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Multiscale Musculoskeletal Modeling of the Lower Limb to Perform Personalized Simulations of Movement

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Multiscale Musculoskeletal Modeling of the Lower Limb to Perform Personalized Simulations of Movement

A Dissertation
Presented to
the Faculty of the Daniel Felix Ritchie School of Engineering and Computer Science
University of Denver

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

by
Alessandro Navacchia
November 2016
Advisor: Dr. Paul Rullkoetter
Abstract

Computational modeling has been used for many decades to inform design and decision-making in several fields of engineering, such as aerospace, automotive, petroleum, and others. However, it still struggles to have a similar impact in fields of medicine, such as orthopaedics. Three of the challenges that have limited the use of computational modeling in the clinical practice and in product development are model validation, personalization, and realism. Validation is a challenge because several internal parameters of the human body, such as muscle forces, are not safely measurable in vivo and, consequently, a thorough comparison between model outputs and experimental measurements is not always possible. Personalization is an additional issue because the inherent variability across a population needs to be accounted for in a model. Finally, the computational burden of simulations performed with a musculoskeletal model limits its level of realism. The purpose of the work presented in this dissertation is to investigate the applicability of state-of-the-art tools, and propose novel approaches to foster an evolution of computational modeling in orthopaedics. Specifically, (1) the reliability of the knee contact force predictions of a musculoskeletal model commonly used in the literature was analyzed using a global probabilistic analysis for three subjects with instrumented implants; (2) subject-specific and activity-specific moment arms of the muscles spanning the knee
were estimated replacing the generic passive cadaveric motion implemented in the knee joint of a musculoskeletal model with *in vivo* kinematics measured from stereoradiography images; (3) subject-specific joint mechanics for 6 total knee arthroplasty patients performing daily activities was estimated with a sequential multiscale modeling approach that combined joint loads estimated with a whole body musculoskeletal model, personalized joint geometries, and subject-specific fluoroscopy-measured kinematics; finally, (4) a closed-loop muscle control strategy was designed to track experimental joint kinematics and concurrently estimate muscle forces and knee mechanics with a finite element musculoskeletal model of the lower limb including a deformable representation of the joint. The utility of the modeling techniques proposed in this dissertation is presented within a clinical perspective in order to encourage the utilization of musculoskeletal modeling for clinical applications and product development.
I would like to thank a number of people that significantly contributed to my personal growth and accomplishments throughout my Ph.D. First, I would like to thank my wife Irene. During the past three years she has always been next to me with a gentle and constant presence that daily supported my effort. Dr. Peter Laz also needs a special thanks for taking care of me and Irene as soon as we arrived to Colorado. His preference and attention for us has been a precious gift. Dr. Paul Rullkoetter has also been an important presence. I always appreciated his honesty and his ability to identify the most meaningful and applicable research questions. Everybody in our lab helped me to feel at home and to grow on a personal level. The many friendships that were born during these three years strengthened my belief that the main purpose of university is to develop the humanity of a student through relationships, and not just to learn a number of technical notions. Especially, I need to thank my friends and colleagues Sean Hu, Azhar Ali, Lowell Smoger, Justin Hollenbeck, Donald Hume, Vasiliki Kefala, Aruna Tumuluri, Brecca Gaffney, Casey Myers and Clare Fitzpatrick. But my most sincere thanks goes to my Ph.D. advisor, Dr. Kevin Shelburne. When I think that I applied to the University of Denver without any idea of what was expecting me, I am extremely grateful for ending up here under his mentorship. I could not imagine a better advisor for my research. His humanity, his brightness, his patience, his passion are only few of the qualities that keep amazing me. ‘Chasing the Mistery’ with him has been an honor and I hope to have the chance to keep following him in the future.
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Chapter 1

Introduction

1.1 Introduction

“There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy” wrote William Shakespeare in Hamlet (1.5.167-8), to describe his wonder in front of the many mysteries that surround us. The human body is certainly one of these mysteries. In a sense, it is the most puzzling one, since it is always at our disposal but we still have not fully grasped its functioning. Experimentation on the body for medical purposes has been performed since prehistorical times. In the past hundred years, the technology advancement and the energy and money invested into research both at the basic level and for commercial purposes have significantly improved medical treatments, and health restoration. Research performed in human musculoskeletal medicine has largely been experimental. Experiments can be performed either with in vivo investigations on live subjects, or with in vitro studies on cadaveric specimens. The clear limitation of in vitro studies is that they cannot replicate “alive” conditions, such as neuromuscular activity and, consequently, can
only be used to investigate passive properties of the human body. On the other hand, studies that involve living subjects have ethical and human safety restrictions and many investigations of interest that would be invasive and harmful for the body cannot be performed. In addition, both *in vivo* and *in vitro* studies can be prohibitively expensive because of the cost of state-of-the-art instrumentation and cadaveric tissue. A viable alternative to the experimental approach is the utilization of computational mathematical models of the body to replicate the living properties of human tissue. Computational modeling has been used to inform design and decision making in several fields of engineering such as aerospace, automotive, petroleum, civil, energy, and others. Whenever a specific decision can have expensive and irreversible consequences, computational modeling can provide a number of tools to predict its effect, analyze different alternatives, and suggest improvements, without putting it into practice. This capacity has an important impact on human safety and economy of a business. Computational modeling has been used in the past few decades for investigations in fields of medicine, such as orthopaedics. For instance, musculoskeletal models have been used to inform tendon transfer surgeries on patients with cerebral palsy [85, 205], estimate the impact of different surgical variables on total knee replacement (TKR) outcomes [82], design rehabilitation exercises after ligament reconstruction [221]. However, computational modeling still struggles to play a significant role in both daily and long term decisions in medicine. If the advantages of modeling have been widespread for decades, what factors have prevented its spread and impact? The human body, the object of medicine, has peculiar characteristics that make it unique when compared to the objects of other scientific disciplines. Even though the body is always “observable” (the researcher himself “is a human body), it is not fully accessible. In fact, only some variables
can be measured and monitored in a live subject, because of safety and ethical reasons. Therefore, one of the most substantial obstacles to the use of computational modeling in medicine is the lack of internal measurements needed for validation purposes. A model obviously has to correctly represent the variables of interest of the human body (validation) in order for it to be useful and meaningful. Although validation still represents a significant challenge, a substantial effort has been put into trying to address it and improve the potential of computational modeling to inform treatment and understanding of pathology. Since several internal variables cannot be accessed \textit{in vivo}, validation is often performed by replicating cadaveric experiments with computational simulations, and comparing model and experiment results [17, 107]. However, some relevant quantities, such as ligament strain and contact pressures, cannot be measured in cadaveric experiments and, consequently, no direct comparison with model outcomes is possible. In addition, \textit{in vitro} studies cannot fully replicate the conditions of a living subject because muscle forces generated by neural activation cannot be produced. Therefore, comparison between \textit{in vivo} experiments and computational models remains necessary. Muscle activity is the main determinant of the forces applied to organs and joints during most daily living activities. Since muscle forces cannot be directly measured in a living subject, alternative strategies have been utilized to compare model predictions to internal forces. Specifically, the use of instrumented joint replacements, which can measure contact forces exchanged by the implant components, opened the doors to a quantitative validation of muscle forces that was not available before [20, 135, 157, 232, 236]. In particular, the Knee Grand Challenge competition has publicly shared a comprehensive dataset that fostered blind predictions of joint contact forces based on muscle forces estimated with musculoskeletal models of subjects implanted with instrumented TKR
Dynamic imaging techniques represent a second example of technological advancements that allows the accurate measurement of internal variables. Specifically, fluoroscopy and stereo-radiography systems can measure relative bone motion with sub-mm and sub-degree accuracy [127, 154].

A second challenge presented by the human body is its inherent variability. Every person has unique features that make them different from every other person. However, most of the available computational models of the body represent generic or average properties and geometries, because of the limited number of measurements that can be taken on a specific subject. A certain level of personalization is needed to inform a decision on a medical treatment to be performed on a specific patient. Subject-specific representations based on medical image reconstructions have shown potential [213, 214], even though soft tissue geometrical and mechanical properties cannot be accessed with sufficient accuracy. Alternative approaches to personalization have been proposed in the literature to model a population instead of a single subject, given the variability in input parameters [177]. Statistical techniques, including sensitivity analyses and Monte Carlo analyses, can be employed to estimate the reliability of model outputs.

A third issue is the high complexity and multiple scales of biological tissues. Biological phenomena can be represented at different scales by including different details and features, from the atomic/molecular level, to the tissue, organ, and whole body levels. Even though representation of the tissues at different scales can be developed, modeling the inevitable interaction between them remains a challenge. These three specific problems undermine the trust in the effectiveness of computational models. To model the inherent complexity of the human body and the interaction between different biological domains, multi-scale approaches have been utilized. Specifically,
a sequential approach that uses muscle or contact forces predicted at the whole body level as boundary conditions for a more detailed model at the organ/joint level has been proposed [225, 121, 135, 93, 21]. The attempt to model multiple scales in the same modeling framework has also been made, but the studies presented in the literature are still at early stages [72, 106, 108, 140].

1.2 Objectives

The objective of this dissertation was to contribute to the improvement of computational modeling in orthopaedics by addressing the three challenges previously presented: validation, personalization and complexity. The first specific objective was to assess the reliability of the outputs provided by commonly used musculoskeletal simulations in order to capture the potential of currently available tools. The second specific objective was to improve modeling personalization by including subject-specific three-dimensional knee joint kinematics and geometry in computer simulations of movement. The third and last objective of this dissertation was to investigate the interaction between the whole body and knee joint domains, and promote the evolution of current multi-scale approaches by proposing a computationally efficient technique to estimate muscle forces in a finite element musculoskeletal simulation.

1.3 Dissertation Overview

Chapter 2 provides an overview of the published literature on the current status of computational modeling for biomechanical applications. The chapter primarily focuses on the distinction between state-of-the-art modeling at the whole body level
and at the organ level. The last paragraph of the chapter targets the specific limitations of musculoskeletal modeling.

Chapter 3 presents *Prediction of in vivo knee joint loads using a global probabilistic analysis* whose objective was to evaluate the uncertainty in knee contact load estimates obtained with a commonly used pipeline of biomechanical analyses performed with a generic whole body musculoskeletal model. This study has been published in the *Journal of Biomechanical Engineering* [181].

Chapter 4 presents *Dependence of muscle moment arms on in vivo three-dimensional kinematics of the knee* whose objective was to quantify the impact of *in vivo* subject-specific and activity-specific three-dimensional knee kinematics on muscle moment arms estimated with a whole musculoskeletal model. This study has been published in the *Annals of Biomedical Engineering* [180].

Chapter 5 presents *Subject-specific modeling of muscle force and knee contact in total knee arthroplasty* whose objective was to estimate subject-specific contact mechanics for six total knee arthroplasty (TKA) patients using a sequential multi-scale approach. Tibiofemoral (TF) contact forces estimated with a whole body musculoskeletal model were used as boundary conditions for a finite element model of the implant. This study has been published in the *Journal of Orthopaedic Research* [182].

Chapter 6 presents *Closed loop muscle control of a finite element musculoskeletal model* whose objective was to develop a computationally efficient technique to estimate muscle forces for gait and chair rise in a finite element framework with a whole body model that included a detailed and calibrated representation of the knee.

Chapter 7 discusses the specific contributions of this dissertation in addition to suggestions for continuing work with multi-scale computational modeling in the field.
Chapter 2

Background information and literature review

2.1 Computational modeling in biomechanics

Biomechanics is the field that studies the mechanics of the human body in terms of its motion as the consequence of forces and moments applied to it. The ideal biomechanical investigation performs experiments on human subjects to understand how the application of loads changes the conditions and the behavior of the body. These kinds of studies are referred to as \textit{in vivo} studies. Forces applied to the body segments can be generally divided into two categories: external forces, which represent the interaction between the body and the environment (e.g. ground reaction forces, reaction force between the foot and the pedal of a bicycle), and internal forces, which include the loads generated by tissues or caused by the interaction between tissues (e.g. ligament and muscle forces, contact forces between bones). Many investigations have been performed that quantify the kinematics and the dynamics of the
body segments, revealing the interaction between external forces, muscle activations, and joint motion [257]. These studies helped answer meaningful questions related to human health. For example, gait analysis studies facilitate the identification of abnormal motor characteristics such as cerebral palsy [55] and can be used to document after-surgery gait-related changes [188, 89, 169]. Muscle activation studies have been used to provide insight into neuromuscular adaptations after TKR [48], and to address rehabilitation questions on specific muscles [96].

*In vivo* investigations typically include kinematics data collected with marker-based motion capture systems or other kinds of imaging systems (e.g. fluoroscopy, dynamic MRI); strain-gauge or piezoelectric transducers are used to measure loads exchanged between the body and the environment (e.g. force plate mounted in the floor); and surface or in-dwelling electromyography (EMG) electrodes are used to collect electric signals that measure timing of muscle activity. In addition, personalized geometries of both bones and soft tissues can be obtained with imaging from CT and MRI. Moreover, mathematical relationships between bone density and mechanical properties can be used to estimate bone material characteristics directly from CT scans [116]. However, *in vivo* studies present some disadvantages that limit their scope. Specifically, the main limitation that reduce the potential of *in vivo* investigations is that, although external body segment kinematics and kinetics can be measured reliably, many internal variables cannot be quantified in a living subject. For example, internal loads like ligament and muscle forces are inaccessible *in vivo* and the subject-specific interaction between them and body segment kinematics remains unknown. Without a clear understanding of muscle function in healthy and pathological conditions, the outcome of a surgical treatment, such as tendon transfer, cannot be assessed before performing it. In addition, measures of internal
forces generated by ligaments and muscles would improve our knowledge of the loads supported by a medical device implanted in the body, such as an internal fixation plate. The same limitation is true for material properties: the personalized geometry of cartilages can be segmented from MRI scans, but the mechanical behavior of these structures cannot be accessed in vivo. In addition, although ligament geometry can be also reconstructed from scans, the location of the attachment on the bony surfaces is challenging. Therefore, the main limiting factor to a successful evaluation of pathology and treatment is that several internal properties cannot be accessed in vivo.

