistic computational models can be simplified to obtain surrogate models, which sacrifice predictive accuracy (of indentation stiffness and layer deformations) to enhance computational efficiency for virtual surgery simulations.

Finite element analysis, incorporating nonlinear mechanics of tissue and tissue-interface, may become computationally costly. Various simplifications in mechanical representation can be employed, e.g., linearization of the whole system and/or constitutive representations and approximation of contact. When detailed information on surface mechanics and internal tissue stress-strains is not needed, surrogate models can provide visually deceptive deformation predictions and haptically deceptive surface forces during indentation. It is expected that such simplifications will result in models solving significantly faster than reference models while retaining gross mechanical response of the multi-layer tissue structures.

Hypothesis 8. Mechanically simplified computational representations of multi-layer tissue structures (surrogate models) can enable visually and haptically realistic simulations of surgical manipulations on aggregates of skin, fat, and muscle covering the musculoskeletal extremities.

With this hypothesis, the expectation is that surrogate models, when implemented in virtual surgery simulation software, are capable of representing surface deformations, interaction of layers, and forces of mechanical acts of surgery beyond the isolated case of indentation.

By adapting an open development and dissemination approach, we anticipate others to reuse data and models to augment the hypotheses listed in here. It is also possible to test new hypotheses relevant to the function of multi-layer tissue structures of the legs and arms and their computational modeling.

3. Scientific Rationale

3.1. Role of Individual Tissue Properties on Multi-Layer Tissue Biomechanics. Mechanical response of a structural system depends on the properties of its underlying constituents. The constituents of multi-layer tissue structures of the musculoskeletal limbs are the skin, fat, and muscle. Each of these tissue exhibit significantly different mechanical properties at the material level, e.g. varying ranges of stress-strain response. Skin exhibits anisotropic and relatively stiff behavior[32], its tensile properties constrain bulging of the tissues during mechanical manipulations at the body surface. Fat is largely compliant with significant damping capacity to manage impact[26]. Muscle, at a passive state, exhibits anisotropic behavior, with mechanical properties falling in between those of the skin and fat[27]. The aggregate response of the multi-layer tissue is essentially a multiscale problem. When a multi-layer tissue region is mechanically manipulated (indentation for example), the resultant deformation and reaction forces will depend on the organization of skin, fat, and muscle, in particular their relative thicknesses. Variations in tissue organization, between musculoskeletal regions and from subject-to-subject, will dictate the natural variability of surface response. Similarly, material properties of skin, fat, and muscle exhibit natural variations due to body region, age, and gender[33] and sometimes as a result of pathology[34], which are reflected on the variability of surface response as well.

Mechanical response of individual tissue layers will also be influenced by the properties of neighboring tissues and the mechanical properties of tissue interfaces[14,15]. For example, fat tissue adjacent to a stiffer muscle may exhibit different local deformations than one adjacent to a more compliant muscle. Similarly, the interactions between layers, fully integrated, e.g., tied, or loosely coupled, i.e., allowing relative sliding, will determine local stresses and strains. With the added knowledge of failure properties for the tissues and the junctions in between, it may be possible to understand where mechanical damage occurs first for a given surface loading. This knowledge will also be essential to understand required forces during surgical operations, to cut through individual layers and detach layers from each other.

3.2. Specimen-Specific Modeling for Prediction of Multi-Layer Tissue Biomechanics. Specimen/subject-specific modeling in computational biomechanics commonly refers to individualization of anatomy only. The material properties for the tissues are routinely adapted from literature or based on data from other specimens and therefore do not necessarily reflect individual variations. The level of specimen-specificity, which is necessary to adequately predict specimen-specific outcome metrics, is not necessarily known. Recent probabilistic approaches in computational biomechanics conducted large scale sensitivity analyses to indicate what model parameters may be important for the predictions of the variables of interest[35]. Nonetheless, without actual knowledge of specimen-specific parameters and data on specimen-specific response (as sought by the simulations), it is difficult to assess how removed model predictions are from reality. This is an issue in computational biomechanics literature in general and in multi-layer tissue modeling literature specifically. Another important aspect of understanding what is lost by the lack of specimen-specificity is that the bounds of appropriateness of a partially customized model based on a minimal set of subject data can be established. This knowledge can improve patient-specific modeling, targeting minimal data collection in the clinics to build individualized models.

3.3. Nonlinear Computational Mechanics of Multi-Layer Tissue Structures. Nonlinear finite element analysis has evolved into a widely utilized computational approach to understand biomechanical function of organs and tissues[6]. The advancement of constitutive representations allowing physiologically realistic modeling of tissue mechanical behavior[7], streamlined workflows for (near) automated representation of anatomy[36], the possibility to prescribe complicated loading and boundary conditions of lifelike situations, and high performance numerical solution algorithms and computing techniques[37], now allow everlasting and extensible computational representations of biomechanical systems. When developed for multi-layer tissue structures and founded on and confirmed against comprehensive data, these models can provide the means for virtual experiments to evaluate interrelated biomechanics of skin, muscle, and fat surrounding the musculoskeletal extremities. Such virtual experiments will permit scientific explorations which are otherwise not feasible to accomplish in vivo or in vitro.

3.4. Simplified Computational Mechanics of Multi-Layer Tissue Structures. Clinical utility of computational models rely on their ease of implementation and their computational efficiency to meet the constraints of the translational healthcare environment. Models can be simplified to realize desirable computability, through model reduction approaches[38] or by relaxing assumptions of physiological representation[20], sometimes retaining high fidelity within real time simulation capabilities[21]. In healthcare practice, clinical validity of computational models is important in lieu of their absolute perfectness. Generation of new scientific knowledge may necessitate higher accuracy and precision in model predictions. For field use, perceived realism is more likely to be sought after, particularly in virtual surgery simulations or for medical training. Nonetheless, questions such as “How much is good enough?”, “When does look and feel seem adequate?” will remain case-specific and they need to be answered to meet the competing demands on practicality and appropriateness of in silico analysis. Surrogate models of multi-layer tissue structures of legs and arms are not exceptions; favorable relative accuracy and cost of simplified models, when established in reference to predictions of more advanced models, will promote their routine use in the clinics.

4. Preliminary Data

4.1. Expertise of Investigators. The proposed study will incorporate a diverse group of personnel including biomechanics researchers, clinicians, modeling and simulation engineers, software developers, 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 of musculoskeletal joints[39–42] and tissue layers of extremities[43–47], and development of novel modeling and simulation strategies[48–53]. Dr. Erdemir is the founder

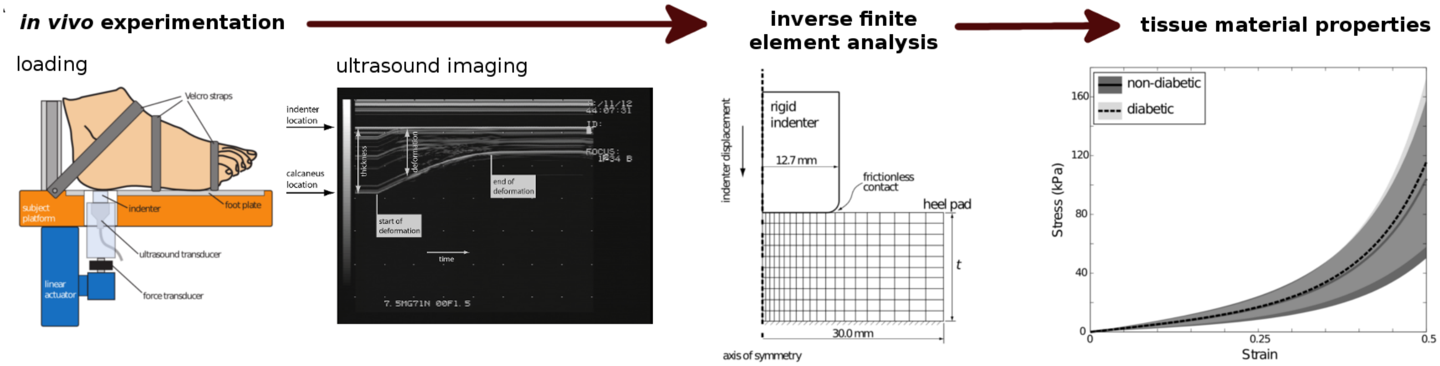

Figure 3. The principal investigator has significant experience in in vivo experimentation and has utilized data from human subjects for in situ determination of anatomical and mechanical properties of superficial tissue layers. Ultrasound was used to measure tissue thicknesses of diabetic and non-diabetic heel pads (80 total) during indentation tests[43]. Combining imaging data with force measurements, the team was able to identify heel-specific material properties.

and the current director of the Computational Biomodeling (CoBi) Core at the Cleveland Clinic. His group (along with interactions with various facilities in the host institution) is also experienced in human subjects testing[43,54–57], anatomical imaging[54,58,59], cadaver experimentation of the musculoskeletal system[58–62], and characterization of the mechanical properties of tissues[43,59,63] and nonlinear man-made materials[64]. Dr. Erdemir is a proponent of reproducible and reusable science and engineering, providing perspectives for good reporting practices, for example, of modeling studies utilizing finite element analysis[6]. He is also the co-chair in the nationwide Committee on Credible Practice of Modeling and Simulation in Healthcare. Dr. Jelovsek, the medical director of the Multidisciplinary Simulation Center at the Cleveland Clinic, will inform Dr. Erdemir and his team about the adequacy and value of the generated models in regard to simulation-based medical and surgical training. Dr. Jelovsek has significant scientific and translational experience in modeling and simulation for medical training and surgical practice[65–70], along with an expertise in clinical trials[71–74]. The infrastructure will be supported by Simbios, National Institutes of Health Center for Biomedical Computation at Stanford University. Dr. Delp and Dr. Ku at the Stanford University bring exemplary expertise in open source biomedical software[75,76] and web-based infrastructure development[77–79]. Dr. Erdemir has a long history of collaborations with the team at the Stanford University (see section 4.4).

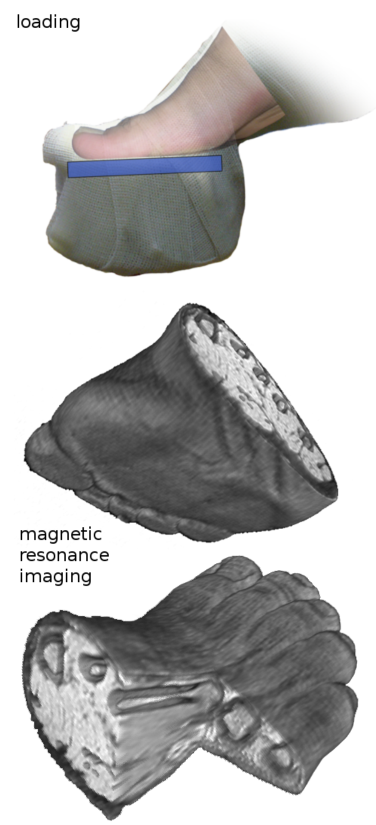

Figure 4. On 10 human subjects, the principal investigator and his colleagues measured the deformation of skin, muscle, and fat layers of the forefoot[54]. Lifelike loading was applied to the plantar surface through a non-magnetic loading device attached to the foot by casting. Magnetic resonance imaging was used for visualization of tissue layers.