Studies using cadaveric specimens (in vitro studies) are a valuable alternative to in vivo investigations [43, 45, 164]. The main advantage of in vitro experiments is that any instrumentation to collect data that would be invasive on a living subject can be used with no restriction. Therefore, internal quantities that are not accessible in vivo can be measured during a cadaveric experiment. For instance, ligament strain [164], tendon elasticity [1], and muscle fiber properties such as sarcomere length [253] can be measured on a cadaveric specimen. A further advantage of in vitro studies is that surgical treatments can be experimented without any risk of damage to a patient. For example, the implantation of a TKR on a cadaveric limb can help to investigate the interaction between the device and the remaining structures such as the ligaments. The stability and laxity of an intact cadaveric knee was compared in a knee simulator to the behavior of the same specimen after the implantation of a replacement [158]. This possibility has important implications regarding the design process of an orthopaedic device. In addition, certain pathologies or injuries such as the rupture of a ligament can be easily simulated in a cadaveric experiment, providing valuable information on the resulting changes in joint stability [45]. However, the
obvious drawback of in vitro studies is that in vivo conditions can be replicated only partially. Specifically, although material properties and forces exerted by passive tissues (e.g. ligaments) can be estimated with mechanical testing and strain-gauge transducers, the contribution of active structures (i.e. muscles) is not available. Although testing machines that can simulate daily living activities, such as walking and squatting, have been constructed [162], no in vitro experiment will provide information about the muscle coordination needed to perform a certain motor task. A second limitation of cadaveric studies is that multiple tests replicating different conditions on the same specimen are not always feasible. For instance, simulation of a joint replacement surgery including examination of variations in implant placement is not possible on a cadaveric specimen. Therefore, even though cadaveric and in vivo studies have an undeniable value for the investigation of musculoskeletal healthy and pathological conditions, they cannot address every question because of the listed limitations.

A third tool that complements in vivo and in vitro methods through the potential to overcome some of their limitations is computational modeling. Computational modeling has been used for decades in several fields of engineering to inform design and decision-making: many examples that demonstrate its potential are available in aerospace, automotive, energy, structural engineering [35, 132, 159, 207]. Computer simulations can replicate a specific experiment or physical condition, and, once the simulation is validated, can be used as a predictive tool. Experiments can be extremely expensive and time-consuming in fields like aerospace. Therefore, computational modeling provides a framework to test several design solutions simulating different boundary conditions in a very cost effective fashion. Computational modeling has been used also in biomechanical applications for many decades. The
objective of musculoskeletal models has been to better understand the interaction between muscle forces, body segment motion and organ internal deformation. The quantification of the relationships between these variables provides useful information that can support clinical decisions. For example, musculoskeletal models of the lower limb have been used to simulate the effect of surgical treatments, such as tendon transfer in patients affected by cerebral palsy [85, 205]; deformable models of the femur have been employed to estimate the fracture risk at the femoral neck after femoral head resurfacing [166]; the relative contribution of design, alignment, and loading variability to knee replacement mechanics has been evaluated with a finite element model to inform implant design [82]; the combination of a whole body musculoskeletal model and a detailed knee joint model has been used to explain the loads in cruciate ligaments during rehabilitation exercises after ligament reconstruction [221].

However, computational modeling is not yet widely applied and trusted in the clinical setting when compared to other disciplines, like aerospace and petroleum engineering. The reasons for this delay can be summarized as follows: first, validation is still a significant challenge. The replication of in vivo conditions is the ideal goal of a computer simulation in biomechanics. However, the lack of available experimental data represents an obstacle for model validation [160]. In addition, current musculoskeletal models are not sufficiently sophisticated to allow a thorough validation, especially when it comes to muscle and contact load predictions. For example, whole body models currently used to estimate muscle forces needed to perform a specific motor task present simplified joint models whose motion is limited to general passive cadaveric behavior [15, 52, 56]. The utilization of computational modeling in biomechanical applications would certainly benefit from an increase in representa-
tion complexity. A further limitation is the inherent difference between subjects in terms of size, weight, body composition, and movement patterns, which introduces the need for model personalization [183]. Outputs of generic musculoskeletal models can be misleading if they do not account for population variability. Finally, the clinical setting requires the interface between the engineers who develop the models and the clinicians that make decisions on medical treatments. This interface represents an additional obstacle to develop the necessary trust in the tool. These challenges are closely interconnected: unless a thorough validation of sufficiently sophisticated and personalized models is performed, computational modeling will not be trusted by all the actors involved, and, consequently, will not be used as an effective tool in a clinical setting.

This chapter will describe the state-of-the-art of computational modeling in biomechanics, focusing especially on the efforts taken by the scientific community to represent the human body at the whole body and joint/organ scales.

2.2 Whole body musculoskeletal modeling

The human skeletal system can be represented with mathematical models in which separate segments of the body are connected through joints and can move relative to each other [191]. These models can provide insight into kinematics and kinetics of the body, and how energy is transferred between segments. Both two-dimensional and three-dimensional models have been used to analyze the motion of the lower limb during gait [95, 171, 192]. However, mathematical models that do not include muscles cannot explain how the coordination of muscle recruitment accelerates the skeletal system and, at the same time, can produce stability. A more
or less complex representation of the muscle needs to be included in the model in order to answer questions related to the interaction between the muscular system and the skeleton. Even a simple task like gait is produced by the action of several muscles spanning the joints of the lower limb and the specific function of each actuator is not obvious because of the complexity of the many structures involved. For example, biarticular muscles (muscle spanning two joints) can contribute to the acceleration of a segment in counterintuitive ways [264]. In general, the dynamic behavior of the musculoskeletal system can be modeled in the form

\[
M(q)\ddot{q} + C(q)\dot{q}^2 + G(q) + R(q)F^{MT} + E(q, \dot{q}) = 0
\]  

(2.1)

where \( q, \dot{q}, \ddot{q} \) are vectors of the generalized coordinates, velocities, and accelerations, respectively; \( M(q) \) is the system mass matrix; \( C(q)\dot{q}^2 \) is a vector of centrifugal and Coriolis forces and torques; \( F^{MT} \) is a vector of muscle forces; and \( E(q, \dot{q}) \) is a vector of external forces and torques exchanged between the body and the environment [191].

### 2.2.1 Muscle path modeling

When muscles and tendons are included in the model, they are usually combined in a single unidimensional element that connects the origin and insertion of the muscle. When tendon attachments are large areas on the bone (e.g. gluteus maximus) the muscle is separated into multiple units, each representing a portion of the muscle. Since several musculotendon units wrap around bones and other muscles, their line of action is not a simple straight line that connects the two attachments. Therefore, more sophisticated strategies have been used to model muscle path, such as via points.
located at the centroid of muscle cross sections fixed to a specific segment [128]. One of the main challenges of modeling muscle path is that, although the centroid line of the muscle may be known for a single body pose (measured on a cadaver or captured in vivo using imaging techniques), it cannot be practically measured when relative motion between segments takes place. Therefore, more sophisticated wrapping surfaces have also been used to represent the behavior of muscle path during motion of the joints [91] (Fig. 2.1). The unidimensional musculotendon units can wrap on specific analytic surfaces or directly on bone geometry meshes in order to obtain a curved path. A correct representation of the musculotendon path is crucial to accurately model the function of a muscle for several reasons: first, the tendon line of action (the direction along which the muscle inserts on the bone) determines both the muscle moment arm and the direction of the force applied to the bone. Second, since the force that a muscle can exert is a function of the length of its fibers, a correct path representation will also provide a more accurate muscle force estimate.

2.2.2 Muscle moment arm

Muscle moment arm is defined as the instantaneous measure of the “effectiveness” with which the contraction force of a given muscle can generate a moment at a “joint of interest”, while in a given configuration [227]:

\[ r_q \triangleq \frac{\tau_q}{s} \] (2.2)

where \( \tau_q \) represents the “effective torque” acting on a joint with angular displacement \( q \), due to the scalar tension \( s \) generated in the muscle. Therefore, moment arms map muscle forces into joint torques and, consequently, into joint motion. An
incorrect assessment of the moment arm of a muscle would generate misconceptions on its specific function about the joint in consideration. Since the path of a muscle depends on the joint configuration, its moment arm is also a function of segment position. Moment arms \textit{in vitro} measurements are currently the gold-standard and are often used to validate model estimates [15, 29]. The most common strategy used to measure moment arms in a cadaver is the tendon excursion method [8], which calculates the moment arm as the ratio between the observed change in the length of the muscle and the corresponding change in joint angle. This technique is derived from the assumption that all the constraints affecting kinematics are workless and the work equivalence can be stated as follows:

\[ sdl = \tau_q dq \]  \hspace{1cm} (2.3)

where \( dl \) and \( dq \) are the change in muscle length and in joint angle, respectively. Combining this equivalence with the moment arm definition, the tendon excursion method is derived:

\[ r_q = \frac{dl}{dq} \]  \hspace{1cm} (2.4)

that is a measure of the instantaneous change in length over the change in joint angle.

\subsection{2.2.3 Contraction dynamics}

Another challenge that musculoskeletal modelers need to account for is that musculotendon units are not simply linear actuators. The force exerted by a muscle is the combination of the forces generated in the fibers that compose it, which are, in turn, composed by a series of sarcomeres. The sarcomere is the basic actuation unit
that generates force in a muscle thanks to the interaction between actin and myosin [99]. Muscle fibers attach to the tendons and they can be either oriented in the direction of the tendon (i.e. parallel-fibered muscle) or at an acute angle to the tendon (i.e. pennated muscle). This complex structure is often simplified when muscles are included in whole body musculoskeletal models. The most common model used to represent musculotendon units is called Hill-type model (Fig. 2.2) [237, 263]. In this phenomenological model the force producing properties of a muscle are described as functions of four parameters:

(a) Optimal fiber length $L_o$, which represents the fiber length at which the muscle is able to generate its peak isometric force;

(b) Maximum isometric force $F_{oM}$, which represents the peak isometric force that the muscle can generate at its optimal fiber length when fully activated. It is assumed to be proportional to the number of fibers in the muscle and, consequently to physiological cross sectional area ($PCSA$) of the muscle;

(c) Tendon slack length $L_{ST}$, which is the resting length of the tendon;

(d) Pennation angle $\alpha$, which is the angle between tendon and fiber lines of action.

These four parameters are unique for each muscle and they are used to scale a generic force-length-velocity relation common to every muscle, shown in Fig. 2.2. This relationship combines:

(a) an active force-length relation, which represents the normalized isometric force $(F_M / F_{oM})$ that can be generated by the muscle as a function of the normalized fiber length $(L_f / L_o)$;
(b) a passive force-length relation, which describes the non-linear elastic behavior of the tissue surrounding muscle fibers. It is non-zero for lengths larger than the optimal fiber length $L_f^o$;

(c) a force-velocity relation, which describes the change in muscle force due to the lengthening/shortening velocity (muscles are able to generate a larger force while they lengthen).

These relationships were obtained in vitro and can be generally applied for every human muscle, even though some exceptions were found [36, 118]. Given a musculo-tendon length, velocity, and activation, the force exerted by the muscle is univocally derived.

### 2.2.4 Activation dynamics

Muscle activation is a variable that can range between zero and one ($0 \leq a_m \leq 1$) and represents the percentage of muscle fibers that are currently contracting (generating force). Muscle activation of the contractile apparatus is the consequence of a neural excitation signal. The relationship between muscle activation and excitation $u$ ($0 \leq u \leq 1$) is referred to as excitation-contraction dynamics and it consists in a delay between the arrival/end of the excitation signal and the actual moment when the muscle starts/stops generating force:

$$\dot{a}_m = \frac{u^2 - u a_m}{\tau_{rise}} + \frac{u - a_m}{\tau_{fall}}$$

(2.5)

where $\tau_{rise}$ and $\tau_{fall}$ are time constants that range between 12−20 ms and 24−200 ms, respectively [263].
2.2.5 Muscle force estimation

As mentioned before, muscle forces cannot be directly measured on a patient. If this information was available, our knowledge and impact in the orthopaedic, sport and rehabilitation fields would be substantially transformed. The measure of muscle forces \textit{in vivo} is limited to few studies that use minimally invasive techniques on superficial tendons such as the Achilles [77] or during a surgical procedure [58]. Therefore, non-invasive approaches such as computational modeling are necessary to estimate muscle forces in the clinical setting.

Musculoskeletal modeling force prediction has significantly improved in the last few decades especially thanks to the remarkable technological advancements. However, there is no technique generally accepted in the research community yet. The specific challenge that modelers have to face is the inherent redundancy of the human musculoskeletal system: the number of muscles present in the body is higher than the number of degrees-of-freedom. Therefore, the set of dynamic equations of motion (Eq. (2.1)) presents a number of unknowns (muscle forces) that is higher than the number of equations. This makes the system undetermined and infinite combinations of muscle forces can solve the system. In order to select a single solution, optimization strategies have been proposed in the past [70]. Specifically, two main approaches have been developed to tackle this problem: a forward-dynamics and an inverse-dynamics based solutions, depending on the research question and on the available data.

A forward-dynamics simulation consists of the forward-integration of the dynamic equations to calculate motion, given the internal and external forces applied to the
Dynamic optimization and optimal control solutions have been used to estimate muscle forces needed to perform a specific task by minimizing an appropriately chosen objective function [2, 11, 194, 198]. In both cases the objective function needs to mathematically describe the goal of the task (e.g., maximum height jump) and possibly convey a minimization of some sort of energy consumption [2, 11]. Quite striking similarities between predicted and measured kinematics were observed for simulations of gait, chair rising and maximum jump. In addition, predicted muscle forces were qualitatively validated by comparing them to EMG signals collected in vivo. However, a number of limitations of this technique still represent a challenge. First, the computational time needed to perform multiple iterations and find the minimum of the objective function can be prohibitive. However, some efficient techniques to perform optimal control simulations have been recently investigated and results look promising [246]. A second limitation is that the goal of the simulated activity needs to be expressed mathematically. If a clear objective can be formulated for activities like maximum height jump where a performance index is trivially identified, this might not be the case for more complex tasks like stair descent.

When the inverse-dynamics approach is chosen, joint kinematics and external forces must be known. This approach is quite common, thanks to the availability of motion capture and ground reaction force data in many laboratories. An inverse-dynamics analysis is first performed to calculate net torques at the joints consistent with measured motion and external forces [68]. Once joint torques are known, static
optimization can be used to isolate a single muscle force solution at each instant of
time that minimizes some objective function. Many criteria for load sharing between
the muscles have been proposed and compared in the literature [44, 63, 242] that
measure levels of overall energy expenditure (e.g. muscle stress). Static optimization
is a valuable technique because of its computational efficiency [12]. Another feature
that makes inverse-dynamics simulations of the lower limb attractive is that they
do not need a contact definition between the foot and the ground, since kinemat-
ics and ground reaction forces are simply applied to the model, and not estimated
[191]. Muscle force predictions obtained with static optimization are widely ac-
cepted for simulations of the lower limb during gait, despite its incapacity to predict
co-contraction of antagonist muscles is debated [117]. A limitation of static opti-
mization is that it cannot accommodate time-dependent performance criteria as total
muscular effort through time, because the optimization is solved at each time frame
independently. In addition, static optimization simulations need experimental data
and, consequently, cannot be predictive. In other words, static optimization cannot
provide an answer to what if questions, contrary to forward-dynamic simulations.

Hybrid approaches that combine forward-dynamics with available experimental
data have also been investigated. It is worth mentioning some of these alternatives
presented in the literature:

(a) Computed muscle control is a forward-dynamics technique that tracks joint
kinematics with feed-forward and feedback controls, instead of enforcing kine-
matics to the model, and solves a static optimization problem at each time
frame [238].

20
(b) A technique that combines forward-dynamics optimal control and experimental kinematics and ground force tracking was used to predict muscle forces for a maximum-height jump activity [217]. This approach was able to track experimental data and, at the same time, minimize a time-dependent cost function.

(c) Several studies have also included measured EMG signals into the muscle force calculation rather than using them for qualitative validation only. EMG signals can either be directly incorporated to drive a forward-dynamic simulation [196, 197] or combined with inverse-dynamics [22]. In general, these approaches are promising because they can reduce the redundancy of the muscular system, but their efficacy highly depends on EMG signal quality and processing.

2.3 Organ/joint level modeling

During motion the organs in our body deform under the action of internal and external loads. An accurate measure or prediction of the deformation that occurs in an organ is of great interest in biomechanics, since excessive tissue deformation can result into damage and injury. Bone fracture and ligament rupture are two examples of traumatic injuries due to high loads causing excessive tissue deformation. Whole body musculoskeletal models provide an insight into motion analysis, segment kinetics and muscle coordination, but the level of detail is not sufficient to estimate what happens at the organ/joint level. Therefore, more detailed representations of single organs and joints have been modeled to capture the tissue deformation.
2.3.1 Finite element method

The finite element method is a widespread tool in the field of solid mechanics and structural engineering [268]. This method is used to calculate approximate solutions for boundary value problems, governed by partial differential equations, by transforming them in a set of algebraic equations. The continuum is sub-divided into a mesh of discrete elements of various shapes and sizes connected to each other, and an approximate solution is found at a finite number of points (mesh nodes). In the case of continuum mechanics, the finite element method calculates local stresses and strains that result from the application of boundary conditions. This approach is well suited for biomechanical applications, since the variability and irregularity of biological shapes can be tackled by meshing them with discrete finite elements (Fig. 2.3) [69]. In addition, the finite element approach facilitates the modeling of the highly non-linear mechanics present in biological structures. The usefulness of finite element analyses in orthopaedic biomechanics and ventricular systems has been demonstrated few decades ago [123, 261].

The main downside of finite element analyses is that they are computationally expensive. Complex simulations with hundreds of thousands of elements and non-linear properties such as non-linear material properties and contact definitions can take several hours to complete. In addition, the model generation is also time-consuming, because manual steps such as tissue reconstruction from images and geometry meshing are necessary. Although these limitations prevent finite element models to become more common in the clinical settings, the continuous technological advancement fosters the hope that computational cost and model creation time become less and less limiting.


2.3.2 Whole bone models

Bones are hard solids and their structure is generally divided into cortical and cancellous regions. Specifically, the cortical bone is the layer that can be seen from the outside, whereas the inside of the bone is filled with a scaffold-like bony structure that is called trabecular bone or cancellous bone. The geometry of a bone can be accurately determined on dissected specimens [269] or using imaging data like CT or MRI. Cortical and cancellous regions can be distinguished in properly calibrated CT data thanks to the different tissue density. However, the exact structure of the trabeculae (beam-like tissue elements in the cancellous bone) can be determined only with micro-CT images.

The different tissue distribution between cortical and cancellous bone needs to be adequately represented in a computational model. Although finite element models of the cancellous bone local morphology can be created from micro-CT images [125], this is not feasible for the entire cancellous region of a whole bone, since micro-CT is an expensive and time-consuming local acquisition. Therefore, whole bone finite element models represent the entire bone as a continuum (no gaps are modeled in the cancellous region), but different material properties are assigned to the cortical and cancellous parts to describe their different structure [27]. In particular, the bone geometry can be divided into three dimensional elements and specific material properties can be assigned to each element (material mapping) according to relationships between CT numbers, tissue apparent density and mechanical properties [234]. An application of finite element whole bone models with subject-specific material mapping is the estimation of bone failure risk [28, 215]. Alternatively, material mapping has been used to predict the implant-bone interface mechanics after total hip replacement [138].
One of the main challenges of bone finite element modeling is deriving appropriate boundary conditions. The majority of the loads applied to a bone are internal forces generated by muscles and ligaments. As already mentioned in Section 1.1, subject-specific muscle and ligament forces cannot be measured \textit{in vivo}. Therefore, many modelers have applied boundary conditions reported in the literature to subject-specific bone models, even though they were derived from different anatomies [230].

2.3.3 Ligament models

Ligaments are short bands of fibrous connective tissue that connect bones across a joint. The main purpose of ligaments is twofold: they guide joint motion in normal conditions, and they restrain joint mobility in case of abnormal motion. The stress-strain relationship of ligaments along the collagen fiber direction (predominant loading axis \textit{in vivo}) is nonlinear. The curve starts with an upwardly concave portion that transitions into a linear region [254]. Computational models of ligaments have been constructed with different complexity according to the research questions that were addressed. Most computational studies have represented ligaments as linear or non-linear unidimensional springs to reduce model complexity, and single ligaments are usually separated into multiple bundles to model the progressive recruitment of different fibers during loading [220]. However, the unidimensional approximation does not allow the prediction of soft tissue stress. In addition, the area of insertion of the ligament on the bone surface is not modeled, and contact that occurs between the ligament and other structures like bones is not represented adequately. Therefore, unidimensional ligament models are mostly used to describe the overall stiffness of the joint and predict joint kinematics. Alternative modeling strategies were preferred when the stress distribution in the ligament and the interaction be-
tween ligaments and other structures was relevant to the study. Specifically, both two-dimensional and three-dimensional ligament models have been constructed with the finite element method. Two-dimensional models present many advantages offered by three-dimensional models, but they are computationally more efficient. Knee ligament models that can wrap around bones have been used to study the contact interaction and to predict soft tissue stress [168]. Continuum three-dimensional finite element models have also been used to capture the complex non-uniform strain fields that occur in the ligament. A validation study was performed on the MCL at different knee flexion angles with a three-dimensional finite element model of the ligament [90].

2.3.4 Cartilage models

Cartilage is the biological material that covers bone surfaces at the joints. It provides very low friction and it can withstand millions of high load cycles in normal conditions. The unique mechanical properties of cartilage are the result of its peculiar composition and organization, which consists primarily of water [110]. The investigation of the mechanical behavior of cartilage in normal and abnormal conditions is of great interest because of the large number of people that are progressively impaired by osteoarthritis (cartilage deterioration). The most common treatment for advanced osteoarthritis is the total or partial replacement of bone surfaces at the joint with devices made of metal alloys and plastic. This treatment is highly invasive for the patient and expensive. Therefore, the investigation of cartilage mechanics under physiological loading condition can provide a significant insight into the causes of its failure. However, the specific process that determines cartilage deterioration is not fully understood yet. Computational modeling of cartilage at the organ level
has been performed with the finite element method, and can provide localized tissue deformation and contact stress distribution, for a better understanding of the cartilage stress-strain and fluid pressure state for a set of specific joint loads [110]. For example, load sharing between medial and lateral compartments of the knee [5], the influence of TF alignment on cartilage distributions [260], and the role that the meniscus plays in contact load distribution [267] have been investigated. Therefore, organ level computational models can offer knowledge of local stress distributions in healthy and diseased cartilage, which can provide a better understanding of potential causes of damage.

2.3.5 Muscle models

Musculotendon units are usually modeled as unidimensional Hill-type elements (lumped-parameter models) in whole body applications, as described in Section 2.2.3. However, the geometrical arrangement of skeletal muscles is complex. As joints move, muscles change shape and interact with each other and with underlying bones. In addition, the unidimensional simplification assumes that all the fibers of the same muscle have identical properties (optimal fiber length and number of sarcomeres) and length. However, in reality separate fibers present different length changes, and different contraction properties can be observed in a single muscle [31]. Fiber’s moment arm and potential to generate active force (dependent on fiber length) can differ significantly inside a single muscle. In addition, the activation of different motor units across the same muscle is not uniformly distributed. Three-dimensional models of skeletal muscles are needed to capture their complex spatial behavior. Muscle geometry can be derived in vivo from MRI [23, 111], but usually only at a single joint configuration. Three-dimensional finite element models of skeletal muscle
that included constitutive properties of muscle and tendon, and the interactions with neighboring structures during joint motion have been proposed in the literature for muscles spanning the hip and knee [24, 25]. Other computational models have also investigated the interaction between local muscle strain and the aponeurosis at the myotendinous junction [78, 79]. Additional complexity of skeletal muscles derives from the concurrent presence of passive and active stresses, due to the intrinsic material properties of the tissue surrounding muscle fibers and the capacity of the fibers to actively produce force. Theoretical formulations that represent the muscle as a self-contracting elastic solid have also been proposed [187]. These models have the potential to address the limitation of unidimensional lumped-parameter models, even though they are computationally expensive.

2.3.6 Joint models

Organ level models can also be combined into a single computational model that aims to predict the interaction between them. In particular, detailed joint computational models have been implemented to understand how forces are exchanged between bones and other structures to generate motion. One of the joints most modeled in the literature is the knee. The knee is mildly constrained by the shape of the articulating bones, contrary to other articulations like the hip. Therefore, although most of the motion occurs in the flexion/extension degree-of-freedom, its motion in the other degrees-of-freedom is highly dependent on the constraint offered by soft tissues (ligaments, cartilages, menisci, and muscles). Finite element or multibody models of the TF and patellofemoral joints have been proposed to investigate contact mechanics, internal stresses, and kinematics [75, 104, 195, 201]. Finite element models of the TF and patellofemoral (PF) soft tissues were calibrated to in vitro experiments to
reproduce measured kinematics and create specimen-specific comprehensive models [7, 115]. Several finite element studies to predict contact mechanics and kinematics of TKRs under several conditions can also be found in the literature [17, 80, 109]. Similar investigations have been performed for other human joints like the hip and ankle [114, 204]. Although the complexity of these computational models can be high, if accurately validated or calibrated they have the potential to uncover the relationships between internal forces and joint motion in several conditions, which would be prohibitive in an experimental setting.

2.4 State-of-the-art: a sequential approach

As described previously, computational modeling is employed to answer questions at different scales of the human body. However, research questions are progressively unveiling the hierarchical interdependence between the different domains. Even though it is common to assume that the effect of forces at higher spatial scales influences behavior at lower scales, and lower scale properties influence higher scale response [235], these interactions have been rarely implemented in computational models. One of the reasons that prevent the spread of multi-scale approaches in biomechanics is the lack of computational tools to accurately and efficiently handle multiple domains. Although tools to develop musculoskeletal simulations are becoming more accessible and computationally efficient, they do not allow yet a sufficient level of model personalization and detail to describe organ/joint mechanics. In addition, finite element analysis packages estimate local deformations and stresses, but their computational cost appears overwhelming for whole body applications. These technological limitation have fostered multi-scale applications performed in a sequen-
tial fashion: a multibody musculoskeletal simulation at the whole body level is used to predict muscle or contact forces, which are consequently applied as boundary conditions to an organ level finite element model [76] (Fig. 2.4). This top-down approach takes into account two different scales and addresses the common problem of selecting suitable boundary conditions for detailed models. The sequence of interconnected computational models at different scales has been used for many applications: examples are the prediction of ligament and contact forces in the natural knee [225], PF joint stress [21], stresses in a total shoulder arthroplasty [121], TF contact loads in an implanted knee [135], and bone adaptation in the femur [93].

2.5 Gaps and opportunities

Although the previously described sequential approach has the potential to reveal interesting relations between spatial scales in subject-specific applications, there are still important limitations that need to be addressed to make an impact in the clinical setting. As mentioned before, a computational model of the human body needs to be validated, personalized, and sufficiently sophisticated in order to be trusted.

2.5.1 Validation

Validation is a challenge common to every musculoskeletal model. Validation is the process of determining how well the model represents the real world through comparison to experimental data [160]. Typically, the lack of available experimental data for the comparison of model outputs is the most significant obstacle to validation. Since non-invasive measurements that can be obtained in vivo are limited, model validation is often performed by simulating in vitro experiments and compar-
ing model and experimental outputs. For instance, a finite element model of the proximal femur was used to predict propagation of fracture and validated against specimen-specific experimental data [6]; long-term TKR wear results were compared between a testing machine and a model of the implant [139] specimen-specific TF finite element models were calibrated and validated against laxity tests on the joints [115]. In vitro experiments that replicate the loads experienced and generated by the human body during daily living activities have also been developed. For example, a knee simulator that applies loads at the hip and ankle, and at the quadriceps tendon to replicate motor tasks such as gait and squat has been utilized [162]. Computational models that simulate these experiments to match in vitro joint kinematics have been performed, and, after validation, can be used as a predictive tool by changing the model conditions [17, 107]. However, even though quantitative direct comparison of in vitro measurements to organ/joint level model outputs has been successful, the impact of these models will substantially improve if they are placed in the context of living conditions. Since direct measurements of muscle force are not feasible, this step represents a core challenge for multibody musculoskeletal models.

Muscle redundancy makes model force estimates just a single solution out of the infinite possible combinations that can achieve the same joint kinematics [165]. Since in vivo direct measurements of muscle forces are not possible, different types of experimental measurements used for model validation have been defined to rank the confidence in computational simulation outputs: indirect measurements and trend measurements Nigg-2000. Specifically, EMG signals collected in vivo are commonly used to validate activation and deactivation times predicted by musculoskeletal models (trend validation) [11, 160, 210]. In addition, measurements of joint contact loads from instrumented implants have encouraged a new generation of model validation,
since they provide direct measurements of a quantity that is mainly determined by muscle forces during daily activities (indirect validation) [20, 87]. However, subjects with instrumented implants are very rare and they do not represent a healthy population. Therefore, in most cases the only accessible option for subject-specific comparison is a trend/qualitative validation using EMG signals [12, 210]. Although qualitative comparison to experimental data is important to provide confidence in model outputs, an objective criterion in controlled conditions is needed to correctly quantify the reliability of a model prediction. For example, it is possible that muscle forces estimated during a musculoskeletal simulation qualitatively agree with EMG signals, but model predictions do not match quantitative measurements such as telemetric implant measurements. In that case, the model would not be considered validated for the estimation of joint loads.