4.2. Experimentation of Tissue Surrounding Musculoskeletal Extremities. Dr. Erdemir and his team previously conducted testing on human subjects to quantify indentation mechanics of the heel pad[43] (Figure 3). Eighty heels (20 healthy subjects, 20 diabetic patients; both sides) were mechanically loaded using an instrumented ultrasound. Indentation forces along with change in heel pad thickness were recorded to compare the mechanics of the heel pads from healthy subjects and diabetic patients. In later studies, in vivo testing also quantified the deformation of plantar tissues of the forefoot for 10 subjects[54]. By devising a foot casting procedure and incorporating an MRI compatible compression and shear loading device, deformation of skin, muscle, and fat tissues of the forefoot were visualized (Figure 4). Most recently, the team explored the possibility to visualize skin, fat, and muscle layers using ultrasound, in unloaded and deformed states. The capacity of ultrasound to delineate these layers, for the upper arm in example, has been promising (Figure 5).

The team has significant experience in cadaver testing of musculoskeletal joints, in particular the foot[58,60,61] and the knee[59], documenting the mechanics of these structures during lifelike loading. In this project, this expertise will be expanded for testing of multi-layer tissue structures of the legs and arms. Previous testing commonly employed acquisition of both organ/joint anatomy, e.g., with MRI, and mechanics, i.e., through robotics testing. For model development, a key aspect is related to the registration of the imaging coordinate system with the mechanical testing coordinate system so that model predictions of mechanics can be adequately compared to experimental measurements. By relying on carefully designed registration markers, i.e., by attaching fluid-filled spheres to femur and tibia, the team can accomplish such registration within 1% accuracy[59]. Recently, the group, with collaborators at the Case Center for Imaging Research, implemented previously reported magnetic resonance imaging protocols[80] for musculoskeletal imaging of cadaver knees (Figure 6). These protocols will be iterated further to acquire high contrast images of multi-layer tissue structures of the legs and arms.

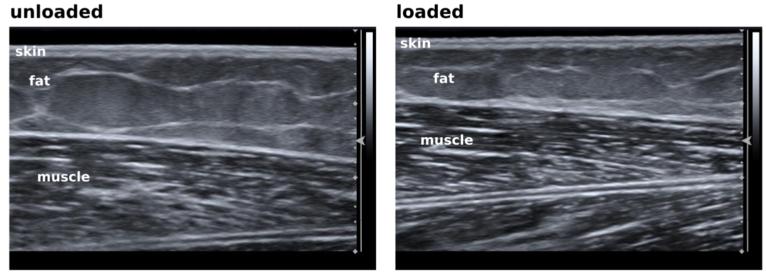

Figure 5. The team can utilize ultrasound to measure unloaded thicknesses of tissue layers and their deformations during indentation of the multi-layer tissue surface using the ultrasound probe. Posterior region of the upper arm is shown with an imaging depth of 30 mm.

Dr. Erdemir and his team have standard operating procedures for mechanical testing of the tissues to characterize tissue stress-strain response. These protocols allow preparation of uniformly shaped tissue samples (cylindrical or thin dumbbell shaped) and measurement of their geometries. Testing procedures include multi-step stress-relaxation in confined/unconfined compression, or in tension while acquiring force-displacement data and optionally single-camera video recordings (Figure 7). Tests to failure can also be conducted. Previously, these protocols helped characterize tissue structures of the knee; cartilage, ligaments, meniscus. These protocols will be adapted for characterization of skin, fat, and muscle from multi-layer tissue structures of the musculoskeletal extremities.

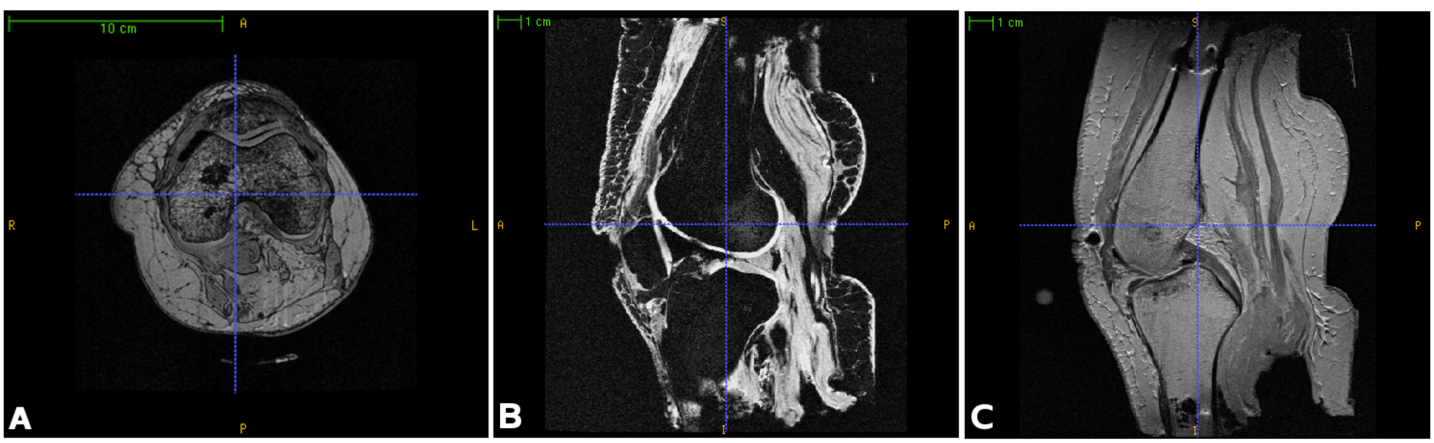

Figure 6. Magnetic resonance imaging will be used to reconstruct tissue geometry. Different image settings have been tested on a cadaver knee joint by the investigating team to understand the influence of imaging parameters on tissue contrast: A. An axial slice from a general purpose 3D T1-weighted imaging without fat suppression (0.5 mm x 0.5 mm x 0.5 mm). B. A sagittal slice from a 3D T1-weighted imaging with fat suppression (0.35 mm x 0.35 mm x 0.70 mm). C. Sagittal plane 2D proton density imaging (0.5 mm x 0.5 mm x 2.8 mm). The latter imaging modality emphasizes the contrast of multiple tissue layers, e.g. muscle and fat.

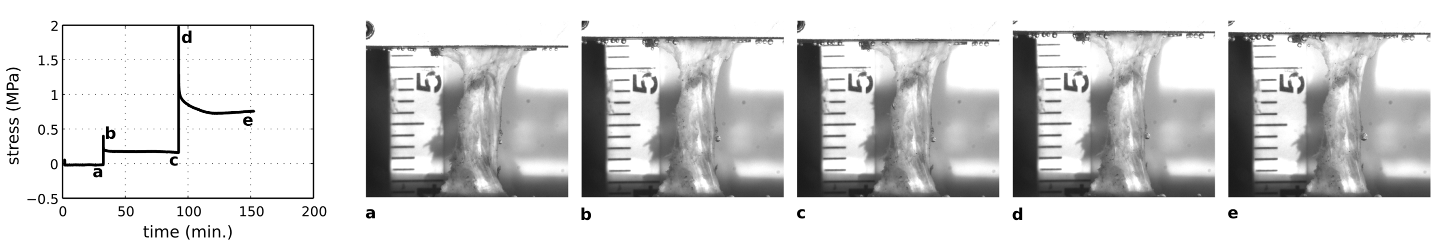

Figure 7. Multi-step stress-relaxation tests will be use to characterize the nonlinear viscoelastic behavior of tissues. Dr. Erdemir and his team has already established workflows for testing of musculoskeletal tissues, e.g., ligaments.

4.3. Computational Modeling of Tissue Surrounding Musculoskeletal Extremities. Finite element analysis work, conducted by Dr. Erdemir and his colleagues to explore the nonlinear external (surface) and internal (layer) mechanics of tissue surrounding the forefoot[14], is directly relevant to the proposed project. The computational model utilized in this study incorporated detailed anatomy and nonlinear elastic mechanical properties of skin, fat, and muscle. Contact pressures (surface mechanics) and stress-strain distribution in skin, fat, and muscle layers were predicted for compression loading of the forefoot through its plantar surface. Relevant to the proposed project, this study provided multiple important findings. First, when predicting contact mechanics (surface response), a lumped tissue representation (single tissue layer) was found to be satisfactory when compared to a multi-layer tissue representation (individual skin, fat, and muscle layers) (Figure 8). Second, the multi-layer tissue representation allowed identification of high-risk (high stress) areas within individual tissue layers and at different regions of the foot (Figure 8). This was not possible with a lumped tissue representation, which predicted a more uniform stress-strain distribution internally. Third, mechanical characteristics of individual tissue layers were found to influence not only their own mechanical response but also the deformations of the neighboring layers. This study was supported with comprehensive subject-specific anatomical and mechanical dataset[54] to prescribe model parameters and to evaluate model predictions.

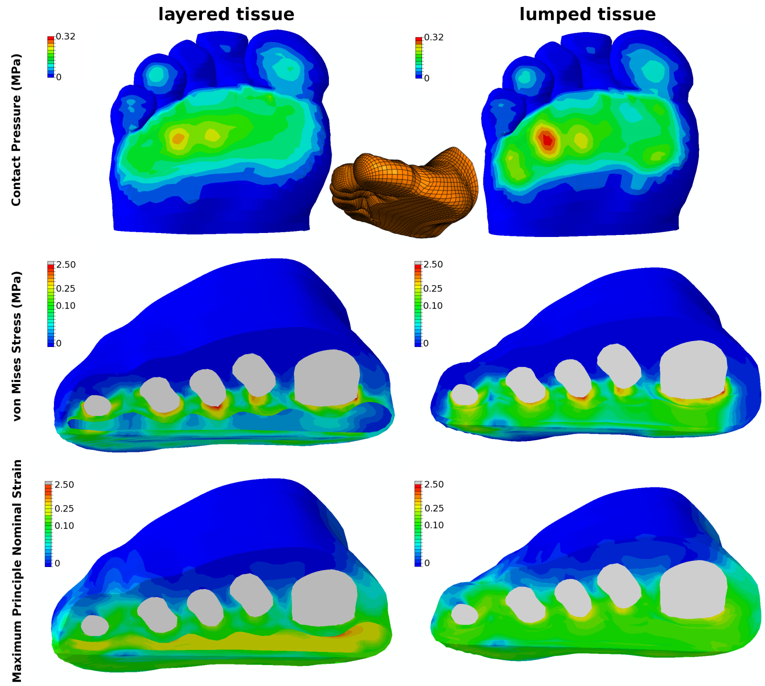

Figure 8. Skin, fat, and muscle layers of the forefoot were modeled by Dr. Erdemir and his colleagues for finite element analysis of the forefoot. The analysis incorporated large deformations, nonlinear elasticity, and contact, and predicted multi-layer mechanical response during compression through the plantar surface. Internal stress-strain distribution exhibited heterogeneous behavior (large stresses in muscle, large deformations in fat), a physiological prediction which was not possible when using a lumped single layer model. Surface mechanics on the other hand, was reasonably comparable between layered and lumped tissue models.