Further model validation opportunities for models simulating living conditions are provided by sub-mm and sub-degree measurements of joint kinematics achievable with stereo-radiography and fluoroscopy systems [127, 154]. Specifically, three-dimensional joint motion predicted with a musculoskeletal model can be compared to kinematics measurements obtained in vivo. Although these comparisons provide confidence that the loading conditions applied to the model by the muscles represents a valid solution, the problem of estimating muscle and joint loads in living subjects remains.

2.5.2 Personalization

A second challenge in musculoskeletal computational modeling is personalization. Musculoskeletal models of the body are defined by the interaction between a multitude of parameters. For example, a single muscle modeled as a Hill-type mus-
culotendon unit is the combination of origin and insertion location, path definition (possibly with wrapping portion and/or via points), maximum isometric force, optimal fiber length, tendon slack length, pennation angle, force-length and force-velocity curves [263]. The human body includes hundreds of muscles and none of these properties can be accurately measured in vivo. This is particularly relevant because a wide range of muscle parameter variability has been previously reported [253] and significant differences between young and elder populations have been observed [111]. Yet these parameter differences can make a substantial impact on the results of a simulation [177]. In addition, as the model complexity increases, a number of other parameters such as soft tissue material properties and joint morphology also need to be estimated to create a subject-specific model. For example, TF laxity response during standard tests also presents a large inter-subject variability [10, 98]. Therefore, most musculoskeletal models use average parameters from cadaveric studies, when these properties are accessible. For instance, state-of-the-art musculoskeletal models use average musculotendon properties from cadaveric studies [15, 52, 200]. When ligaments are modeled, properties are either adopted from the literature [220] or tuned against average laxity behavior [150]. This approach creates a generalized model that provides a valuable insight into the average behavior of the human body. However, conclusions on a specific patient cannot be reliable when a generic model is used and the intrinsic variability of the human body is not taken into account. The lack of tools for accurate subject-specific model identification also impacts model validation. Specifically, an accurate estimate of an output from a generic model with intrinsic uncertainty does not guarantee that future estimates of the model will be accurate in different conditions.
A viable strategy to partially address the lack of personalization is to develop image-based musculoskeletal models. CT or MRI can be collected to reconstruct tissue geometry. Bones, ligaments, cartilages and muscles can be segmented to obtain subject-specific geometries and develop organ/joint level computational models. Full lower limb MRI has also been used to improve muscle path representation in whole body musculoskeletal models [41, 212, 249] and significant differences with generic-scaled models have been observed [213, 214]. Full lower limb imaging can also provide an estimate of muscle PCSA, which is assumed to be proportionally related to muscle maximum isometric force [244]. However, the tradeoff between advantages and processing time of manual segmentation of muscle geometry is still a challenge. In addition, uncertainty in several other parameters such as Hill-type muscle properties remains and can substantially affect model predictions [177]. Alternative strategies to tune subject-specific muscle properties to torques generated during maximum isometric contraction of lower limb muscle groups have been utilized [220]. However, this approach only provides a reliable model behavior in terms of muscles groups, and the force distribution between single musculotendon units is not captured.

Griffin [101] stated that it is meaningless to refer to a model as being a validated model and that it is more helpful to quote the limits of its applicability and its quantitative reliability. In fact, an alternative approach to deterministic subject-specific modeling is population modeling. Since accurate deterministic parameters are rarely available, probabilistic input parameters can be used instead. Specifically, if a probability distribution for a specific parameter is known, for example from cadaveric investigations with a sufficient number of specimens to describe a population, probabilistic analysis can be performed and output variability will provide a quantification of the possible error in the prediction [148, 177]. Even though new techniques that
can measure unknown parameters in living subjects would be ideal to address model identification, a quantification of the model reliability can provide more confidence in simulation outcomes.

2.5.3 Complexity and concurrent multi-scale approach

Another issue of current musculoskeletal modeling is the lack of meaningful complexity at the whole body level. *State-of-the-art* musculoskeletal models used to estimate muscle and joint loads at the body level present several simplifications to improve their computational efficiency. First, joints that in reality present complex activity-dependent motion are modeled as one-degree-of-freedom articulations [11]. For example, several musculoskeletal models developed in OpenSim [51] or Anybody [47] represent the knee as a joint with a single degree-of-freedom in which PF kinematics and secondary TF kinematics are constrained functions of knee flexion. In addition, the motion prescribed to the joint may be derived from average passive cadaveric motion [15, 200, 251] or from two-dimensional general models [52]. Therefore, inter-subject and inter-activity motion differences previously reported in the literature [66] are not taken into account. Another important simplification of whole body models is that ligament and contact forces are not included in the muscle force calculation [252]. Generally, the lack of complexity is a current limitation of whole body musculoskeletal models.

This limitation also introduces a lack of consistency between models at different scales when the sequential approach previously described is employed. Muscle loads estimated at the whole body level are applied to more detailed organ/joint models whose complexity is not included at the larger scale. Although the tools currently available encourage the use of sequential simulations to model multiple scales, a
concurrent multi-scale modeling approach is necessary to represent the interactions between different domains. In fact, the separation of the human body into discrete scales is an abstraction utilized to simplify the complexity of our biological structure, but there is no clear division in nature. A clinical case that exemplifies the need for concurrent simulations is presented below. Neuromuscular control plays a significant role in anterior cruciate ligament (ACL) injury and repair [100, 235]. If a physical therapist wants to design a set of exercises for progressive rehabilitation of a specific patient that underwent ACL reconstruction, they will need to estimate what movements and muscle contractions will stimulate the ligament, and at the same time generate limited stress in it. This question might be addressed if a computational model could include an accurate representation of the muscles acting on the knee and the model at the continuum level of the subject-specific ACL that could wrap on surrounding tissue and describe fiber orientation and viscoelasticity.

A first type of investigation that addressed the lack of consistency between scales increased the level of detail of a whole body rigid musculoskeletal model. Specifically, a detailed knee joint representation was included in a multibody model in both the natural [150] and implanted case [239]. Joint ligaments with properties from the literature and average laxity behavior were included, and contact at the TF and PF joints was modeled with an elastic foundation definition. Although these studies represent a step forward in the analysis of the interaction between scales, multibody modeling has limited potential in comparison to the finite element method. For example, deformable material properties cannot be assigned and more complex contact definitions, such as between a three-dimensional ligament and a bone, are not possible.
Some pioneering investigations that simulated multiple scales in a simultaneous simulation including tissue deformation have been performed. Ezquerro et al. combined a finite element analysis with an optimization-based force prediction technique to model lumbar spine biomechanics [72]. This study was able to estimate back muscle forces including in the muscle optimization the loads transferred by deformable representations of the disc annuli and ligaments. Koolstra and van Eijden used a forward dynamics finite element simulation to estimate mandible stresses [140]. No muscle optimization was performed, but a priori defined muscle activations drove the model dynamics, to analyze the deformation distribution in the cartilaginous structures of the jaw. Halloran et al. have developed a concurrent simulation of whole body musculoskeletal dynamic and finite element analysis of the foot to simulate gait and maximum height jump [106, 108]. These two studies, to the author’s knowledge, represent the most advanced example of concurrent simulations that includes tissue deformation in the calculation of whole body muscle forces. In both studies optimal control was used to predict optimal motion of a two-dimensional musculoskeletal model that interfaced with a deformable finite element model of the foot during each dynamic iteration. The simulation of gait included a strain minimization term in the optimization cost function together with fatigue minimization to identify realistic walking strategies that reduce plantar tissue pressure, which is thought to contribute to diabetic foot ulceration [106]. This study represents an example of why the interaction between movement and tissue can be clinically meaningful. The study that simulates maximum height jump models the interaction between the two scales with a surrogate system that invokes the finite element analysis only when the current solution is not within a defined tolerance from previous results [108]. The surrogate modeling system only used the finite element model in 5% of the iterations,
significantly reducing the total computational time. All of these studies represent a significant step forward in the direction of concurrent simulation of multiple scales. However, the computational cost needed to concurrently estimate muscle forces and simulate local tissue deformation remains burdensome, because of the inherent cost of the finite element method and the multiple iterations of the same simulation necessary for optimization and optimal control strategies. Alternative strategies that can reduce the computational cost of concurrent simulations should be investigated in order to enhance the potential of modeling tools in the clinical setting.
Figure 2.1: Musculotendon unit representation in whole body musculoskeletal models often includes wrapping surfaces (left) and via points (right) to describe more accurately the path of the muscle, which can wrap around bones and other soft tissues. The figure shows examples from a model created in OpenSim.
Figure 2.2: The most common model to represent the passive and active properties of a musculotendon unit is the Hill-type model. An active contractile element (CE) that can generate force is modeled in parallel to a nonlinear spring type element (passive curve in subfigure a) that represents the inherent elasticity of the muscular tissue. The tendon is also represented as a nonlinear spring in series to the muscle (subfigure c). The contractile element can generate force according to experimental-based curves that are function of the muscle length and velocity (subfigures a) and b) on the bottom).
Figure 2.3: The complex and irregular shape of biological tissues can be approximated with the finite element method. An accurate model of geometry and material properties can provide estimates of the local tissue deformation and the mechanical interaction between organs.
Figure 2.4: Current multiscale modeling approaches in biomechanics simulate different scales in separate models that interact only through their outputs and inputs. Specifically, when the interaction between the whole body level and the organ/joint scale is modeled, the muscle/joint forces estimated with a whole body musculoskeletal model (a) are used as boundary conditions for a more detailed finite element model at the organ/joint level (b). However, this sequential approach introduces a lack of consistency between the two representations, since the muscle forces estimate at the whole body level will not depend on the organ/joint detailed behavior, but only on a simplified version of it.
Chapter 3

Prediction of in vivo knee joint loads using a global probabilistic analysis

3.1 Abstract

Musculoskeletal models are powerful tools that allow biomechanical investigations and predictions of muscle forces not accessible with experiments. A core challenge modelers must confront is validation. Measurements of muscle activity and joint loading are used for qualitative and indirect validation of muscle force predictions. Subject-specific models have reached high levels of complexity and can predict contact loads with surprising accuracy. However, every deterministic musculoskeletal model contains an intrinsic uncertainty due to the high number of parameters not identifiable in vivo. The objective of this work is to test the impact of intrinsic uncertainty in a scaled-generic model on estimates of muscle and joint loads. Un-
certainties in marker placement, limb coronal alignment, body segment parameters, Hill-type muscle parameters and muscle geometry were modeled with a global probabilistic approach (multiple uncertainties included in a single analysis). 5-95% confidence bounds and input/output sensitivities of predicted knee compressive loads and varus/valgus contact moments were estimated for a gait activity of three subjects with telemetric knee implants from the ñGrand Challenge Competitionñ. Compressive load predicted for the three subjects showed confidence bounds of $333 \pm 248 N$, $408 \pm 333 N$ and $379 \pm 244 N$ when all the sources of uncertainty were included. The measured loads lay inside the predicted 5-95% confidence bounds for 77%, 83% and 76% of the stance phase. Muscle maximum isometric force, muscle geometry and marker placement uncertainty most impacted the joint load results. This study demonstrated that identification of these parameters is crucial when subject-specific models are developed.

### 3.2 Introduction

Musculoskeletal models are powerful tools that allow subject-specific investigations of biomechanical quantities that are not measurable \emph{in vivo}, and predictions of the effects of clinical treatments [54, 205, 211, 245]. The main challenge of subject-specific modeling is the lack of validation strategies, because predicted outcomes of musculoskeletal models can rarely be compared to measurable experimental data [160]. In particular, when muscle forces are involved in model predictions, two quantities measurable \emph{in vivo} have been used to verify the reliability and accuracy of the model: 1) muscle EMG signals that allow for a mostly qualitative comparison of muscle activity [11, 210], and 2) joint loads measured with instrumented joint implants.
that allow for an indirect validation of muscle forces [20, 135, 157, 232, 236]. Instrumented implants have significantly enhanced the awareness of the ability of musculoskeletal models to predict contact loads with surprising accuracy [87, 136, 163, 232], even though only for implanted joints. In particular, blinded predictions of TKR contact loads on an instrumented tibial component were possible due to the Grand Challenge Competition, which made joint load, human movement and imaging data sets available to the scientific community [87].

All previous attempts to match experimental contact loads have used deterministic models whose final output depended on several input parameters necessarily estimated from the available data (e.g. joint kinematics, segment inertial parameters or musculotendon parameters). However, deterministic musculoskeletal models are characterized by an intrinsic uncertainty that is often ignored. For example, segment masses cannot be directly measured from the subject and are often estimated with scaling techniques. Musculoskeletal models are usually developed and validated with the purpose of predicting and estimating biomechanical quantities not measurable in vivo. If an accurate estimate of an output is obtained by means of a model with intrinsic uncertainty, there is no guarantee that future estimates of the model will be accurate in different conditions. Therefore, it is important to take into account this variability in order to assess the robustness of a model. Many studies have partially included model uncertainty and analyzed its influence on biomechanical outputs of interest. When the possible amount of an uncertainty is not available, the sensitivity of a particular output (e.g. joint kinematics, muscle moment arms, muscle function) to the change of an uncertain input (e.g. musculoskeletal geometry, musculotendon properties, joint axis location) can be quantified and provide valuable insights into the possible effects of lack of knowledge [9, 148, 160]. The impact of
the uncertainty in different input parameters on several outputs of interest has been analyzed for musculotendon parameters [4, 26, 49, 203, 216], musculotendon geometry [32, 39, 243], joint center location [167], degree of freedom classification [40], joint models [64, 65, 67], skin marker placement [67], and pose estimation algorithms [175]. On the other hand, when the amount of possible uncertainty is known, an accurate evaluation of the output variability can be quantified. In particular, uncertainty has been evaluated in video motion capture marker placement [50], segment inertial parameters [147, 202], kinematics and muscle origin-insertion location [189].