Using inverse finite element analysis combined with in vivo[43] or in vitro[44] data, the team has previously quantified nonlinear material properties of the heel pad. This approach relies on indentation response and tissue deformation measurements and couples finite element analysis with optimization to calculate material properties of the tissue of interest. This method helped compare heel pad properties of healthy and diabetic subjects with simplified models[43] (Figure 3). In a latter study, using a realistic anatomical representation, it was expanded to evaluate the predictive capacity of calculated tissue properties under complicated mechanical manipulations of the tissue surface[44], e.g., compression and shear with an indenter (Figure 9). For the proposed project, similar types of experimentation and modeling will be conducted on human subjects and cadaver specimens, this time with a focus on multi-layer tissue structures of the legs and arms.

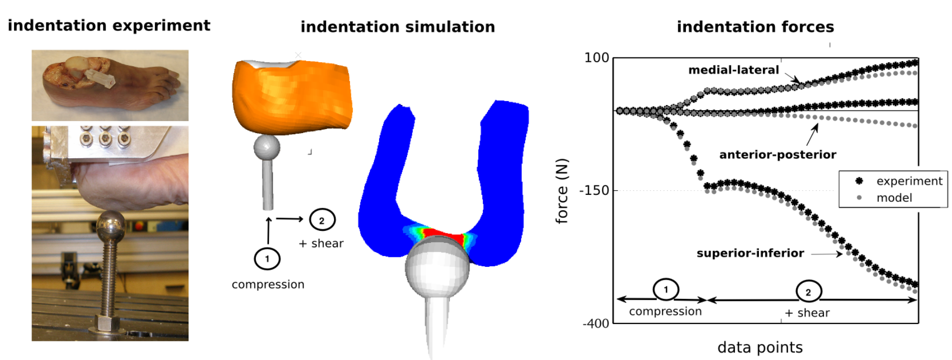

Figure 9. The team conducted cadaver experimentation to quantify three-dimensional indentation forces on tissue surrounding musculoskeletal extremities, in this case the heel pad of the foot[44]. Modeling and simulation of the tool interacting with the tissue layer predicted tissue deformation and stresses along with tool forces. A registration phantom allowed alignment of experiment and model coordinate systems.

Model simplification approaches of the investigators have importance to conduct computationally cost-effective simulations while retaining major features of the tissue system for adequate mechanical representation. For example, for inverse finite element analyses of the heel pad (conducted with data from 80 heels), reduction of three-dimensional anatomy to axisymmetric geometry allowed large-scale iterative nonlinear analysis[43] (Figure 3). The team has also devised adaptive surrogate modeling approaches, which utilized a solution database of previous model predictions, to avoid computationally costly finite element analysis during iterative, coupled simulations[48,49] (Figure 10). Such approaches significantly reduced computational cost of complicated biomechanical analysis of the musculoskeletal system and allowed solutions for problems previously deemed to be infeasible, e.g., on-the-fly prediction of local tissue stress and strain distributions during optimal control of musculoskeletal movements[48].

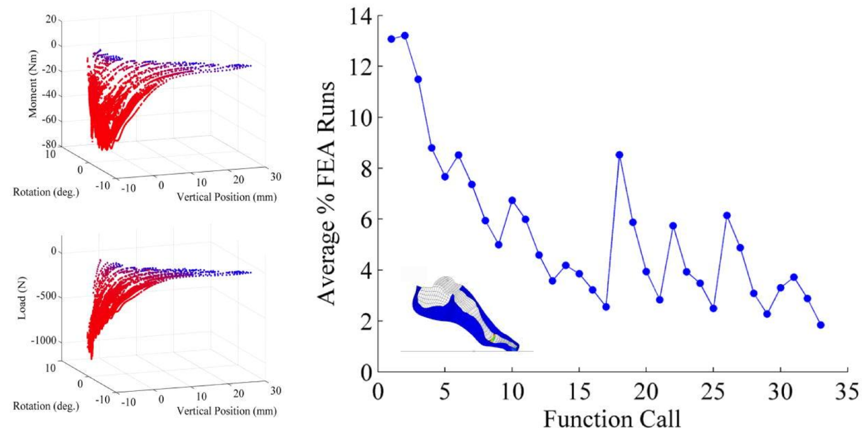

Figure 10. Solutions of problems coupled with finite element analysis, e.g., optimization, require multiple simulations at each iteration, e.g. evaluation of objective function. This requirement commonly dictates computational cost and may render the solution approach infeasible. In finite element analysis of the foot coupled with optimal control of movement simulation, the principal investigator and his co-workers utilized adaptive surrogate modeling, where a database of previous solutions (generated on-the-fly) provided reaction loads as a function of model position and rotation[48]. This significantly reduced the need to run finite element analysis as optimization iterations (function calls) moved forward.

An underestimated cost of modeling and simulation is related to the labor required for model development. Directly relevant to modeling of multi-layer tissue structures, the investigators have developed mesh morphing strategies to accommodate subject-specific tissue thickness on bony prominences[81]. Recently, Dr. Erdemir's group developed computer scripts to automate generation of layered representation of tissues (anatomical and mechanical), e.g., for the cartilage. The team constantly relies on model templating, automation of model development, and scripting of post-processing to realize timely implementation of modeling and simulation workflows. Examples of such efforts include generation of tissue models representative of the cellular organization within[51], and post-processing of tissue-scale and cell-scale models for extraction of physiologically important biomechanical markers[53].

4.4. Web-based Interfaces. Dr. Erdemir and the team at the Stanford University have had past and ongoing activities to provide web-based interfaces for collaboration, dissemination, and computing. These activities have utmost relevance to the proposed project, as they provide the foundations for development of online data curation strategies, databases of raw data, tissue properties, and models, and processing workflows to assemble models, run simulations, and post-process results. The team at the Stanford University launched Simbios, which provides the infrastructure for collaboration via SimTk.org, a web-based platform for biomechanics software and model development and dissemination[77]. In a past collaboration, Dr. Erdemir and the members of Simbios launched a wiki feature at SimTk.org to facilitate online documentation of hosted projects. Most recently, as part of a federally funded project for finite element analysis of the knee joints[30], the group started working on a cloud computing prototype, where users of the web site can submit simulations by changing template models. This prototype has been launched at a staging server (Figure 11) and is currently under testing. In a nutshell, this web interface allows the user to choose the server, simulation software, and model, and gives him/her the opportunity to modify the model before submitting it to a compute server for simulation. The user receives multiple e-mails, informing the status of the simulation. Once completed, the user can download simulation results from his/her user page. Other interfaces can be developed relying on similar web development strategies; to access databases of tissue anatomy and mechanical properties, to assemble models for download, and to conduct simulations with existing models from model databases.

4.5. Public Dissemination and Community Engagement. The proposed project will implement an open development approach, i.e., all activities, raw data, processing and modeling approaches will be visible to public during the progression of the project. This is not necessarily limited to viewing the progress of research but it also provides mechanisms for feedback and contribution. This is a significant step, which moves beyond free and open dissemination of data and models. Previous and ongoing work by the principal investigator, his team and his collaborators illustrate their capacity to incorporate transparency in their scientific and engineering work, and their outreach for dissemination and reuse of data and models. For example, recently, Dr. Erdemir and his team have adapted an open development approach for modeling and simulation of musculoskeletal joint mechanics, in particular that of the knee[30]. As an ongoing collaboration with the team at the Stanford University, that project utilizes SimTk.org infrastructure[77] for community-driven science in biomechanics of the joints. The relevant project site had 25,940 unique visitors in the past 180 days; the first generation knee model, shared with the public through the web site, has been downloaded 584 times. Dissemination of this computational model already had an impact on the scientific conduct of the biomechanics community by removing the technical barrier to enter modeling and simulation practice of musculoskeletal joints. Powered by the access to such models, many investigators conducted scientific studies based on this model, some focusing on development of novel simulation techniques[82], others exploring the mechanical function of the knee[83,84].

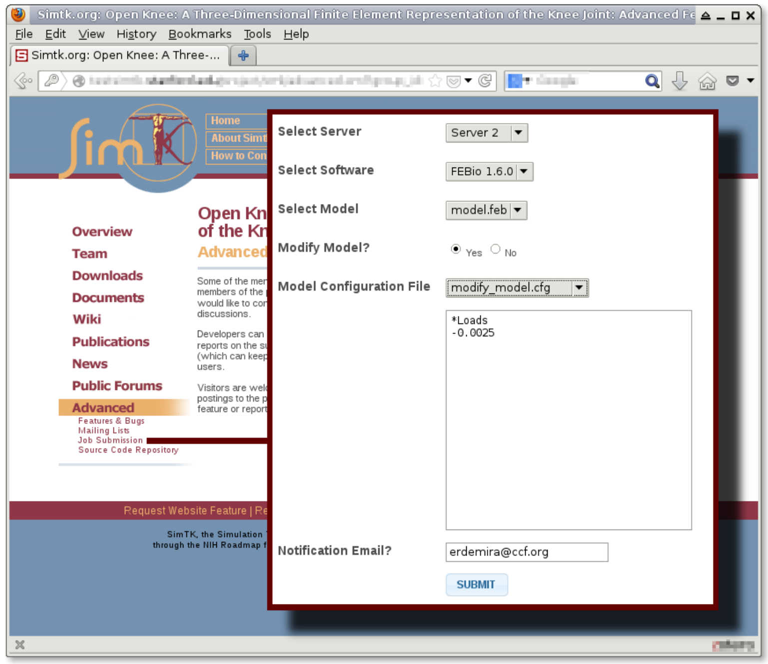

Figure 11. In an ongoing project (for open development of knee joint models), the collaborating teams have implemented a cloud computing prototype at SimTk.org, host for the collaboration and dissemination infrastructure of the project. With this interface, computational simulations are possible through selection of a compute server, software and the model, and by modifying the model. Similar web-based interfaces will be developed to populate and access tissue properties and model databases, and to utilize them to develop new models and conduct simulations to generate in silico data for mechanics of multi-layer tissue structures.

Dr. Erdemir and his team have an ambitious public dissemination approach to augment the new scientific knowledge they generate with data, computer code, models, and simulation results. Free and open provision of supporting information to reproduce modeling and simulation work is a common practice in their publications. The team has disseminated comprehensive data sets, e.g., anatomical and mechanics data of the foot[58], and a variety of computer code to automate modeling and simulation procedures such as generation of tissue models with cellular inclusions[51] and post-processing of cell-scale simulations to quantify cellular mechanics[53]. Their multiscale simulation approaches, with models and coupling strategies, were also provided; to understand the relationship between musculoskeletal movements and tissue deformations[48] and to explore the mechanics of cartilage cells during loading of the knee[53,83]. Data and models, to extract tissue properties using inverse finite element analysis, e.g. for the heel pad[44], and to evaluate performance of finite element meshes, e.g. for contact simulation of tissue regions[52], were also disseminated.

5. Technical Objectives

The overall goal of the proposed research is to provide open and freely accessible databases of mechanical and anatomical models and data from multi-layer tissue structures of musculoskeletal extremities; all with proven utility in surgical simulations. The data will also serve to understand the internal and external mechanics of multi-layer tissue structures as a function of skin, fat, and muscle properties, and their interactions. With this long-term vision in mind, the technical objectives of the study incorporate (i) augmentation of existing web-based infrastructure with development of new features for data curation and building databases; (ii) acquisition of data to establish the foundations of the mechanics of multi-layer tissue structures, (iii) development, evaluation, and dissemination of physiologically realistic nonlinear computational models of multi-layer tissue structures, and (iv) development, evaluation, and dissemination of physiologically simplified yet computationally efficient models with lifelike perception of multi-layer tissue mechanics. Specific technical objectives are listed below along with their relevance to the hypotheses of the project:

Objective 1. To implement web-based interfaces (i) to upload, accumulate, and navigate raw data on multi-layer tissue structures of musculoskeletal extremities, (ii) to create and populate queryable databases of anatomical and mechanical properties of skin, muscle, and fat layers of legs and arms, and (iii) to assemble and curate models of skin, muscle, and fat layers of legs and arms in queryable databases.

Objective 2. To collect anatomical properties of skin, muscle, and fat layers of legs and arms of human subjects along with external and internal mechanical response of these multi-layer tissue regions during indentation.

This objective will allow testing of Hypotheses 1 and 2 and provide data to support testing of Hypothesis 6.

Objective 3. To collect anatomical and mechanical properties of skin, muscle, and fat layers of legs and arms from cadaver specimens along with external and internal mechanical response of these multi-layer tissue regions during indentation.

This objective will allow testing of Hypotheses 3 and 4 and provide data to support testing of Hypothesis 5.

Objective 4. To collect tool forces during incision, retraction, and peeling of multi-layer tissue structures of cadaver upper legs along with tissue mechanical response.

This objective will provide data to support testing of Hypothesis 8.

Objective 5. To build and evaluate physiologically realistic reference computational models of skin, muscle, and fat layers of legs and arms representative of specimen-specific, detailed anatomical and nonlinear mechanical properties acquired from cadaver specimens.

This objective will allow testing of Hypothesis 5.

Objective 6. To develop and execute computational tools for building and evaluating physiologically realistic reference computational models of skin, muscle, and fat layers of legs and arms with generic mechanical properties and representative of gross anatomical features customized to measurements from human subjects.

This objective will allow testing of Hypothesis 6.

Objective 7. To build and evaluate computationally efficient surrogate models of skin, muscle, and fat layers of legs and arms with plausible deformation and indentation response.

This objective will allow testing of Hypotheses 7.

Objective 8. To demonstrate deformation and haptic capacity of computationally efficient surrogate models of skin, muscle, and fat layers of upper legs during incision, retraction, and peeling.

This objective will allow testing of Hypotheses 8.

Objective 9. To populate and disseminate raw data, anatomical and mechanical properties, and computational models of the mechanics of skin, muscle, and fat layers of legs and arms through web-based interfaces.

6. Methods

6.1. Web-based Infrastructure. Simbios will provide the infrastructure for collaboration via SimTk.org, a web-based platform for software development and dissemination[77]. Communication between investigators, and developers and users from the community will be facilitated by a project web site at SimTk.org. 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. 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. Recently, the team has been exploring the implementation of a cloud-computing infrastructure to modify and submit models for simulation (Figure 11).

Specifically for the proposed project, Simbios team will implement new web-based interfaces for curation and storage of raw data and for establishing and populating databases of tissue properties and models (Figure 12). Web-based workflows, provided as part of an extended cloud computing interface, will allow utilization of databases to build new models to download and to conduct simulations with (on a local computer or through a web-interface) (Figure 12).

The proposed activity will result in a plethora of heterogeneous data and models (see the following sections). Organization and accumulation of this data by the investigating team will be conducted through Midas Platform (Kitware Inc., Clifton Park, NY), which will be integrated to the project site at SimTk.org (Figure 12). The Midas Platform is an open source software platform allowing web enabled data storage and access, facilitating handling of large data sets, and providing tools for search and annotation. Processing of the raw data will result in anatomical and mechanical information from multi-layer tissue structures in a usable form, geared towards enabling development of models, and if desired, comparison of tissue features among individuals or between populations. The processed data, specifically tissue properties, will be populated, stored, and accessed through a web interface connected to a relational database management system, specifically MySQL (Oracle Corp., Redwood City, CA) (Figure 12). MySQL is an open source database system, permitting features for data entry and query in a relational form. Such databases will incorporate demographics of the subject/donor from which the tissue belongs to (age, gender, height, weight, etc.), the anatomical region, e.g., leg, and location-specific tissue properties, e.g. thickness, modulus, etc. Further processing of data and reuse of tissue information in the databases will result in computational models that can be stored and accessed in relevant databases (Figure 12). It is possible that relational databases relying on tabular forms may not be effective for management of the models. As a result, the team will utilize open source NoSQL databases for population, query, and retrieval of models of multi-layer tissue structures, e.g., MongoDB (MongoDB, Inc., New York, NY). The collaborating team at the Stanford University launched and has been managing databases of magnitude higher than those proposed in this study. For example, Simbios handles +700 projects (with various download packages) and +30,000 members (with varying access to the projects).

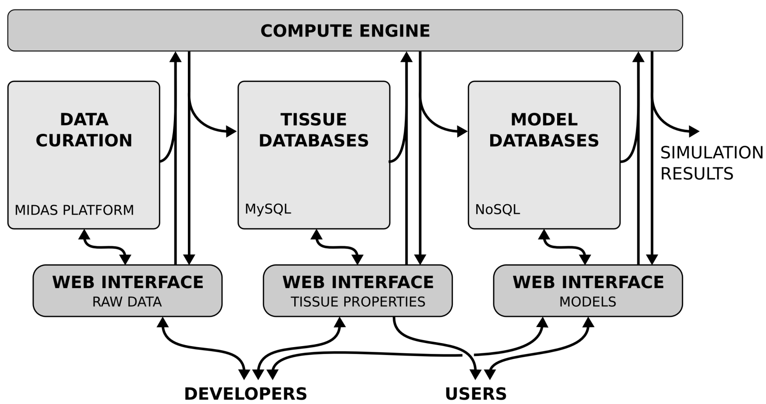

Figure 12. Web-based infrastructure will require implementation of new features to SimTk.org[77], the collaboration and dissemination site for the project. Web interfaces will provide developers and users streamlined access to data and databases, and to utilize workflows to process data (to extract tissue properties), to assemble models (using tissue properties) and to conduct simulations. A low level compute engine linked to the proposed web interfaces and the intermediate framework will facilitate these activities.

Web-based data processing, model assembly, model modification, and model simulation interfaces will complement the data curation and database interfaces to provide a complete framework for modeling and simulation of multi-layer tissue structures of musculoskeletal extremities. Midas Platform (Kitware Inc., Clifton Park, NY) already provides features to build workflows automating processing of data by pushing the workload to a compute server. The team has also implemented a cloud computing interface in SimTk.org, that allows the user to modify a model, to submit a simulation job to a compute server, and to retrieve results (Figure 11). In the proposed project, the data processing web-interface will give user/developer access to execute template or modified workflows to calculate tissue properties, model parameters, etc. and to populate relevant databases. The model assembly web interface will allow user/developer to query databases to access model parameters and use them to build a new model, which can be downloaded, stored in a model database and/or simulated through the web computing interface. The model modification web interface will allow user/developer to query the model database, to retrieve the desirable model as template, to modify it, and to download the updated model and/or to simulate through the web computing interface. The web computing interface will allow user/developer to submit a model for simulation and to retrieve results. It should be noted that the simulation results, in an abridged form for example, can also be stored in a database.

All these web-based infrastructures will significantly enhance curation and sharing of data and models during the course of the activities (not only after all the work is done). The open development and dissemination approach exploiting this web-based platform will likely advance biomechanics research in multi-layer tissue structures of musculoskeletal extremities and expedite development and reuse of relevant translational computational models. This approach will likely inspire involvement of other researchers and the public to the proposed activities, which may in turn facilitate building a theme focused community.

6.2. Experimentation. The proposed activity will rely on three batteries of tests. Human subjects testing will provide a large set of data on tissue thicknesses of multi-layer tissue structures of musculoskeletal extremities along with indentation response. First set of cadaver experiments will aim to augment this data by collecting specimen- and region-specific anatomical information, tissue and tissue interface properties, and indentation response of multi-layer tissue structures of legs and arms. Second set of cadaver experiments will focus on the quantification of forces exerted by surgical tools during mechanical manipulations of multi-layer tissue regions of upper legs.

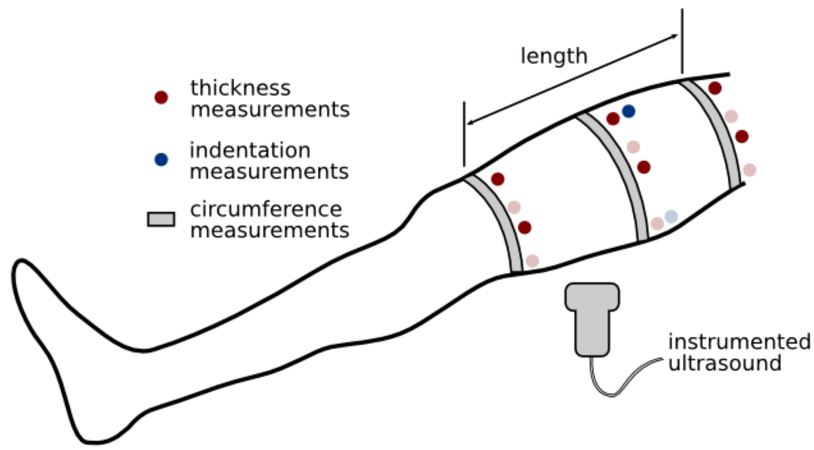

Figure 13. For each region of interest (upper and lower legs and arms), tissue thickness will be measured at 12 locations; proximal-middle-distal locations, anteriorly, posteriorly, medially, and laterally, along with anthropometric measurements. Indentation mechanics; indentation force and deformation of skin, fat, and muscle layers will be measured at mid-sections, anteriorly and posteriorly. An ultrasound probe instrumented with a spatial load transducer will be used. Data will be collected on both human subjects and cadaver specimens.

6.2.1. Subject- and Region-Specific Tissue Thickness and Mechanical Response. A total of 100 adult subjects will be tested irrespective of age, gender, race, and ethnicity. The target population is the general population as everyone is potentially at risk of injury, and therefore candidates for surgical operations on their extremities. The sample population will also include subjects reflecting general characteristics of military personnel[85] and their potentially high activity level. The goal is to establish a reference range for tissue thicknesses and indentation response of layered tissue structures of musculoskeletal extremities, specifically the legs and arms and various anthropometric measures. Hence, the targeted number of subjects is deemed to be adequate based on our previous studies of anatomical and mechanical characterization[43]. A screening questionnaire will permit recording of subject specifics including age, weight, height, gender, race, and ethnicity, and in addition, their activity level. The study protocol is currently under review by the Institutional Review Board of the Cleveland Clinic. Upon approval, the investigators will request additional approval by the USAMRMC ORP HRPO. This approach will ensure human subjects protection along with meeting the regulatory requirements of DoD, Army, and USAMRMC.