While many studies have used probabilistic tools to analyze the effect of uncertain parameters on the output of interest [4, 26, 32, 39, 40, 49, 64, 65, 67, 167, 175, 203, 216, 243], few of them have performed probabilistic analyses that combine multiple uncertainties belonging to different categories of parameters (described hereafter simply as “global”) [177, 244]. These global analyses allow a more complete investigation of the overall reliability of a model. Valente et al. [244] used a full limb MRI-informed musculoskeletal model in OpenSim that included uncertainties of anatomical landmark location, muscle attachments sites and maximum muscle tension. Myers et al. [177] used a scaled-generic musculoskeletal model in OpenSim that included marker placement error, segment inertial parameters uncertainty and Hill-type muscle parameters uncertainty. However, Myers et al. [177] did not account for variability in muscle geometry and did not investigate the impact of the included uncertainties on joint reaction forces. Moreover, these two studies used data from a single healthy subject and did not perform a quantitative validation of their results because joint load measurements were not available for the subjects.

The present study proposes a global probabilistic analysis to investigate the influence of uncertainty in multiple parameters of a musculoskeletal model on knee joint
load while simulating level gait for three TKR patients. The goals of this study are: (1) to include common sources of uncertainty present in a musculoskeletal model in a probabilistic framework with realistic input distributions while predicting the TKR contact loads of patients with telemetric implants; (2) to quantify the influence of each input uncertainty on the desired output (knee contact loads) and therefore to identify the most critical parameters whose knowledge must be improved to develop more accurate subject-specific models; and (3) to compare the obtained variability of the prediction to the available in vivo contact loads. This will allow an estimate of the musculoskeletal model’s reliability for prediction of muscle forces and knee joint loads.

3.3 Methods

3.3.1 Experimental data

Walking data of three subjects (169.0 ± 2.6 cm, 71.7 ± 6.0 kg) implanted with an instrumented TKR from the Grand Challenge Competition was used [87]. The three subjects walked at similar self-selected speed (1.2, 1.1 and 1.0 m/s respectively). The first subject was implanted with an instrumented tibial prosthesis with four uniaxial load cells to allow the measurement of medial and lateral contact forces separately [137]. The other two subjects were implanted with telemetric implants that allowed the measurement of knee contact forces in 6 degrees of freedom by means of a single load cell [60]. The available data includes video motion capture marker locations, ground reaction forces, and TF contact forces (https://simtk.org/home/kneeloads). A modified Cleveland Clinic marker set that included extra markers on the feet.
and trunk was used for motion data collection [87]. Surface EMG signals were also collected for the major muscles spanning the knee of each subject.

### 3.3.2 Baseline musculoskeletal model

A previously developed musculoskeletal model with a total of 10 segments and 92 musculotendon units was modified in OpenSim to obtain the baseline model for this study [51, 52]. The lower limbs included a ball-and-socket hip joint and a revolute ankle joint. In the current study, the knee joint was modified to implement a coupled mechanism (one degree of freedom) with translations of tibia and patella prescribed by the knee flexion angle [15]. In addition, a varus/valgus degree of freedom of the tibia with respect to the femur was introduced in the knee model for subsequent analysis of uncertainty in lower limb coronal alignment and was fixed to zero in the baseline model. The geometry of the quadriceps muscles in the original OpenSim model was refined to insert on the tibial tubercle with via points placed on the superior and inferior poles of the patella [56]. This enabled resultant quadriceps force to be correctly included in the calculation of TF contact forces in OpenSim. Via point locations of the quadriceps were manually adjusted to assure that the moment arm of each of the musculotendon units lied inside the $\mu \pm \sigma$ area of the patellar tendon moment arm measurements presented by Krevolin et al. [141]. Finally, geometry and properties of the two gastrocnemius musculotendon units (medialis and lateralis) of the original model were replaced with the gastrocnemius units from the musculoskeletal model of Arnold et al. [15], as these better matched the moment arms measured by Buford et al. [29].

Body segment dimensions and inertial properties were scaled to the subjects using scale factors calculated from motion capture marker locations. The dimensions of
the scaled segments were also checked by comparing them to the CT images of the subjects’ implanted lower limb.

Baseline joint kinematics and inverse dynamics for each subject were determined with OpenSim. To achieve the pose of the subject, the recorded marker locations are matched to virtual markers on the kinematic model of the subject. This matching technique is performed by solving a weighted least squares problem that minimizes marker errors at each time frame [51]. Net forces and moments needed at the joints to achieve the desired motion were obtained through the inverse dynamics solution. Baseline muscle forces were predicted with a static optimization technique that solves the equations of motion while minimizing the summed muscle activations squared at each time frame [12]. Baseline joint loads were calculated in OpenSim from the inverse dynamics and muscle forces by calculating loads exchanged between segments through a free body diagram analysis [56].

3.3.3 Probabilistic workflow

A previously developed Probabilistic Toolbox [177] that alters OpenSim input files within a Monte Carlo simulation was customized to introduce the desired uncertainty in the baseline model’s parameters. The uncertainty of all the parameters considered in this study was propagated to the joint contact analysis through the stages of the workflow (Fig. 3.1). In particular, four main sources of uncertainty were taken into account: the uncertainty (1) in the motion capture marker placement on the anatomical landmarks, (2) in the coronal alignment, (3) in the segment inertial parameters, (4) in the Hill-type muscle model parameters and in muscle geometry.
1. Marker placement: errors in marker placement result from the inherent uncertainty that occurs when an examiner places a marker on the skin relative to a palpated bony landmark. This uncertainty was modeled as a constant offset between the anatomic landmark and the marker [177]. Marker placement uncertainty was modeled by sampling the magnitude of the offset in each direction from a normal distribution. Previously reported intra-examiner variances were used [50] for anatomical landmarks present both in the marker set used in this study and in the marker set used by Della Croce et al. [50] (Tab. 3.1). To assess intra-examiner precision, the same examiner performed the anatomical landmark identification six times and the standard deviation (std) across the six measurements was calculated. For markers in the present study that were not described by Della Croce et al. [50], two different stds were used. To represent the uncertainty along the two directions of the anatomical plane (either sagittal, coronal or transverse) that best represents the surface tangent to the anatomical landmark, the average of the maximum stds in Della Croce et al. [50] was used (7.9mm). Along the direction perpendicular to that same surface, the average of the minimum stds in Della Croce et al. [50] was used (3.7mm). The uncertainties calculated this way were applied also to the markers on the foot because the patients in our study wore shoes, which likely created greater uncertainty than the subjects in Della Croce et al. [50] who were barefoot. Although uncertainty in marker placement occurs during the experimental session, they were more easily accounted for by perturbing the location of the virtual markers in the local coordinate system of the corresponding segment on the musculoskeletal model. Since the kinematics were resolved by minimizing the distance between experimental and virtual markers, perturbations
in the virtual or experimental marker location have the same effect on joint angles.

2. Limb alignment in the coronal plane: although an implant aligned to the mechanical axis of the lower limb is usually the surgical objective, it can be challenging to achieve. Coronal alignment, besides affecting the survivorship of the implant [73], influences the distribution of the TF contact load on the lateral and medial side [151]. The uncertainty in this postoperative TF angle was included in the present study. The varus/valgus degree of freedom was introduced in the knee model and locked to a constant offset sampled from a normal distribution with null mean and std of 2.5°, since this is the std of the postoperative TF alignment for 6070 TKA patients reported by Fang et al. [73].

3. Inertial parameters: body segment parameters are usually estimated by considering them linearly proportional to their dimensions, obtained by scaling a general model according to marker distance ratios. This approximation of the actual parameters does not account for other factors such as mass distribution, density and amount of soft tissue. Therefore, uncertainties in mass, moment of inertia and center of mass location of the lower limb segments were modeled by perturbing the parameters of the baseline scaled model with estimated variances [202] (Tab. 3.2). Rao et al. [202] calculated variability in inertial parameters by estimating them with six different parameter identification models. Input distributions for the current study were defined using baseline model parameters as the means and stds defined by coefficients of variation (COV = std/mean) from Rao et al. [202]. Inertial parameters of the pelvis and the
segments of the upper body were not perturbed because they do not influence the calculation of ankle, knee and hip net joint moments calculated via inverse dynamics, and consequently do not significantly affect the prediction of muscle forces and joint reaction loads in the lower limb [177].

4. Muscle path and parameters: musculotendon units were modeled as Hill-type muscles. A Hill-type muscle is completely described by: (a) its path, (b) the active and passive force-length relationships [237], (c) the force-velocity relationship [52] and (d) four parameters (maximum isometric force, optimal fiber length, tendon slack length and pennation angle) [263]. While force-length and force-velocity relationships are consistent among different muscles and subjects [122, 142], there can be significant variability in muscle path and parameters. Uncertainties in Hill-type muscle parameters of 20 musculotendon units were modeled by sampling them from input distributions defined according to the dataset in Ward et al. [253] (Tab. 3.3), where means and stds of PCSA, fiber length ($L_f$) and pennation angle ($\alpha$) from 21 cadavers are presented. Since maximum isometric force ($F_{OM}$) can be calculated as $PCSA$ times muscle tension [199], the COVs from $PCSA$ measurements in Ward et al. [253] were used to calculate stds for maximum isometric forces by multiplying them times the baseline values (considered the mean values). Fiber lengths in Ward et al. [253] were obtained by first measuring a raw fiber length ($L'_f$) from three to five regions in each muscle and scaling it with a sarcomere length-based ratio [155]:

$$L_f = \frac{2.7 \cdot L'_f}{L_s}$$  \hspace{1cm} (3.1)
where $L_s$ is the bundle sarcomere length measured by laser diffraction from each muscle region, and $2.7 \, \mu m$ represents the optimum sarcomere length for human muscles [155]. Therefore, the fiber length measured in Ward et al. [253] is an approximation of optimal fiber length, since this is the length at which most of the sarcomeres are at their optimal length. The baseline optimal fiber length values were used as mean values of the input distributions, and stds were calculated by means of the fiber length COVs from the cited dataset [253]. COVs from pennation angle measurements were used to calculate stds for this parameter. Since tendon slack length ($L_o^T$) variability was not found in the literature, this parameter was calculated from the sampled optimal fiber length and pennation angle by keeping a constant musculotendon total length:

$$L_{T_{\text{pert}}}^S = L_{T_{\text{bl}}}^S - (L_{M_{\text{pert}}}^o - L_{M_{\text{bl}}}^o) \cdot \cos(\alpha_{\text{pert}})$$  \hspace{1cm} (3.2)$$

where the subscripts pert and bl indicate the perturbed value and the baseline value, respectively [92]. Uncertainty in the paths of the same 20 muscles was included by perturbing the location of muscle attachments and via points. Uncertainty in muscle attachments on the femur (origins of vasti, biceps femoris short head, gastrocnemius medialis and lateralis, and insertions of glutei maximus, glutei medialis, psoas and iliacus) were modeled according to the variability reported in a cadaver study with 6 specimens whose femur lengths were scaled to a mean model to allow inter-specimen comparison [62]. Attachment and via point locations not investigated in Duda et al. [62] were perturbed in all directions according to a normal distribution with a 5 mm std, comparable
to the range of landmark location errors reported in the literature [134, 255] (Tab. 3.3).

Output variability of joint kinematics, net joint torques, muscle forces and joint contact loads were determined with OpenSim by performing several combined Monte Carlo analyses (Fig. 3.1). In particular, the output variability of each step was used as the input distribution for the following step (e.g. joint kinematics outputs from the kinematics Monte Carlo analysis were used as one of the random inputs for inverse dynamics, static optimization and joint reaction analysis).

### 3.3.4 Data analysis

The 5-95% confidence bounds of the output variables (joint kinematics, kinetics, muscle forces and joint contact loads) were calculated at each time frame, which represents the region in which the true result would lie with a confidence of 90%. Mean and std of the 5-95% confidence bounds were used to evaluate an average impact of the uncertainties on the analyzed output [177]. The relative contribution of each source of uncertainty was assessed by comparing the sizes of the confidence bounds when only single sources of uncertainty were included in the Monte Carlo analysis. When mean and std of muscle force bounds were calculated, only time frames when the muscle was active were included. A total of 15 Monte Carlo analyses were performed for each subject to assess the relative contribution of each source of uncertainty to output kinematics, kinetics and muscle forces: 3 inverse kinematics analyses in which just inverse kinematics was performed (perturbing marker location, TF alignment and both); 4 inverse dynamics analyses in which inverse dynamics was performed (perturbing marker location, TF alignment, inertial parameters and all
of them combined); 8 static muscle optimization analyses in which static muscle optimization was performed (perturbing marker location, TF alignment, inertial parameters, muscle paths, maximum isometric force, fiber properties, pennation angle and all of them combined). Joint contact loads were estimated for each static optimization solution of each Monte Carlo analysis.

One thousands simulations per Monte Carlo analysis ensured convergence for the main outputs: knee superior/inferior (compressive) force and varus/valgus contact moment 5-95% confidence bounds. Specifically, means and stds of output confidence bounds lay within 1% of each final mean and std over the last 100 simulations for every Monte Carlo analysis [4, 244]. When maximum isometric force and/or muscle path were perturbed, a limited number of simulations (always less than 2% of the total number for each Monte Carlo analysis) failed because of the muscular system’s weakness. However, every failed simulation was replaced by another simulation to ensure a total of 1000 simulations per Monte Carlo analysis.

Sensitivity of knee loads was assessed by calculating the Pearson Product-Moment Correlation between the input parameter and the two compressive loading peaks that normally occur during gait. Significant correlations were divided into three groups according to their absolute value: weak (0.2<|r|<0.4), moderate (0.4<|r|<0.6) and strong (|r|>0.6). The slope of each correlation was also calculated and multiplied by the standard deviation of the input uncertainty to assess the potential influence of the input parameter on the analyzed output. Sensitivity was evaluated for Monte Carlo analyses where only individual groups of parameters were perturbed (e.g. only maximum isometric force of all the muscles) in order to assess the influence of a single parameter in comparison to other parameters of the same kind. Therefore, a total of 6 additional Monte Carlo analyses were performed per each subject to evaluate
sensitivity: one with only marker and coronal alignment uncertainties, one with only BSP uncertainty and one for each source of uncertainty in the muscles (maximum isometric force, fiber parameters, pennation angles and muscle path).

Root mean square (RMS) errors and squared Pearson Product-Moment Correlations were calculated between joint loads predicted with the baseline musculoskeletal model and joint loads measured from the subjects [87, 136]. The percentage of the stance phase in which loads measured by the telemetric implants were within the predicted 5-95% confidence bounds was also calculated. EMG signals were first processed with a 10-400 Hz band-pass 8th order Butterworth filter, then rectified and filtered with a 6 Hz low-pass 2nd order Butterworth filter, and finally, normalized to signals collected during maximum voluntary contractions [167]. The processed EMG signals were used to confirm predicted muscle forces were appropriate.

Inter-subject differences were identified through comparison of 5-95% confidence bounds and sensitivity analysis results for the three subjects. For each subject, input variables were ranked from largest to smallest according to the mean 5-95% bounds they produced on each output (kinematics, kinetics and joint loads). In addition, rankings were compared among subjects of most affected outputs when all input variables were perturbed. Finally, moderate and strong correlations between input variables and the first and second joint load peaks during the gait cycle were compared between subjects.
3.4 Results

3.4.1 Kinematics

The impact of marker placement error and coronal alignment on kinematics was quantified by the size of the 5-95% confidence bounds of each joint angle (Fig. 3.2). For the three subjects, the degree of freedom with the largest mean bound size was hip flexion/extension ($\mu \pm \sigma = 8.4 \pm 0.5^\circ$ for subject 1).

3.4.2 Kinetics

The confidence bounds of net joint moments quantified the impact of marker placement, coronal alignment and BSP uncertainties on inverse dynamics (Fig. 3.3). Bounds for hip flexion/extension moment ($5.7 \pm 1.8$ Nm) and hip internal/external rotation ($2.0 \pm 0.9$ Nm) in subject 1 were the largest and smallest bounds, respectively. Marker placement error had the most significant impact also on all joint moments for the three subjects except internal/external rotation of the hip of subject 1, on which coronal alignment had the largest effect (Fig. 3.3).

3.4.3 Muscle forces

By combining all the uncertainties in the workflow (Fig. 3.1), soleus presented bounds substantially larger than other muscles (e.g. $500 \pm 362$ N for subject 1) (Fig. 3.4). Other musculotendon actuators with average 5-95% confidence bounds above 250 N were psoas ($305 \pm 235$ N), iliacus ($297 \pm 229$ N), medial gastrocnemius ($264 \pm 287$ N), anterior gluteus medius ($273 \pm 192$ N) and central gluteus medius ($262 \pm 176$ N) (Fig. 3.4).
3.4.4 Joint loads

Knee compressive load and varus/valgus contact moment of subject 1 showed confidence bounds of 333±248 N (Fig. 3.5) and 16±11 Nm (Fig. 3.6), respectively, when all the sources of uncertainty were considered. The variables that had a substantially higher impact on muscle forces and knee loads were muscle maximum isometric force and muscle fiber path (Fig. 3.5). Their contribution to compressive load variation was 3.4 and 2.5 times higher than the contribution of marker placement error, which was the third most impactful variable. Varus/valgus contact moment bounds were also influenced by coronal alignment uncertainty (80% of muscle maximum isometric force influence) (Fig. 3.6).

3.4.5 Sensitivity analysis

When only the marker placement and coronal alignment uncertainties were included in the Monte Carlo analysis, compressive load for subject 1 was just moderately correlated to the anterior/posterior location of the right Thigh Inferior marker at its first peak, and to the anterior/posterior location of the right ASIS marker (see Tab. 3.3 for correlations and responses to 1 std change in the input parameters). Strong correlations between alignment in the coronal plane and both peaks of varus/valgus contact moment were found. Tibial inertial parameters showed the highest correlations when only BSP uncertainties in subject 1 were investigated, but relatively small impacts on the outputs were observed (Tab. 3.4). Several significant correlations were found when only individual muscle parameters were perturbed in subject 1. The muscles that showed the strongest correlation to first and second peaks of compressive load were vastus medialis (maximum isometric force) and ante-
rior gluteus medius (pennation angle) for the first peak, and gastrocnemius medialis (fiber parameters and pennation angle) for the second peak (Tab. 3.4). The varus/-valgus contact moment was strongly affected by vastus lateralis (maximum isometric force and fiber parameters) and vastus medialis (fiber parameters) at its first peak, and by gastrocnemius medialis (maximum isometric force, fiber parameters and pennation angle) at its second peak (Tab. 3.4).

3.4.6 Validation

Simulation of walking for the three subjects produced RMS errors of 218 N ($r^2 = 0.85$), 229 N ($r^2 = 0.91$) and 229 N ($r^2 = 0.85$), respectively, between compressive load predicted by the baseline deterministic model and the measured value. The measured loads were within the predicted 5-95% confidence bounds for 77%, 83% and 76% of the stance phase. The 5-95% bounds size of compressive load for the three subjects was $43 \pm 12\%$, $50 \pm 15\%$ and $55 \pm 18\%$ (mean $\pm$ std) of the deterministic prediction during the stance phase. RMS error between measured and predicted varus/valgus moments was 8 Nm ($r^2 = 0.53$), 12 Nm ($r^2 = 0.11$) and 14 Nm ($r^2 = 0.37$) for the three subjects (Fig. 3.5). The measured moments were within the confidence bounds for 73%, 51% and 25% of the stance phase (Fig. 3.6). Timing and magnitude of processed EMG signals were consistent with estimated muscle activation 5-95% confidence bounds (Fig. 3.4). Specifically, knee flexors were active at the beginning and end of the gait cycle, whereas knee extensors and ankle plantarflexors were active in correspondence of the first and second peak of the knee compressive force, respectively.
3.4.7 Comparison between subjects

When 5-95% confidence bounds of kinematics outputs were compared, the ranking of most affected degrees of freedom was consistent among subjects, with marker placement error having a larger impact than TF alignment on all degrees of freedom (Fig. 3.2). Similarly, marker placement error had the largest impact on kinetics outputs when the three subjects were compared (Fig. 3.3). Joint loads 5-95% bounds showed the same ranking for the three subjects (Fig. 3.5 and 3.6). Uncertainty in maximum isometric force had consistently the largest impact on both compressive force and varus/valgus moment; TF alignment and BSP uncertainties consistently had the smallest influence on compressive force and varus/valgus moment, respectively. Inter-subject differences were revealed in the muscles when results from the sensitivity analysis were compared across subjects. Similar to subject 1, only a few individual marker placement uncertainties showed moderate correlation with joint load in subject 2 and 3. Uncertainties in coronal alignment and in medio-lateral (M-L) location of tibial center of mass were strongly correlated with both peaks of varus/valgus moment for all the subjects. The muscles that showed strong correlations with the first peak of compressive load were different among subjects: vastus medialis (subject 1), anterior gluteus medius (subject 1 and 3) and semimembranosus (subject 2 and 3). Varus/valgus moment first peak was strongly correlated to changes in parameters of vastus lateralis, vastus medialis and anterior gluteus medius for subject 1 and 3, and to biceps femoris long head, semimebranosus and central gluteus maximus for subject 2. Conversely, all muscle parameters of gastrocnemius medialis were either moderately or strongly correlated to the predicted second peak of both compressive load and varus/valgus contact moment for all the subjects.
3.5 Discussion

A global probabilistic analysis that evaluated the influence of experimental and model uncertainties on joint kinematics, joint dynamics, muscle forces and knee contact loads was presented. Marker misplacement strongly influenced the calculated joint kinematics and net torques, whereas muscle maximum isometric force and muscle path had the largest impact on muscle forces and compressive load variability. These results demonstrate the necessity of including subject-specific musculoskeletal parameters and geometry for the assessment of joint loading.

The 5-95% confidence bounds of the predicted compressive load captured the general shape and timing of the experimental contact force for the analyzed activity with RMS errors and $r^2$ values comparable to Grand Challenge competitors (Kinney et al., 2013). The compressive loads measured in vivo were within the bounds for most of the stance phase (77%, 83% and 76% for the three subjects). In particular, the predicted bounds captured the experimental value at the two peaks (weight acceptance and contralateral heel strike). Only during the swing phase of gait was the compressive load consistently underestimated by the model, although the trend of the predicted bounds was clearly similar to the measured load (Fig. 3.5). This may be explained by a muscle activation strategy used by the subjects that includes muscle co-contractions that was not enforced in the static optimization algorithm and can be interpreted as preparatory mechanism of joint stabilization [46].

Predicted varus/valgus contact moments for the three subjects were generally less accurate than compressive loads. Correlation between deterministic predictions and experimental measurements were significant for all subjects ($p < 0.05$) but $r^2$ values were on average 0.34. Measured values were captured by confidence bounds for 73%,
51% and 25% of the stance phase. These results show that the musculoskeletal model and the optimization technique used in this study to solve the muscle redundancy problem provide satisfying predictions of muscle force allocation among main muscle groups (quadriceps, hamstrings, gastrocnemius), whereas predictions of the distribution of load on the tibia may require more sophisticated estimates of muscle forces, contact point location and the inclusion of passive tissues such as the TF ligaments.

There are limitations of our study that should be considered. First, although several sources of uncertainty were included in the probabilistic analysis, some features of the model remain uncertain. For example, the employed scaling technique affects inertial parameters, muscle fiber parameters, muscle attachment and via point locations, segment dimensions and joint center locations according to marker-based ratios. While uncertainty in inertial, muscle fiber parameters and muscle geometry was addressed in the present study, uncertainty sources such as segment dimensions and joint location may influence simulation outputs but were left out to focus the investigation on the most common sources of uncertainty.

The second limitation was that maximum isometric forces of muscles in the same limb were not assumed to be correlated. Correlations were not taken into account in this study because no quantitative data was found in the literature to support this assumption (e.g. similar scaling of the maximum isometric force of the medial and lateral gastrocnemius). If correlations between fiber strengths of the same muscle group were included, maximum isometric force uncertainty might have a smaller impact on varus/valgus contact moment because activation distribution among fibers on the medial and lateral sides of the knee might be more similar. Although the modeled uncertainty in maximum isometric force was significant and a limited number of simulations failed for not achieving dynamic equilibrium, its source [253] was
considered the most complete dataset with the given information about the subjects (measurements from 21 cadavers).

The third limitation of this study was related to the input data used to model the uncertainty in muscle path. Moment arms, which represent the effectiveness of a muscle in generating force or torque along a degree of freedom, are mainly defined by the geometry of the muscle and therefore by the location of the attachments and via points used to describe it in the model [4]. Uncertainty in attachment and via point locations not investigated in Duda et al. [62] was modeled with a normal distribution with a 5 mm std that is an approximation of the uncertainty in locating an anatomical landmark and estimating attachment sites as points from irregular areas on the surface of the bones [134, 255]. However, straightforward scaling does not account for all inter-subject variability in muscle size, shape and path point sites [214]. Since a 5 mm std has a significant impact on joint loads, we assume that greater uncertainty in attachment sites would produce even larger output bounds.

The combined effect of all the included sources of uncertainty significantly impacted joint load. Different sources of uncertainty had significantly different impacts on the analyzed outputs. Valente et al. stated that uncertainties in parameter identification of their subject-specific model had a moderate effect on model predictions (knee compressive load included) and that no specific parameter was crucial to model robustness [244]. However, Valente et al. measured muscle cross sectional area using full lower limb MRI that allowed better identification of muscle maximum isometric force values and, consequently, a smaller uncertainty. In addition, other musculo-tendon parameters (optimal fiber length, tendon slack length and pennation angle) were not modeled. These parameters were shown to have a significant effect on muscle force and function predictions [4, 49, 177]. Myers et al. showed that muscle
force predictions were mostly influenced by uncertainty in muscle parameters and, in particular, by tendon slack length variability [177]. In the present study maximum isometric force and muscle path points location had the highest impact on muscle forces and compressive load, whereas tendon slack length was less impactful (27% of maximum isometric force bounds size for subject 1). This can be explained by the different input distributions used by Myers et al. First, maximum isometric force uncertainty was chosen from a cadaver study that included just two specimens [88]; second, tendon slack length was included by using the COVs specified in Ward et al. for optimal fiber length. However, variability in fiber parameters can be assumed to have a stronger influence on muscle forces when activities with high range of motion and muscle length changes are analyzed (e.g. squat, chair rise).

The three input uncertainties that had the largest impact on compressive load were maximum isometric force, muscle path and joint kinematics. Estimates of muscle and joint loading might be improved by more accurate subject-specific determination of these inputs. Maximum isometric force derived from measurements in cadavers is most often tuned in musculoskeletal models to match measurements of isometric and isokinetic torque. This strategy can be used to obtain baseline maximum isometric values by averaging results for different subjects [52], but also to tune subject-specific strength values to peak torques measured during isometric contractions [220]. Alternatively, subject-specific maximum isometric forces have been estimated from the physiological cross-sectional area of the muscle obtained from MRI or CT images [41, 111, 244]. However, image-based models can be expensive and especially challenging and time-consuming to create. Correlations between muscle strength and anthropometric measurements could be used to assess subject-specific parameters or reduce the inter-subject variability in probabilistic analyses. Rela-
tionships between 35 lower limb muscles to height and body mass were investigated in a group of 24 young, healthy subjects using MRI [111] and several correlations between the volumes of muscle groups and the product of body mass and height were observed. However, Handsfield et al. acknowledged their results cannot be generalized to all humans because many factors like inactivity, disease-related atrophy or obesity can affect muscle volumes in different populations [111]. An increase of publicly available musculoskeletal parameter data is needed for more rendering of subject-specific parameters from population-based databases.

The second most impactful uncertainty in this study was muscle geometry. This variable has a large influence on muscle force predictions because it determines the moment arm of the muscle, and therefore its effectiveness in joint torque generation. Muscle attachment and via point location also influence the joint load calculation since it affects muscle lines of action, and therefore the joint force direction. Muscle attachment sites and geometry can be identified from MRI images to obtain more realistic subject-specific moment arms and lines of action [23, 214, 244]. However, the geometric description of a muscle cannot be reduced to one single joint configuration because muscles wrap around many structures (especially bones and other muscles) and take on different shapes. Models with linear representations of muscle fibers that make use of via points and wrapping surfaces provide moment arms in good agreement with average values measured in vitro [14], but an intrinsic uncertainty remains in subject-specific moment arms.

Inaccuracies of marker-based measurement of joint kinematics are challenging to overcome. Techniques such as videofluoroscopy allow sub-millimeter and sub-degree accuracy [240]. However, this solution is not always accessible and requires subject exposure to x-ray. In addition, it is limited to acquisitions of a single joint at a time,
and tracking kinematics involves time-consuming manual work. Therefore, the need for non-invasive accurate solutions is still a priority. Results from the present work show that joint kinematics and subsequent calculation of joint loads can be affected by uncertainty in single markers, which demonstrates the importance of quantifying and accounting for this kind of uncertainty when drawing conclusions.