Specific regions for data collection will include upper and lower legs and arms of the subjects at a single side (Figure 13). The length of the region will be measured along with three circumference measurements at distal, central, and proximal sections (Figure 13). Skin, fat, and muscle thickness (at an unloaded state) will be acquired at twelve points; distal, central, and proximal locations – anteriorly, posteriorly, medially, and laterally (as in Figure 13). An ultrasound system (Teratech Corp., Burlington, MA), will be used for this purpose.

The ultrasound system (Teratech Corp., Burlington, MA) will be fitted with a spatial load transducer (ATI Industrial Automation, Apex, NC) to measure loaded and unloaded tissue thicknesses along with forces exerted on the multi-layer tissue structures of the legs and arms during indentation (Figure 13). Similar testing setups were used in our work for measurement of in vivo heel properties[43]. Two regions within each extremity will be tested using this system; centrally located tissue areas, anteriorly and posteriorly. During the tests, ultrasound images for the unloaded tissue layers will be recorded first, then deformation of individual tissue layers and indentation forces will be measured as the ultrasound probe compresses the tissue.

This human subjects experimentation will result in a comprehensive data set from 100 subjects, acquired on 4 regions (upper and lower legs and arms): gross anatomy of the limb (circumference and length); skin, fat, muscle thicknesses at 12 points; and indentation forces and layer deformations at 2 points. To test Hypothesis 1 of the project, the role of multi-layer tissue thicknesses on indentation response will be examined by multiple linear regression[86]. To perform the analysis, indentation stiffness will be calculated (as the slope of the linear region of indentation force vs displacement (total tissue thickness change) response). Data from indentation sites for all regions will be pooled. Correlation matrices between individual layer thicknesses will be calculated and interactions between these variables will be explored. A similar analysis will be conducted to test Hypothesis 2, this time deformed layer thicknesses will be used as outcomes. It should be noted that these analyses may also incorporate subject characteristics, e.g., age, gender, height, weight, etc., if the influences of such demographics on multi-layer tissue response are deemed to be of interest.

6.2.2. Specimen- and Region-Specific Full Anatomy, Mechanical Response, and Tissue Properties. A total of 40 multi-layer tissue regions from 20 cadaver specimens (10 legs, 10 arms, both upper and lower sections) will be tested to capture a foundational database of detailed tissue anatomy, indentation response, and tissue and tissue-interface mechanical properties. The target specimen sample population is the general population irrespective of age, gender, race, and ethnicity. Nonetheless, sampling will also include at least 4 leg and 4 arm specimens (2 from male donors and 2 from female donors each) reflecting general characteristics of military personnel[85]. Cadaver specimens will be acquired from various suppliers, e.g., Science Care Inc. (Phoenix, AZ). The goal is to establish a reference range for anatomical and mechanical properties of layered tissue structures of musculoskeletal extremities; the targeted number of subjects is deemed to be adequate based on our previous studies of anatomical and mechanical characterization[54]. Cadaver studies are not considered research involving human subjects and treated to be exempt from human subjects protections regulations by the Institutional Review Board of the Cleveland Clinic. Nonetheless, the investigators will request additional approval by the USAMRMC ORP HRPO. This approach will ensure human subjects protection along with meeting the regulatory requirements of DoD, Army, and USAMRMC.

Each extremity region will be prepared by first separating legs and arms into upper and lower regions. A gross evaluation of the specimen will ensure that it matches the desired specimen specifics, including preliminary assessment using magnetic resonance images. Both imaging (MRI) and ultrasound-based indentation testing will be conducted on the extremity region. To match the image (potentially defining the model) and mechanical testing coordinate systems, registration marker sets (three hollow plastic spheres filled with water based gel) will be placed on the bone of the multi-layer tissue structure. This registration setup has a relative accuracy within 1% for measuring the distance between two markers. For imaging, the specimen will be secured to a non-magnetic holder designed to keep the segment at a neutral alignment. MRI will be acquired at the Case Center for Imaging Research at University Hospitals, using a 3 Tesla scanner (MAGNETOM® Skyra, Siemens Medical Solutions USA, Inc., Malvern, PA). Two different imaging protocols will be implemented: a general purpose 3D isotropic T1-weighted imaging protocol without fat suppression (0.5 mm x 0.5 mm x 0.5 mm voxel size); an axial plane proton-density imaging protocol (0.35 mm x 0.35 mm in-plane resolution; 3 mm image thickness) to achieve high contrast between skin, fat, and muscle[80] (Figure 6). MRI will provide the necessary information for geometric construction of the registration markers, e.g. sphere centers, and multi-layer tissue anatomy of the extremity of interest.

In addition to detailed anatomical data collection, gross anthropometric information on the extremity specimens will be collected: length and circumferences at distal, central, and proximal sections (Figure 13). The ultrasound system (Teratech Corp., Burlington, MA) will quantify skin, fat, and muscle thickness (at an unloaded state) at twelve points on the specimen; distal, central, and proximal locations – anteriorly, posteriorly, medially, and laterally (as in Figure 13). The ultrasound system (Teratech Corp., Burlington, MA) will be fitted with a spatial load transducer (ATI Industrial Automation, Apex, NC) to measure deformed tissue thickness along with forces exerted on the multi-layer tissue structures of the specimens (Figure 14). One section of the extremity region will be tested in this fashion; bulk tissue area, anteriorly or posteriorly located (depending on the extremity region) at the mid-point of the extremity. The specimen will be secured on a platform for this purpose (Figure 14). The movement of the ultrasound probe will be measured relative to the specimen using a motion analysis system (Optotrak Certus, Northern Digital Inc., Waterloo, Ontario, Canada). The Optotrak probe will be used to digitize points on the outer surface of registration markers on the specimen, to find their center using a sphere fit. The locations of these registration markers will establish the relationship between imaging and testing coordinate systems (also see above). Ultrasound based tissue thickness measurements will be compared against information from MRI to confirm the adequacy of thickness measurements and provide a path to reconstruct geometry when MRI is not always feasible, e.g., for large scale human subjects testing (see 6.2.1). The indentation response data will provide overall response of the multi-layer tissue structure that can be correlated to anatomical and mechanical properties of the tissues and tissue-interfaces of multi-layer tissue structures.

Upon completion of imaging and indentation testing on cadaver extremity regions, uniformly shaped samples will be extracted from skin, fat, and muscle (and possibly from muscle fascia) (Figure 15). All samples will be acquired from the indentation region of the specimen. For skin, three strips of samples (dumbbell shaped) with 45° orientation to each other will be acquired and tested under tension (Figure 15). For fat, a cylindrical sample will be acquired and tested under unconfined compression (Figure 15). For muscle, a cylindrical sample along the transverse axis will be acquired and tested under unconfined compression and a dumbbell shaped sample along the axis of the muscle will be obtained and tested under tension (Figure 15). Each sample will undergo stress-relaxation tests to characterize nonlinear viscoelastic stress-strain response of the tissue. Anisotropic behavior of tissues will be accommodated by extracting and testing samples oriented in different directions. Failure tests will also be conducted to characterize yield and ultimate strength and failure strain for each tissue. During all tests, video data will be collected to characterize sample stress-strain. Tissue testing will be performed using a mechanical testing equipment integrated with a load transducer and a single camera (MACH-1™ V500 CSS; Biomomentum Inc., Laval, Quebec, Canada). A three-dimensional strain measurement system (VIC-3D™ system; Correlated Solutions, Inc., Columbia, SC) will support characterization of three-dimensional deformations. When and if necessary, additional tissue samples will be acquired for specimen- and region-specific characterization of tissue material properties. Our research team has successfully implemented these protocols for testing of man made materials[64] and tissue samples[59] (also see Figure 7).

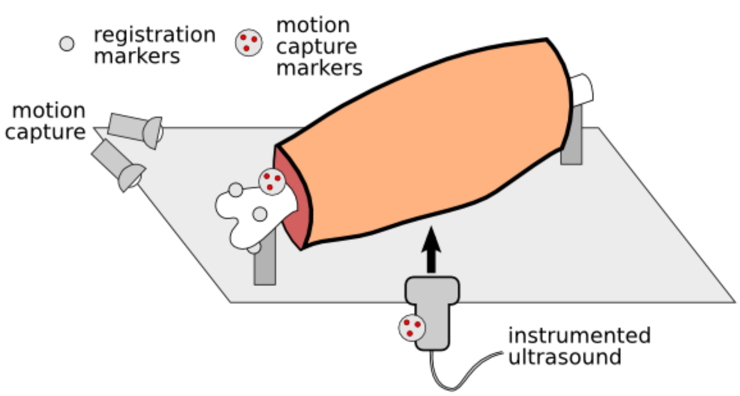

Figure 14. Cadaver specimens will be secured on a testing platform for indentation testing, using the ultrasound probe as the indenter. During testing, a motion analysis system will record probe movements relative to the specimen. The instrumented ultrasound will measure indentation forces and capture images of deformed tissue layers. Registration markers will allow alignment of mechanical testing coordinate systems to magnetic resonance imaging (also the model) coordinate system.

Uniformly shaped samples will also be extracted from skin-fat, skin-muscle, fat-muscle (if any), and muscle-muscle interfaces from the indentation region of the specimen (Figure 15). Four samples will be obtained from each interface; a cylindrical sample across the interface for characterization of compression response; two strips of samples (one across, the other along the interface) for characterization of directional

Figure 15. A cadaver specimen illustrates the multi-layer tissue organization in the upper leg. Tissue samples will be acquired from skin, fat, and muscle and from tissue junctions. Uniform shaped samples will be extracted for tension (<>) and compression (><) testing, to eventually characterize mechanical properties.

tensile response; a strip of sample along the interface to characterize shear response. Similar to isolated tissue samples, stress-relaxation tests will provide nonlinear viscoelastic stress-strain response and tests to failure will quantify the load bearing capacity of these tissue interfaces. Video data will be collected to characterize strain field at the interface, supported by a strain measurement system (VIC-3D™ system; Correlated Solutions, Inc., Columbia, SC). All testing will be performed using the same mechanical testing equipment described above (MACH-1™ V500 CSS; Biomomentum Inc., Laval, Quebec, Canada). When and if necessary, additional samples will be isolated from the extremity of interest.

This cadaver experimentation will result in a comprehensive data set from upper and lower legs and arms (10 each): detailed multi-layer tissue anatomy of the limb; gross anatomy of the limb and tissue thicknesses (as in the human subjects testing); indentation forces and layer deformations at one bulk tissue region including probe movements relative to the specimen; coordinate system registration information; and specimen-specific material properties of skin, fat, muscle, and the interfaces in between. To test Hypothesis 3 of the project, the role of multi-layer tissue elasticity (tangent modulus at linear region of stress-strain response) on indentation response will be examined by multiple linear regression[86]. To perform the analysis, indentation stiffness will be calculated (as the slope of the linear region of indentation force vs displacement (total tissue thickness change) response). Data from indentation sites for all regions will be pooled. Correlation matrices between individual layer moduli will be calculated and interactions between these variables will be explored. It should be noted that this analysis can be informed by the results of human subjects testing described above. The statistical model depicting the influence of tissue thickness (see section 6.2.1) can provide insight to develop regression approaches accommodating both layer thickness and material properties for in vitro data. A similar analysis will be conducted to test Hypothesis 4, this time deformed layer thicknesses will be used as outcomes. It should be noted that the analysis may also incorporate subject characteristics, e.g., age, gender, height, weight, etc., if the influences of such demographics on multi-layer tissue response are deemed to be of interest.