When results of the probabilistic analysis were compared between the three subjects, relevant differences were not observed in the relative contribution of input distribution groups to the output variability size. The most notable difference was related to the muscles correlated to compressive load and varus/valgus contact moment first peaks: while for subject 1 and 3 the peaks showed strong correlations with vasti parameters, high correlations to hamstrings were observed for subject 2. This can be partially explained by the need of a higher hip extension torque during weight acceptance (i.e. when the first joint load peaks occur) in subject 2. The similarity among subjects strengthens the conclusion of the present study that correct identification of subject-specific maximum isometric forces, muscle geometries and marker placements is more crucial than for the other perturbed parameters when muscle forces and joint loads are estimated.

In conclusion, our study demonstrated that uncertainty in the large number of parameters that must be estimated to perform a pipeline of biomechanical analyses with a commonly used musculoskeletal model has a significant impact on joint kinematics, muscle forces and contact loads. Results for subjects with TKR during gait were most sensitive to uncertainties in kinematics, muscle strength, and muscle geometry. Although better subject-specific measurements may provide more precise knowledge of these inputs and improve estimates of muscle and joint loads, demonstrating the reliability of these estimates requires evaluation of uncertainty.
<table>
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<tr>
<td>R ASIS</td>
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<tr>
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<td>R PSIS</td>
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</tr>
<tr>
<td>Patella</td>
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<tr>
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</tr>
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<tr>
<td>Thigh Inf</td>
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<tr>
<td>Thigh Lat</td>
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<tr>
<td>Toe Med</td>
<td>7.9 3.7 7.9</td>
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Table 3.1: Uncertainty in marker placement relative to anatomical landmarks expressed in OpenSim coordinate systems (based on Della Croce et al. [50]). Shaded standard deviations (stds) represent anatomical landmarks directly investigated in Della Croce et al. Not shaded stds were selected according to the anatomical plane that best represents the surface tangent to the anatomical landmark. Along the two direction of this plane a std of 7.9 mm was used (average of maximum stds in Della Croce et al.). Along the direction perpendicular to the same surface a std of 3.7 mm was used instead (average of minimum stds in Della Croce et al.).
Table 3.2: Uncertainty in body segment parameters. Inertia tensor and center of mass components are expressed in OpenSim coordinate systems (based on Rao et al. (Rao et al., 2006)).

<table>
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<th>Body</th>
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<th>Inertia Tensor</th>
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<td>(y)</td>
<td>(z)</td>
<td>(x)</td>
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<td>0.225</td>
<td>0.3</td>
<td>0.2</td>
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</table>
Figure 3.1: Workflow of the study. Monte Carlo analyses were performed with OpenSim at each step of a pipeline that included inverse kinematics, inverse dynamics, muscle force prediction with static optimization and joint reaction analysis. Every probabilistic input was described as a normal distribution with standard deviations from the literature. Specific description of each uncertainty can be found in Table 1 (marker error), Table 2 (Inertial parameters) and Table 3 (muscle paths and properties). Only uncertainty in TF alignment (varus/valgus alignment) is not described in a table since it is a single distribution with null mean and std of $2.5^\circ$ [73]. The propagation of the uncertainties was obtained by using output distributions of each step as input uncertainty for following steps. The final output of the workflow was knee compressive load and varus/valgus contact moment.
Figure 3.2: (a) Effect of marker and limb coronal alignment uncertainties shown as 5–95% confidence bounds on joint angles for subject 1. The baseline results are represented by the black line. (b) Mean and standard deviation of 5–95% Bounds for each individual source of uncertainty that affected kinematics (subject 1).
Figure 3.3: (a) Effect of marker, limb coronal alignment and body segment parameters uncertainties shown as 5 – 95% confidence bounds on joint moments for subject 1. The baseline results are represented by the black line. (b) Mean and standard deviation of 5 – 95% Bounds for each individual source of uncertainty that affected inverse dynamics (subject 1).
Figure 3.4: Effect of all sources of uncertainty shown as $5-95\%$ confidence bounds on muscle activation predictions for subject 1. Activation confidence bounds are compared to processed EMG signals (black dashed line). Vastus medialis processed EMG signal was not included in the graph because it was not considered reliable.
Figure 3.5: (a) Effect of all the uncertainties shown as 5 – 95% confidence bounds on knee compressive load for the three subjects. The baseline results are represented by the solid black line. Corresponding measured data are represented by the black dashed line. (b) Mean and standard deviation of 5 – 95% bounds for each individual source of uncertainty that affected compressive loads for the three subjects.
Figure 3.6: (a) Effect of all the uncertainties shown as 5 – 95% confidence bounds on varus/valgus contact moment for the three subjects. The baseline results are represented by the solid black line. Corresponding measured data are represented by the black dashed line. (b) Mean and standard deviation of 5 – 95% bounds for each individual source of uncertainty that affected contact moment for the three subjects.
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<th>Muscle</th>
<th>$F_M^O$</th>
<th>$L_M^O$</th>
<th>$\alpha$</th>
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<th>Insertion</th>
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Table 3.3: Uncertainty in muscle parameters. Shaded stds for origin and insertion locations are from Duda et al. [62]. For origin and insertion locations not investigated in Duda et al., a std of 5 mm along each axis was used according to the range of landmark location errors reported in White et al. and Kepple et al. [134, 255]. A std of 5 mm along each axis was also used for all the via points of the 20 muscles included in the study.
Table 3.4: Correlations and 1std changes between joint load peaks and input variables that presented a correlation $|r|>0.4$ for subject 1. Gray and Yellow shaded values represent moderate ($0.4<|r|<0.6$) and strong ($|r|>0.6$) correlations, respectively. Corresponding 1std changes have same color shades. Vas Lat PP4 = path point of the vastus lateralis muscle fiber on the distal patella. A/P = antero/posterior, S/I = superior-inferior, M/L = medio-lateral, V/V = varus/valgus.

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<th>1std change</th>
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Chapter 4

Dependence of muscle moment arms on in vivo three-dimensional kinematics of the knee

4.1 Abstract

Quantification of muscle moment arms is important for clinical evaluation of muscle pathology and treatment, and for estimating muscle and joint forces in musculoskeletal models.Moment arms estimated with musculoskeletal models often assume a default motion of the knee derived from measurements of passive cadaveric flexion. However, knee kinematics are unique to each person and activity. The objective of this study was to estimate moment arms of the knee muscles with in vivo subject- and activity-specific kinematics from seven healthy subjects performing seated knee extension and single-leg lunge to show changes between subjects and activities. Three-dimensional knee motion was measured with a high-speed stereo-
radiography system. Moment arms of ten muscles were estimated in OpenSim by re-placing the default knee motion with $in vivo$ measurements. Estimated inter-subject moment arm variability was similar to previously reported $in vitro$ measurements. RMS deviations up to 9.0 mm (35.2% of peak value) were observed between moment arms estimated with subject-specific knee extension and passive cadaveric motion. The degrees of freedom that most impacted inter-activity differences were superior/inferior and anterior/posterior translations. Musculoskeletal simulations used to estimate $in vivo$ muscle forces and joint loads may provide significantly different results when subject- and activity-specific kinematics are implemented.

4.2 Introduction

An accurate quantification of muscle moment arms is necessary to evaluate muscle function and estimate forces needed to actuate movement. Moment arm is defined as the instantaneous measure of the “effectiveness” with which the contraction force of a given muscle can generate a moment at a “joint of interest,” while in a given configuration [227]. The standard calculation of moment arm of a force as minimum distance between its line of action and the axis of rotation of a joint cannot always be readily achieved in biomechanics because of the complexity of the involved structures. The line of action of most muscles cannot be simply defined as a straight line between origin and insertion because of wrapping around bones and other muscles [91], and complex biological joints like the knee present coupled rotations and translations that complicate the identification of a simple joint rotational axis [190, 209, 251]. Muscle moment arms have been measured and estimated through experiments (both $in vivo$ and $in vitro$) and computational models. Each one of these three approaches
presents peculiar advantages and limitations. Historically, *in vitro* measurements performed on a number of specimens [29, 231] have been the gold-standard for the quantification of moment arms. Notably, moment arms of the muscles spanning the knee were measured *in vitro* by Buford et al. using the tendon excursion method [8]. This technique enables comprehensive measurement of moment arms using cadaver specimens because of the direct access to tendon length measurements and precise control of the motion of the joint. Although *in vitro* measurements are currently the gold-standard, they are an approximation of *in vivo* moment arms since they are obtained in unloaded conditions, during passive motion of the joints, and with resting muscles. In reality, the kinematics of the knee are affected by the muscle and external load demands of different activities, and these changes will affect the moment arms of the muscles. For example, internal/external rotation and anterior/posterior translation of the knee during seated knee extension can differ from extension of the knee in a weight bearing activity [146, 178]. Since the 6 degrees-of-freedom (rotations and translations) at the knee determine the location of the instantaneous axis of rotation of the joint, they also affect the muscle moment arm calculation. For this reason, researchers have developed techniques for measuring moment arm *in vivo* using imaging [23] like static MR images [131, 256], computed tomography [184] and ultrasound [126]. These studies revealed subject and activity-specific variations in moment arm measures. Although these works have significantly enhanced the knowledge of *in vivo* muscle function, in most cases moment arm calculation relied on measurements of the orthogonal distance between the tendon and an estimate of the joint center on two-dimensional images, and most MR-based measures are based on static acquisitions, precluding their use in assessment of moment arms for normal activities of daily living. Musculoskeletal models have also been used to estimate
moment arms of the lower limb through representation of the musculoskeletal geometry [14, 15, 52, 189], and prescription of the complex motion of the knee as a function of knee flexion angle [15, 52, 174, 200]. However, the motion prescribed to the joint is commonly derived from the mean passive motion of cadaveric knees [209, 251]. Since the \textit{in vivo} kinematics of individuals differs from passive cadaveric motion [120, 146], moment arms estimated with musculoskeletal models may not be representative of muscle effectiveness \textit{in vivo} during daily living activities. The influence of \textit{in vivo} subject-specific and activity-specific kinematics on moment arms of muscles spanning the knee has never been investigated. The overall goal of this study was to investigate the dependence of muscle moment arms on joint kinematics by combining musculoskeletal modeling and 3D knee kinematics measured \textit{in vivo} to overcome some of the limitations of current approaches. Specifically, our purpose was to: (1) analyze moment arms of the muscles spanning the knee estimated with \textit{in vivo} subject-specific knee kinematics and compare these results to those obtained with passive cadaveric motion frequently used in musculoskeletal models; (2) investigate differences in moment arms estimated with \textit{in vivo} subject-specific knee kinematics from a non-weight bearing activity (seated knee extension) and a weight bearing activity (single-leg lunge); (3) identify the degrees-of-freedom of the knee that affect moment arm estimates. We hypothesized that substantial differences would be found between moment arms predicted from \textit{in vivo} kinematics and those reported from \textit{in vitro} motion, and further, moment arm estimates would change between weight bearing and non-weight bearing activity.
4.3 Methods

4.3.1 Experimental session

Seven healthy subjects (age 63 ± 8, 170 ± 9 cm, 72 ± 9 kg) performed knee extension and deep lunge activities. This study was approved by the University of Denver Institutional Review Board and all participants provided informed consent. The volunteers had no history of injuries or surgeries to the lower limbs. While performing the knee extension task, the subjects were in a seated position and were asked to slowly extend their knee from high flexion to full extension. No resistance was applied at the leg. The subjects were then asked to perform a single-leg lunge. Dynamic stereo radiographic images were collected using two matching custom radiography systems with 40 cm image intensifiers positioned at a relative angle of 60°. High-speed, high-definition cameras interfaced with the image intensifiers captured the motion at 50 frames/sec in a ‘low-dose pulsed’ x-ray mode [127]. A custom calibration cube with 52 beads was positioned inside the capture volume to determine the precise position and orientation of the two image planes. Image distortion, caused by the image intensifiers, was corrected by imaging a perforated steel plate positioned in front of each image plane. Tracking of bone motion was performed by optimizing the position of bone geometry models to the two-dimensional stereo radiographs using Autoscoper (XROMM, Brown University, RI) and relative TF and PF positions were obtained [172]. Bone geometry (femur, tibia, fibula and patella) was semi-automatically reconstructed from static CT images with slice thickness of 1.0 mm. The coordinate system of the femur was placed at the midpoint of the centerline of a cylinder fitted to the medial and lateral posterior condyles (Fig. 4.1) [241]. The medial/lateral axis was defined as the axial direction of the cylinder,
whereas the superior/inferior axis was aligned to the posterior line of the femur. The anterior-posterior axis was defined according to the right-handed coordinate system notation. The femoral coordinate system was assigned to the tibia and patella at full extension during the knee extension activity. Tracking accuracy was previously validated and errors were sub-mm and sub-degree [127].

4.3.2 Musculoskeletal model

Subject-specific full body musculoskeletal models with subject-specific representations of TF and PF kinematics were created in OpenSim [51] (Fig. 4.2). The models incorporated the knee kinematics from knee extension and the lunge activity. Each model included a total of 12 segments (torso, pelvis, femurs, tibiae, tali, calcanei, toes). Coordinate systems of the segments were defined as in Arnold et al. [15]. In order to compare moment arm estimates with different knee kinematics, a distal coordinate system was defined for the femur, coincident with the coordinate system described above. Its origin was located at the midpoint of the femoral condyles and its axes were parallel to the main femoral system at the femoral head. The coordinate system of the tibia and patella were defined coincident to this second femoral system at full extension. The lower limb included a ball-and-socket hip joint, a revolute ankle joint and a knee joint with prescribed TF and PF relative motion calculated from stereo radiography. TF and PF kinematics were decomposed into a sequence of intrinsic Euler angles and a translation vector. The sequence of rotations was the following: $z$ (medial/lateral axis), $y'$ (superior/inferior axis, after the first rotation), and $x''$ (anterior/posterior axis, after the second rotation) [258]. All TF degrees-of-freedom were prescribed, whereas the degrees-of-freedom prescribed to the
PF joint were flexion/extension, superior/inferior translation and anterior/posterior translation.

Ten musculotendon units per limb [237, 263] were included: rectus femoris, vastus medialis, vastus intermedius, vastus lateralis, semimembranosus, semitendinosus, biceps femoris long head and short head, gastrocnemius medialis and lateralis. Musculotendon geometry (origin and insertion sites) was based on a previous model [52]. The patellar tendon was also modeled as a point-to-point muscle component that connects the lower part of the patella to the tibial tuberosity. Wrapping surfaces were included in the model and were used to represent muscle paths over other muscles and underlying bones. Semimembranosus and gastrocnemius (medialis and lateralis) wrap on a cylindrical surface at the femoral condyles and the quadriceps wraps on a similar surface that approximates the anterior face of the femoral cartilage. Subject-specific muscle attachment sites on the patella (quadriceps and patellar tendon) were selected for each subject since proximal and distal portions of the bone were easily identifiable anatomical landmarks.