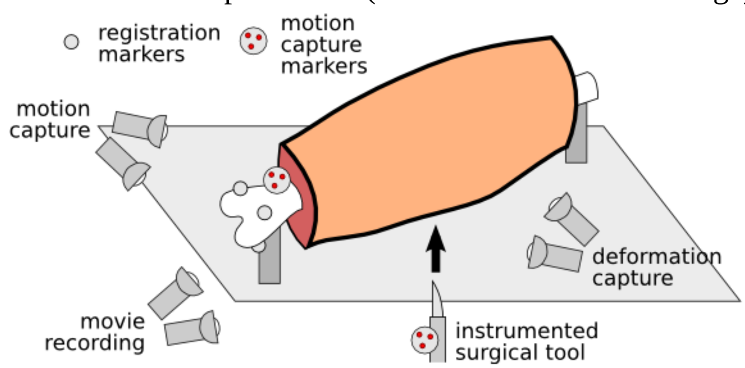

Figure 16. Cadaver specimens will be secured on a testing platform for quantification of mechanical forces of surgical acts. During testing, a motion analysis system will record surgical tool movements relative to the specimen. The instrumented surgical tools will measure tool forces. A strain measurement system will capture three-dimensional deformations at tissue surfaces. Registration markers will allow alignment of mechanical testing coordinate systems to magnetic resonance imaging (also the model) coordinate system.

6.2.3. Mechanical Environment of Multi-Layer Tissue Structures during Surgical Procedures. Ten upper legs from cadaver donors will be tested to acquire reference data sets on the forces of mechanical manipulations of multi-layer tissue structures during surgical procedures. While the target specimen sample population is the general population, at least 4 upper legs (2 from male donors and 2 from female donors each) that fit to general characteristics of military personnel[85] will be acquired. Cadaver specimens will be obtained from various suppliers, e.g., Science Care Inc. (Phoenix, AZ). The goal is to establish a reference range of loads applied to the multi-layer tissue structures during activities of surgical intervention (to support testing of Hypothesis 8). The targeted number of subjects reflects feasibility, while expanding the dataset as much as possible. Previously, we have successfully acquired reference datasets on a population with comparable size for anatomical and mechanical characterization of multi-layer tissue structures of the forefoot[54]. Cadaver studies are not considered research involving human subjects and treated to be exempt from human subjects protections regulations by the Institutional Review Board of the Cleveland Clinic. Nonetheless, the investigators will request additional approval by the USAMRMC ORP HRPO. This approach will ensure human subjects protection along with meeting the regulatory requirements of DoD, Army, and USAMRMC.

Surgical blades, probes, retractors, and clamps will be equipped with spatial load transducers (ATI Industrial Automation, Apex, NC) to measure forces exerted during surgical procedures conducted on multi-tissue layers of cadaver upper legs (Figure 16). The tools will also host markers to record their movements using a motion analysis system (Optotrak Certus, Northern Digital Inc., Waterloo, Ontario, Canada). The specimen (fitted with registration markers) will be secured on a platform during testing (Figure 16). Bulk tissue area at the mid-anterior region of the specimen will be operated on. The mechanical environment (tool movements and loads in relation to the specimen) during incision, retraction, and peeling of multi-layer tissue organization will be quantified (Figure 17). A three-dimensional strain measurement system (VIC-3D™ system; Correlated Solutions, Inc., Columbia, SC) will measure full deformation field of the surface and visible regions of the layered tissue structures during incision, retraction, and peeling. Movie recordings of each experiment with multiple cameras will also be conducted.

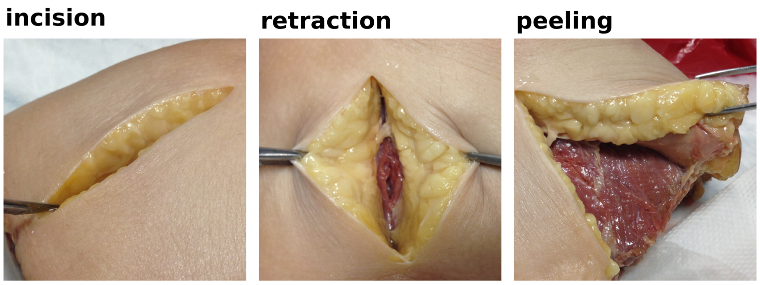

Figure 17. Experimentation will quantify tool forces during various surgical actions exhibited on multi-layer tissue structures of the upper leg.

In addition to the quantification of the loading environment during surgical procedures, each specimen will go through data collection steps employed for the first round of cadaver testing (see 6.2.2). Specifically, each specimen will go through MRI, measurements using ultrasound system (thickness and indentation response), and characterization of tissue properties. Registration markers (with centers measured both in MRI and in mechanical testing) will establish the relationship between imaging and testing coordinate systems.

6.3. Modeling & Simulation. The proposed activity will rely on two different modeling modalities: reference models incorporating nonlinear mechanics of multi-layer tissue structures of musculoskeletal extremities; and surrogate models simplified for cost-effectiveness yet with reasonable deformation and force feedback characteristics. Each modeling path will rely on in vivo and in vitro data collected through procedures described above (see section 6.2).

6.3.1. Reference Models of Nonlinear Mechanics of Multi-Layer Tissue Structures. Detailed computational representations of cadaver legs and arms will be developed for nonlinear finite element analysis (Figure 18). From cadaver experimentation data set described in section 6.2.2, two donors will be selected; 1 male and 1 female that fit to the general characteristics of military personnel[85]. Each upper and lower leg and arm regions of the donors will be modeled, resulting in a total of 8 models. Utilizing comprehensive imaging and mechanical data sets, fully specimen-specific modeling will be possible. The geometry of individual skin, fat, and muscle layers and the bone will be segmented from magnetic resonance images using 3D Slicer[87]. These geometries will be meshed using TrueGrid (XYZ Scientific Applications Inc., Livermore, CA) to obtain high quality hexahedral meshes. Anisotropic and nonlinear hyper-viscoelastic constitutive models[88] will be fit to stress-strain data acquired for skin, fat, and muscle during stress-relaxation tests. Bone will be assumed as rigid for the purpose of investigating soft tissue mechanics of individual layers surrounding the skeletal extremity. Interactions between tissue layers will be modeled based on specimen-specific tissue-interface mechanics data acquired during cadaver testing. It is anticipated that skin-fat layers will be tied, and a sliding contact type of an interface between fat-muscle and muscle-muscle will be

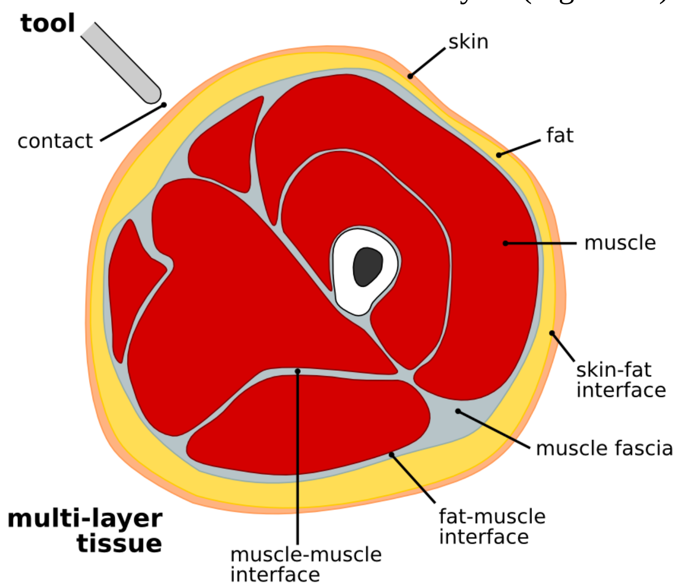

Figure 18. Predictive simulations of the mechanics of multi-layer tissue structures of legs and arms require the models to accommodate anatomical and mechanical details of individual tissue layers and how they interface with each other. Mechanical manipulations will be through a tool contacting with the extremity; a probe for indentation simulations and surgical tools for medical simulation. A partial cross-section perpendicular to the longitudinal axis of the musculoskeletal extremity is illustrated.

implemented. Muscle fascia will be represented as a membrane surrounding the muscle mass, with material properties informed by tissue testing data described in section 6.2.2. For indentation simulations, a rigid probe representing the geometry of the ultrasound probe will be modeled. The interaction between the probe and the skin will be represented as frictionless contact, relying on the use of an ultrasound gel in between. All modeling procedures will be scripted using Python[89] to expedite model development phases. All simulations will be conducted using FEBio, an open source finite element analysis software specifically designed for the investigations of biomechanical systems[90].

For each model, indentation simulations will be performed to evaluate the performance of reference models against experimentation. First, the model coordinate system (also the magnetic resonance imaging coordinate system) will be aligned with indentation test setup coordinate system using registration markers attached on the bone (Figure 14). The movement of the ultrasound probe will then be simulated based on motion analysis data collected during the experiment. Finite element analysis will predict the time history of indentation forces and deformation of skin, fat, and muscle layers, which can all be compared to the data acquired with the instrumented ultrasound system. 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. The indentation data will be used as an independent dataset for confirmation of model predictions. 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, i.e., due to registration of mechanical testing data to anatomical imaging, geometric segmentation, etc. For each metric of interest, specifically indentation forces and thickness changes of individual layers, a root-mean-square-error will be calculated between model predictions and experiment measurements. This metric will indicate the absolute predictive capacity of all 8 models during indentation of multi-layer tissue structures. 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. In addition, Bland-Altman plots will be used along with 95% limits of agreement to evaluate the agreement between simulation results and experimental measurements[91]. One should note that these analyses will generate a plethora of in silico data; full stress-strain field within skin, fat, and muscle layers and forces and relative displacements at the tissue-interfaces.

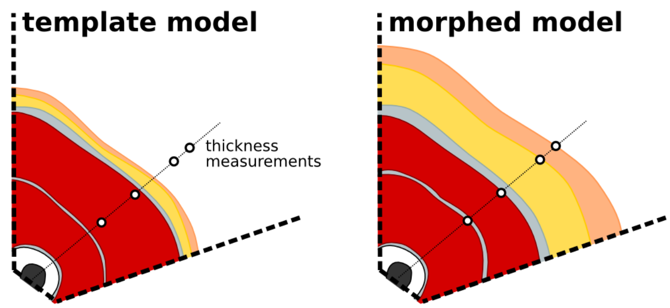

Figure 19. Geometry and mesh morphing approaches will allow customization of template models (built using in vitro data) to reflect subject-specific thickness measurements of skin, fat, and muscle (acquired in vivo). A partial cross-section perpendicular to the longitudinal axis of the musculoskeletal extremity is illustrated.

Computational representations of legs and arms of human subjects will also be developed for nonlinear finite element analysis. From in vivo experimentation data set described in section 6.2.1, two subjects will be selected; 1 male and 1 female that fit to the general characteristics of military personnel[85]. Each upper and lower leg and arm regions of the donors will be modeled, resulting in a total of 8 models. As full imaging data for these subjects will not be available, geometry/mesh morphing strategies[81,92] will be used to customize models of cadaver specimens to tissue thicknesses measured at multiple locations of the extremities of the human subjects (Figure 19). This strategy will provide a semi-subject specific anatomical representation. The material properties of the tissues and the representation of tissue-interfaces will be the same as their counterparts used for cadaver specimens. Scripts will be developed in Python[89] to automate model generation relying on morphing of a template mesh. All simulations will be conducted using FEBio[90].

For each model, indentation simulations will be performed to evaluate the performance of reference models (of human subjects) against experimentation. Indentation location and orientation on the region will be approximated. Indenter displacement will be estimated from total tissue thickness change, as acquired by ultrasound. Finite element analysis will predict the time history of indentation forces and deformation of skin, fat, and muscle layers, which can all be compared to data acquired with the instrumented ultrasound system. These models will have partial subject-specificity; customized anatomy (albeit based on morphing assumptions) and tissue properties of cadaver specimens. Alas, the discrepancies in model predictions and experimental data will be expected to be larger than the case for complete specimen-specific modeling (see above). Root-mean-square errors will be calculated for each metric of interest to quantify the absolute predictive capacity of these 8 models, which are partially representative of the musculoskeletal extremities of live subjects. Linear correlations between model predictions and experimental data will also be explored. In addition, Bland-Altman plots will be used along with 95% limits of agreement to evaluate the agreement between simulation results and experimental measurements[91]. These analyses will illustrate the role of specimen-specificity on predictive power of the reference models for simulations of deformation and loading response of multi-layer tissue structures.

6.3.2. Surrogate Models for Virtual Surgery Simulations of Multi-Layer Tissue Structures. All reference models described in section 6.3.1 will be simplified to evaluate the reduction of computational cost, which will likely enable representation of multi-layer tissue structures of the legs and arms in surgical and training simulations. SOFA, Simulation Open-Framework Architecture, will be used for simulations. SOFA is an open-source software utilizing a multi-model approach. While allowing (and relying on) the simplification of the underlying mechanics, it provides visually detailed representations of tissue/organ anatomy and its deformations[20]. Tissue representations in SOFA include a visualization model (a fine grain representation of tissue surface), a collision model (a coarse grain representation of tissue surface to evaluate interactions with other tissues and tools, e.g., contact), and a deformation model (a coarse grain representation of tissue volume to simulate internal mechanics) (Figure 20). Mapping in between these models allow simplifications at any of these compartments to optimize performance.

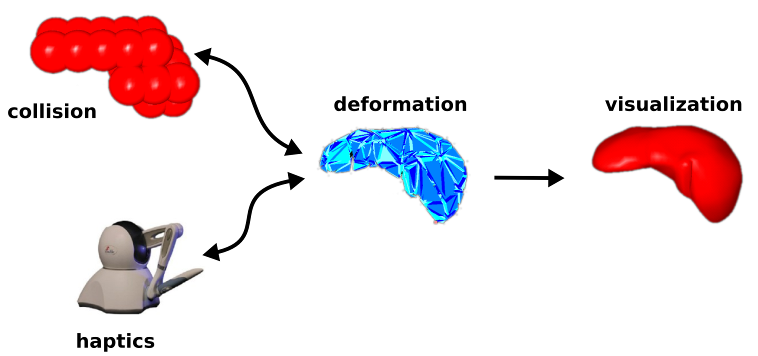

Figure 20. For medical simulations, surrogate modeling of multi-layer tissue structures of legs and arms will be implemented in SOFA[20]. SOFA utilizes multiple representations; a collision component for interactions with tools and/or other structures, a haptics component for integrating force feedback using haptic devices, a visualization component for realistic display of deformations. The deformation component provides physics-based rules to predict internal mechanics and it handles communications with other components to map forces and deformations.

Surrogate models of multi-layer tissue regions of 16 musculoskeletal extremities will be implemented in SOFA. For each individual soft tissue layer; skin, fat, and muscle, and for bone, visualization models will utilize the same surface geometries/meshes used in finite element analysis in order to capture anatomical details. Collision models will utilize coarser versions of these surface geometries/meshes to reduce degrees of freedom. Collision models will implement penetration-based surface contact between indenter and skin. Collision models will be spring based between tissue layers; for skin and fat, stiff springs will approximate a tied interface, for fat and muscle or muscle and muscle, more compliant springs will allow sliding between surfaces. Tissue and tissue-interface properties will be determined from tissue testing procedures described in section 6.2.2. The deformation models will be based on coarse finite element meshes to reduce degrees of freedom; the internal mechanics will be simplified, down to a level of isotropic linearly elastic tissue represented within co-rotational finite element analysis. As done for the reference models, the performance of these surrogate models will be evaluated against indentation data. Incorporating the ultrasound probe as a tool, indentation simulations in SOFA will predict the time history of indentation forces and deformation of skin, fat, and muscle layers, which can all be compared to data acquired with the instrumented ultrasound system. As these models will be largely simplified, the discrepancies in model predictions and experimental data will be expected to be larger than the case for reference models. Nonetheless, root-mean-square errors will be calculated for each metric of interest to quantify the absolute predictive capacity of these 16 models, keeping in mind the training purpose of these models. Linear correlations between model predictions and experimental data will also be explored. In addition, Bland-Altman plots will be used along with 95% limits of agreement to evaluate the agreement between simulation results and experimental measurements[91]. Comparison of computational cost, e.g. CPU time, wall-clock time, etc. between these surrogate models and reference models to simulate the same indentation problem will illustrate the premise of model simplification approaches to realize potentially near real time simulations. A paired *t*-test will be used for this purpose, with significance level set to 0.05.

Surrogate models will also be developed for two additional upper leg specimens. From in vitro experimentation data set (to quantify tool forces during surgical operations, see section 6.2.3), two specimens will be selected; 1 from a male donor and 1 from a female donor that fit to the general characteristics of military personnel[85]. Same modeling approaches (as described above) will be utilized to generate simplified representations of upper leg anatomy and individual representations of its multiple soft tissue layers. These models will also incorporate failure strength and elongation of the skin, muscle, and fat and the interfaces in between (as obtained from tissue level mechanical tests described in sections 6.2.2 and 6.2.3). These properties will dictate detachment thresholds for nodes at the surface of the tissues, internally within the tissue and at the interfaces. Such modeling allows element deletion and topology changes in SOFA, to simulate cutting of surfaces or carving of three-dimensional volumes[21]. Simulation of surgical tool movements (as obtained from motion analysis and in reference to bone position, see section 6.2.3 and Figure 16), will predict tool forces and tissue deformations during surgical acts of cadaver experiments; specifically for incision, retraction, and peeling (Figure 17). The tool forces will be compared against recordings of instrumented surgical tools. Tissue deformations will also be compared with the measurements of three-dimensional deformation field on visible tissue regions. As done for previous models, root-mean-square errors will be calculated for each metric of interest to quantify the absolute predictive capacity of these 2 models. Linear correlations between model predictions and experimental data will also be explored. In addition, Bland-Altman plots will be used along with 95% limits of agreement to evaluate the agreement between simulation results and experimental measurements[91].

SOFA also provides the possibility to incorporate haptic devices to the surgery simulation environment. For demonstration of virtual surgery on the 2 upper leg surrogate models, a haptic device will be interfaced with SOFA, to provide force feedback during virtual surgical acts. Geomagic® Touch™ X (3D Systems Inc. Rock Hill, SC) will be used for this purpose. This device is compatible with OpenHaptics® Toolkit to allow its integration with open source virtual surgery simulation tools.

6.4. Public Dissemination. The project will generate a large heterogeneous set of knowledge, raw data, databases of tissue anatomy and mechanical properties, models, and simulation results (see sections 6.2 and 6.3). All these will collaboratively establish an understanding of the mechanics of multi-layer tissue structures of musculoskeletal extremities and their simulation for research, medical training, and surgical practice. The project will rely on the web-based infrastructure (described in section 6.1) and will adapt an open development approach where public access to ongoing and completed work will be available. The team has been utilizing this approach in the Open Knee(s) project, which has been aiming towards modeling and simulation of musculoskeletal joints[30]. With this added transparency, any interested party will be able to freely access and download data and models through the project site and web-based interfaces (see section 6.1). All information, ongoing or mature, will be provided as they are generated and/or curated, including specifications associated with data collection and model development, source code (for scripts and models), intermediate model components (geometries, meshes), raw and processed data (latter in the form of databases) and any relevant documentation. A necessity of open model development is that any computational tool used for relevant work need to be accessible. Web-based interfaces will be accessible to the community through SimTk.org[77]. All supporting model development, and analysis scripts will be written in Python programming language[89], which is free and open for any entity. Finite element analysis with reference models will be conducted using FEBio, an academic free and open source software for biomechanics simulations[90]. Surrogate models will rely on SOFA, a free and open source framework for medical simulations[20]. More detailed description of the project's dissemination approach can be found in the Data Sharing Plan.

This open science approach also enables active contributions from the community, when and if possible. For those who want to get involved with the project, mechanisms will be 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 will likely enhance potential future collaborations and the outreach of the deliverables of the project.

6.5. Limitations & Alternative Strategies. The proposed project can be hindered by various logistical, experimental, and computational challenges through its progress. A project of this magnitude will certainly require careful execution and planning of a multitude of activities. Therefore, a full-time project coordinator will be assigned for management, delegation, and execution of day-to-day operations. While the team is confident to timely recruit human subjects, delays in acquisition of cadaver specimens are possible. Cadaver experimentation is spread out to the first two years to accommodate any potential postponement of specimen-specific experimentation. The activity will acquire data from large number of extremities, from human subjects and from cadaver donors. For logistical reasons and for feasibility, models will be generated for only subjects/donors representative of military personnel[85]. If necessary, simulations, particularly with reference models, will be conducted using high performance computing facilities, in-house and elsewhere. It should be noted that the data set will establish the diversity of multi-layer tissue anatomy and mechanical properties, which will be publicly disseminated. If desired, additional models of different individuals can be built in future, by the team or by others.

The team does not expect any significant challenges for the implementation of web-based interfaces. Similarly, no major surprises are expected during experimentation. Many of the proposed procedures have been previously developed and used by Dr. Erdemir, his team, and his collaborators albeit on different regions of the body (see section 4). The team may need to optimize these protocols to adequately acquire imaging and mechanics data from tissue layers of legs and arms; to minimize discomfort during human subjects testing; and to limit freeze-thaw cycles for cadaver specimens and tissue samples. Experimentation protocols will include increasing levels of data collection to quantify specimen/subject-specific anatomy and mechanical properties for skin, fat, muscle layers of musculoskeletal extremities and for their interactions. This approach is aimed to answer the specificity needed for appropriate modeling and simulation of multi-layer tissue structures. Similarly modeling approaches will include varying levels of complexity to represent multi-layer tissue behavior virtually. Even then models may not adequately represent reality, e.g., tissue material properties acquired from cadaver specimens may not be suitable for accurate predictions of in vivo behavior. It may be possible to utilize inverse approaches previously developed by the team, to fine tune in vivo material properties[14]. The team also realizes that even at the proposed level of detail, many important aspects of musculoskeletal extremity modeling, particularly when intended for medical training, may be missing from the proposed models. For example, arteries, veins, nerves, tendons will not be represented, muscle contraction will be neglected, simulations of swelling and bleeding will not be explored, and all models will be representative of uninjured states. Also, the surrogate models will incorporate the looks as in deformation of the tissue, not as in their texture. While the focus of this project will be the aggregate and individual mechanical behavior of skin, muscle, and fat layers of legs and arms, the models delivered by this project can be expanded to incorporate various missing components and physiological phenomena depending on the goals of prospective simulations. Magnetic resonance imaging data for example, can be used to reconstructed many other tissue components to prospectively include in the models. Free and open access to data and models will enable the team and other investigators to pursue such extensions and to address limitations in the existing models, which may be overlooked by the development team.

7. Project Milestones

The project milestones and timeline are closely aligned with the technical objectives and the hypotheses they aim to test. Each objective is considered as a critical event to assess the performance of the project and to remain within the proposed schedule and budget. Table 1 provides details on these milestones and outlines the timeline.

8. Military Significance

The primary immediate utility of the proposed study for military is related to the knowledge and data acquired, and models built to understand the mechanics of protective tissue layers of the musculoskeletal

Table 1. Tentative timeline for the proposed activities. Each item signifies a milestone to collectively establish the fundamental understanding for computational modeling and simulation of the mechanics of multi-layer tissue structures of musculoskeletal extremities. Each year corresponds to the budget year of the project, which is divided into quarters. It is anticipated that the start date of the project will be in October, 2014.

EVENTS	YEAR 1				YEAR 2				YEAR 3			
Objective 1. Web-based interfaces for data curation, queryable data and model databases (see 6.1).	PROTOTYPE DEVELOPMENT ■	■	■	■	UPGRADES & MAINTENANCE ■	■	■	■	■	■	■	■
Objective 2. In vivo multi-layer tissue anatomy and indentation mechanics of musculoskeletal extremities (see 6.2.1).	■	■	■	■								
Hypothesis 1. Influence of skin, fat, and muscle thicknesses on indentation stiffness.					■	■						
Hypothesis 2. Influence of skin, fat, and muscle thicknesses on layer deformations.					■	■						
Objective 3. In vitro multi-layer tissue anatomy, tissue and tissue-interface mechanical properties, and indentation mechanics of musculoskeletal extremities (see 6.2.2).	■	■	■	■	■	■						
Hypothesis 3. Influence of skin, fat, and muscle material properties on indentation stiffness.							■	■				
Hypothesis 4. Influence of skin, fat, and muscle material properties on layer deformations.							■	■				
Objective 4. In vitro quantification of tool forces during surgery of multi-layer tissue structures of musculoskeletal extremities (see 6.2.3).					■	■	■	■				
Objective 5. Physiologically realistic, fully specimen-specific, nonlinear ***reference models*** of cadaver multi-layer tissue structures of musculoskeletal extremities for finite element analysis (see 6.3.1).					■	■	■	■				
Hypothesis 5. Capacity of fully specimen-specific reference models to predict indentation stiffness and layer deformations.							■	■				
Objective 6. Physiologically realistic, partially subject-specific, nonlinear ***reference models*** of live subjects' multi-layer tissue structures of musculoskeletal extremities for finite element analysis (see 6.3.1).					■	■	■	■				
Hypothesis 6. Capacity of partially subject-specific reference models to predict indentation stiffness and layer deformations.							■	■				
Objective 7. Computationally efficient ***surrogate models*** of multi-layer tissue structures of musculoskeletal extremities for deformation and haptic representation in virtual surgery software (see 6.3.2).									■	■	■	■
Hypothesis 7. Simplification of reference models to develop cost-effective surrogate models with plausible indentation response and layer deformations.											■	■
Objective 8. Demonstration of efficient ***surrogate models*** of multi-layer tissue structures of musculoskeletal extremities during surgical operations (see 6.3.2).									■	■	■	■
Hypothesis 8. Capacity and cost-effectiveness of surrogate models to provide plausible haptic response and layer deformations during surgical acts.											■	■
Objective 9. Population and dissemination of data and models (see 6.4).	■	■	■	■	■	■	■	■	■	■	■	■
Publications							■	■			■	■

extremities. Musculoskeletal extremities, the legs and arms, have been frequent sites of injury during combat[2]. In particular, in recent operations of the United States, musculoskeletal extremity injuries constituted almost 50% of the combat wounds, primarily caused by explosive mechanisms[4]. Skin, fat, and muscle layers of legs and arms, which provide a protective layer over the skeleton, are directly exposed to damage (Figure 2). Mobility requirements of combat makes using body armor to protect of these regions a potentially difficult task[93]. It is not surprising that these tissue layers suffer from injury and require surgical reconstruction. By acquisition of data on (and building models of) aggregate and individual response of these tissue layers, including subjects and cadaver donors with physiological characteristics representative of military personnel[85], this study will establish dependable knowledge base and tools for medical training and potentially for certification of personnel to serve in the field, or in military hospitals. The data and models of the project directly provide grounding for healthy external and internal mechanics of multi-layer tissue structures for different sections of the limbs. From a field application perspective, this information can establish the reference “feel” and “look” during palpation, which may potentially help the field medic to assess extent of internal injuries. Using surrogate models, army surgeons can practice surgical operations on skin, muscle, and fat layers and the junctions in between.

In the short-term, databases on skin, fat, and muscle anatomy and mechanical properties, characteristics of tissue interfaces, the reference models and their surrogate counterparts can be useful to address other musculoskeletal extremity problems commonly seen in the military[94,95]. For example, pathomechanics of the compartment syndrome[96] can be clearly delineated. This may be accomplished by first adapting models to incorporate swelling; then by conducting simulations to predict altered internal and external mechanical states of the limb. Simulations can further predict potential outcomes of interventions, e.g., fascia release, on returning the mechanical environment to a healthy state.

The reference knowledge on the mechanical environment of multi-layer tissue structures of the legs and arms have long-term implications on scientific and engineering research relevant to military interests. The natural protective capacity of skin, fat, and muscle layers and the strength of these tissues and tissue-interfaces can serve as mechanical specifications for development of tissue grafts intended to reconstruct various regions of the limbs[97]. Such information can also help improve stump reconstruction[98], when amputation is not avoidable. Reference models of multi-layer tissue structures provide the long-term opportunity to evaluate the function of skin, muscle, and fat in extreme conditions, i.e., for a-priori assessment of blast induced mechanical stresses and deformations (and potentially damage). These models can be used for virtual prototyping of protective equipment[99], i.e., to minimize undesirable mechanical loads on the legs and arms while retaining their mobility. By utilizing database of tissue properties, models of stumps can be generated for simulation-based design of sockets for artificial limbs[100]. Similarly, models of bony prominences surrounded by tissue layers, e.g. buttocks, can be developed. Such models will be imperative to design cushions and mattresses to prevent pressure ulcers in service men disabled through spinal cord injuries[101].

9. Public Purpose

Data, databases, reference and surrogate models of this project will drastically improve physiological realism of multi-layer tissue structures, specifically of the skin, fat, and muscle, for virtual surgery of and in silico medical training on musculoskeletal limbs. Legs and arms are sites for bruises, major accidental trauma, and sports related injuries in civil life. The premise to utilize this project's deliverables to build dependable models for medical training (and potentially for practitioner certification) is therefore highly imperative. With data from a general population (allowing development of models with individual variations), the trainees will have a chance to establish the “look” and “feel” of normative behavior for musculoskeletal limb forces and deformations, including those of the underlying tissues. This will provide them the heuristics to identify situations when “look” and “feel” do not make sense. Equipped by customizable models, physicians can set up virtual mock-up surgeries based on individual anatomy of the patient. Such approaches, may allow individualized planning of complex surgeries[102], this time on musculoskeletal extremities.

Currently, the scientific knowledge on how skin, fat, and muscle act in concert to dictate internal and external mechanics of musculoskeletal extremities is lacking. At a basic level, this knowledge can provide the correlations between individual layer properties in health, disease, and aging. Pathological conditions and aging are known to change tissue properties, anatomical and mechanical. However, how the disease progression or the aging process affect different tissues of the same person is not known. When delineated, this information can pinpoint compensatory mechanisms to maintain gross mechanical function of the layered architecture. Furthermore, data, databases, and models of this study are directly relevant to propel research in haptics[103] and to explore mechanical pathways of tactile sensation[104]. With dependable data and databases on surface mechanics and internal deformations, along with tissue properties, virtual experiments can be conducted to generate novel hypotheses. Data and models incorporating tissue junctions have the potential to propel the area of tissue interface research, where fundamental knowledge is scarce. Tissue interface has been noted as a significant challenge in tissue engineering[105]. This activity will provide such knowledge for skin-fat, fat-muscle, and muscle-muscle interfaces. It is likely that the data and models will also inform scientific approaches to resolve pressing clinical problems. For example, pressure ulcer development is a major healthcare issue, occurring at bony prominences of immobilized patients[1]. Their etiology are commonly attributed to contact pressures[1], yet the importance of internal deformations of tissue layers on compression-induced damage is well-established[16]. In the United States, pressure ulcers were diagnosed in approximately 500,000 hospital stays in 2006, costing a total of $11 billion[106]. Prevention of pressure ulcers has become a high priority[107], as Medicare and Medicaid services announced the limitations on reimbursement of hospital acquired pressure ulcers[108]. For effective healthcare, understanding (and predicting) the mechanics of skin, fat, and muscle layers as they interface with a support surface has significant value; and models similar to those of the proposed activity can deliver this. It should be noted that virtual prototyping approaches, e.g., of support surfaces, integrating aggregate and individual mechanics of tissue layers for optimal function, can be extended to the design of consumer products to enhance musculoskeletal protection, performance, and comfort.

Specifically related to computational biomechanics, potential impact of the project on public knowledge is twofold: (i) the opportunity to translate the modeling and simulation tools and strategies to other regions of the body, (ii) the possibility to utilize databases and models as test cases to develop new modeling and simulation methods. Layered organization of tissues is not necessarily limited to musculoskeletal extremities. The face, which is a common site of surgery, constitutes from layers of skin, fat, and muscle[23]. The abdomen hosts organs stacked on each other, underneath layers of skin, fat, and muscle[109]. Data collection and modeling specifications of this study can be adapted, this time to focus on another region of the body in an effective manner. Lifelike data and physiologically realistic (and commonly nonlinear) tissue properties provide challenging scenarios to be tackled by computational modeling. Robustness, adequacy, and performance of simulation techniques can be evaluated comprehensively, when such scenarios and relevant reference data and solutions are available. Fast numerical solution algorithms for highly nonlinear biomechanical systems[38,110], advanced constitutive models for finite element analysis[7], model reduction techniques[38], model customization approaches[111], and virtual surgery implementations[21] can be stressed with these scenarios. By curation of data, tissue property databases, and models, the proposed project enables development of such case studies.

The open development and dissemination approach of the project will likely have the utmost public influence. This philosophy aims to be inclusive, allowing any stakeholder to utilize the knowledge, data, and models for their respective needs. It will not be surprising to see students use the project's outputs for learning, engineers to develop products, scientists to expedite their research, and clinicians for medical training. With free and open access, interested members of the community will not have to go through the laborious tasks already outlined in this proposal.

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