4.3.3 Moment arms calculation

Moment arms of the muscles included in the model were calculated with respect to knee flexion angle for knee extension, lunge and passive cadaveric motion. Moment arms were calculated using OpenSim, which employs the ‘generalized force method’ described in Sherman et al. [227]. Since the patellar tendon was described by a point-to-point segment and was assumed inextensible, its moment arm could not be estimated using the ‘generalized force method’. Therefore, it was calculated as the minimum distance between its line of action and the TF instantaneous helical
axis [231]. The consistency of the estimates obtained with the two methods was verified.

4.3.4 Data analysis

_in vivo_ knee motion for the two activities was described as a function of flexion, and compared inside the minimum flexion range available across subjects. Specifically, paired Student’s t-tests were performed at every flexion angle (1° intervals) to compare knee extension and lunge kinematics. Knee motion collected _in vivo_ was also compared to translations and rotations measured by Walker et al. [251] and used in previous musculoskeletal models [15, 52, 259]. Differences between moment arm estimates were calculated by means of root mean square deviations (RMSD) and Pearson Product-Moment Correlations (r). RMSD is a quantification of the absolute difference, whereas r measures the trend difference between two moment arm curves. For example, a relatively large RMSD (greater than 25% of the peak value) and a correlation r close to 1 indicate that the compared moment arms have similar trends but a relatively constant shift occurs between them. Specifically, moment arms estimated with activity-specific knee motion were compared for each subject to quantify the intra-subject variability. In addition, subject-specific and activity-specific moment arms were compared to estimates obtained with the same musculoskeletal model but with prescribed knee kinematics from a previously published model [15]. Moment arms measured in cadaveric studies [29] were also included in the comparison. Moment arms were compared between the two activities with paired Student’s t-tests at every flexion angle (1° intervals) inside the common flexion range. Average ȯIr were also compared between muscles to identify which muscles presented the largest inter-subject variability. To identify which TF degrees-of-freedom had the largest impact
on differences between moment arms with different kinematics, five additional conditions were simulated. Specifically, each subject-specific knee extension TF motion was replaced by the corresponding motion from Walker et al. [251] (TFW) (e.g. the anterior/posterior translation for knee extension of subject #2 was replaced by the same degree-of-freedom from TFW). Moment arms were estimated for the five conditions, and RMSD and $r$ with respect to moment arms with baseline knee extension kinematics were calculated. Low $r$ correlation and large RMSD indicate that the degree-of-freedom changed in the model strongly influences the differences between moment arms.

4.3.5 Robustness analysis

A Monte Carlo analysis that models the uncertainty in muscle attachment sites was performed for each subject and activity in order to evaluate the robustness of our results. Attachments of every muscle in the model were perturbed in all directions according to a normal distribution ($\mu = \text{baseline location}, \sigma = 5 \text{ mm}$). A 5 mm $\sigma$ is comparable to the range of landmark location errors reported in the literature [134, 255]. Only attachments on the patella (quadriceps and patellar tendon) were not perturbed, since the correct anatomical landmark was easily identified on the subject-specific geometry. RMSD and $r$ between moment arms for different activities were calculated for every instance of the Monte Carlo analysis and compared to the same results obtained with the baseline model. In addition, 5-95% confidence bounds (the region in which the true result would lie with a confidence of 90%) were calculated for each Monte Carlo analysis. One thousand instances ensured a sufficient convergence of the results: $\mu$ and $\sigma$ for RMSD and $r$ over the last 100 instances lay within 5% of the final results for every subject and muscle, except for
biceps femoris short head of subject #6 who’s mean $r$ was within 8.5% of its final mean $r$.

4.4 Results

4.4.1 Kinematics

RMSD of the kinematics between activities averaged across subjects were under $3.7^\circ$ and 2.5 mm for rotations and translations, respectively (Fig. 4.3). Statistically significant differences ($p < 0.05$) were observed for TF internal/external rotation, anterior/posterior translation, and PF flexion/extension when kinematics for the two activities were compared (Fig. 4.3). The greatest difference between TFW and average in vivo knee extension kinematics was found for superior/inferior translation (RMSD: 4.6 mm). The largest differences between the PF motion adopted by Arnold et al. (Arnold et al., 2010) (PFA) and in vivo PF kinematics during knee extension were observed for flexion/extension (RMSD: 6.7$^\circ$) and anterior/posterior translation (RMSD: 4.4 mm).

4.4.2 Moment arms

The muscles with greatest RMSD between moment arms estimated when in vivo knee extension and passive cadaveric motion were prescribed to the model were the biceps femoris long and short head (8.8 mm and 9.0 mm on average, respectively), whereas gastrocnemius lateralis presented the smallest RMSD (2.9 mm on average) (Fig. 4.4). Biceps femoris long and short head moment arms also showed the smallest correlations with moment arms calculated with passive cadaveric motion (-0.17 and
0.18 on average, respectively). When moment arms were compared between activities, similar trends were observed (Fig. 4.4). Knee extension showed larger mean $\sigma$ for all the muscles (+15% on average). The largest mean $\sigma$ (indicating the greatest inter-subject variability) was observed for biceps femoris long head moment arm (6.7 mm). Statistically significant differences ($p < 0.05$) between moment arms for the two activities were found for the medial hamstrings, the biceps femoris short head and the gastrocnemius medialis and lateralis, for a maximum flexion range of 13° (see horizontal bars in Fig. 4.4). RMSD and $r$ between moment arms for different activities of single subjects were calculated and compared to the same results averaged across Monte Carlo instances (Fig. 4.5). Largest RMSD and smallest $r$ were observed for biceps femoris short and long head (RMSD: 7.8 and 8.2 mm, respectively), and gastrocnemius medialis ($r$: 0.19). Patellar tendon showed smallest RMSD and largest $r$ (2.6 mm and 0.96). RMSD averaged across Monte Carlo instances was within 2.4% of baseline values for every muscle (Fig. 4.5). Averaged Monte Carlo $r$ was within 2.0% for every muscle except for gastrocnemius medialis (Fig. 4.5). The muscle that showed the largest 5-95% confidence bounds from the Monte Carlo analyses was semimembranosus (17.2 mm during lunge), whereas the smallest bounds were observed for rectus femoris (0.33 mm during knee extension) (Fig. 4.6). Muscle groups were affected differently by the change of single degrees-of-freedom from knee extension to TFW motion (Fig. 4.6). RMSD and $r$ between baseline models and models with changed degrees-of-freedom were calculated and compared (Fig. 4.7). Large RMSD and small $r$ indicate that the altered degree-of-freedom has a large influence on the difference between moment arms estimated for different kinematics. All the muscles presented relatively larger RMSD and smaller $r$ when superior/inferior translation was changed to the spline from TFW (RMSD
averaged across subjects peaked at 7.2 mm for semitendinosus) (Fig. 4.7). Biceps femoris was also affected by changes in internal/external rotation (peak RMSD: 4.9 mm for biceps femoris short head), whereas gastrocnemius was influenced by changes in anterior/posterior translation (peak RMSD: 4.3 for gastrocnemius lateralis).

4.5 Discussion

Moment arms estimated with \textit{in vivo} knee kinematics from two activities showed several differences in comparison to those obtained with cadaveric passive motion and also in moment arm estimations between activities. These results are relevant because they show that muscle forces estimated with non-subject-specific joint kinematics can over or under estimate muscle forces generated by the subject. In addition, the degrees-of-freedom that most influenced moment arm estimates were identified as superior/inferior translation, internal/external rotation, and anterior/posterior translation. This result shows which degrees-of-freedom of the knee are crucial for more accurate estimates of moment arms and, consequently, muscle forces. Moment arms calculated in the present study were activity dependent. A comparison between \textit{in vivo} activities performed by the same subject reveals RMSD averaged across subjects up to 8.2 mm and \( r \) values down to 0.19. The hamstrings muscles, particularly the short and long heads of biceps femoris, were the most affected by changes in TF kinematics (Fig. 4.5). Moment arms changed because, at corresponding flexion angles, the tibia assumed a more anterior and more internally rotated position during the lunge (weight bearing). These changes in kinematics were not unexpected as the \textit{in vivo} kinematics measured in the present study upholds previously reported data that compared TF motion in weight bearing and non-weight bearing activities.
Moment arms estimated with subject and activity-specific kinematics also showed differences when compared to moment arms calculated with passive cadaveric motion. The largest difference in terms of RMSD was found for biceps femoris short and long head (8.8 mm and 9.0 mm on average, respectively), moreover correlation $r$ was negative for biceps femoris short head. Nonetheless, moment arms estimated with passive cadaveric knee motion from Walker et al. [251] closely resembled previously reported in vitro measurements [29] (dashed red line vs grey region in Fig. 4.4). Model estimates lay inside $\mu \pm \sigma$ areas from Buford et al. [29] throughout the analyzed flexion range ($0 - 120^\circ$) for most of the muscles and for the patellar tendon. Some disagreement was present in quadriceps moment arms estimated with the musculoskeletal model that exceeded those measured by Buford et al. [29] in early flexion. However, peak quadriceps moment arms similar to our predictions (40-50 mm) have been reported using either the tendon excursion method [53, 231] or the definition of moment arm (torque over force) [103]. Implementing the same type of motion used in the experiment (passive cadaveric motion) in the knee model isolates the dependence of moment arm estimates on muscle geometry. Therefore, the close resemblance of estimates with passive cadaveric motion (TFW and PFA) prescribed to the model and in vitro measurements provided confidence in the modeled muscle geometry (combination of attachment locations and wrapping surfaces). The moment arms estimated in this study represent the ‘effectiveness’ of muscles to generate torque at the knee [227]. However, given the results of this study, the torque generated by the muscles at the joint can be substantially different depending on the knee kinematics implemented in the musculoskeletal model. For example, since average biceps femoris moment arms estimated with in vivo knee extension kinematics peak at 25.3 and 30.1 mm, calculated RMSD (8.8 mm and 9.0 mm) represent 30% of
the peak. A 30% increase in moment arm during a musculoskeletal simulation to estimates muscle force from inverse dynamics joint torques would approximately produce a 30% decrease in the force prediction for that same muscle. Consequently, substantial changes in TF contact loads would also be estimated. Therefore, simplifying knee kinematics by using normative data, such as provided by Walker et al. [251], will not provide the same estimates of moment arms and muscle forces as subject-specific knee kinematics. Similarly, depending on the kinematic assumptions implemented in the knee model, in a forward dynamics simulation the same muscle activations will produce different muscle forces and moments at the knee, producing different motions of the model. The degrees-of-freedom that most influenced the moment arm estimates were superior/inferior translation, internal/external rotation, and anterior/posterior translation. This finding is relevant because it provides the information needed to focus on estimating the motion of the knee that is crucial to muscle force estimation. While internal/external rotation of the knee may be measured in vivo with conventional motion capture methods and incorporated into the model knee [89], capturing activity-specific differences in knee translations is more challenging without techniques such as stereo radiography. However, it may be possible to use a principal component approach to leverage relationships between specimen-specific TF/PF kinematics and anatomy [229]. Given subject-specific geometries of femur and tibia, such a technique may allow inference of TF translations in anterior/posterior and superior/inferior directions for a given knee flexion task. The results of the present work suggest that, although muscle geometry and path in a model should be validated by comparing moment arms estimated with passive motion of the knee to cadaveric measurements, more accurate muscle force estimates for in vivo activities would be achieved if subject- and activity-specific knee kinematics were implemented.
A previous study has shown similar dependencies of moment arm estimates on joint kinematics. Arnold et al. [14] compared estimates from an MRI-based specimen-specific musculoskeletal model to in vitro measurements from the same specimen. The study showed that using specimen-specific kinematics measured during the experiment provided substantially more accurate moment arm estimates (see Fig. 8 in Arnold et al. [14]). There were two primary limitations associated with this investigation. Muscle attachments in the musculoskeletal models were not subject-specific. Moment arms mainly depend on muscle path (attachment sites, via points and wrapping surfaces). Average muscle attachment locations from cadaveric investigations were used [52]. Prior work has shown that variations in muscle geometry can affect estimates of muscle force and joint load [177]. This uncertainty in muscle geometry may propagate to moment arm estimates [189]. To address this limitation a Monte Carlo analysis that modeled the uncertainty in muscle attachment location was performed for each subject and activity (a total of 14 Monte Carlo simulations were performed). Although large 5–95% confidence bounds were predicted for each muscle, RMSD and $r$ between activities averaged across Monte Carlo instances agreed with baseline results (Fig. 4.5). The explanation for this result is that perturbing attachment locations generates a shift in moment arm estimates, but the same shift happens for both the knee extension and lunge activities. Therefore, the difference between activities for each instance remains similar to the baseline difference. However, this limitation does not allow an accurate estimate of inter-subject variability because the 5–95% confidence bounds calculated for each muscle were comparable in size to the inter-subject variability estimated with baseline muscle geometry. Therefore, without knowing the actual location of muscle attachment sites, an estimate of the moment arm variability among subjects would be biased by the geometry
chosen for the baseline model. The second limitation was that some uncertainty in the *in vivo* kinematics due to tracking errors may be present. If the errors were comparable in scale to RMSD between moment arm predictions, the results showing the effect of knee kinematics on moment arms would be invalidated. However, the accuracy of the stereo radiography system was previously validated [127] and the translational and rotational tracking errors are $0.15 \pm 0.13$ mm and $0.41^\circ \pm 0.30^\circ$. Therefore, the authors have confidence that differences observed in moment arms due to different kinematics were not an artifact of tracking errors. In conclusion, the influence of *in vivo* subject- and activity-specific knee kinematics measured with a stereo radiography system on muscle moment arms was evaluated. The comparison with moment arms evaluated with kinematics from *in vitro* measurements of knee passive motion revealed that differences in superior/inferior translation, internal/external rotation and anterior/posterior translation had a relevant impact on moment arm trends throughout a $0 - 120^\circ$ flexion range. In addition, intra-subject activity-specific kinematics also influenced moment arms estimates. Musculoskeletal models that lack subject-specific knee kinematics may over or under estimate muscle forces utilized by the subject.
The coordinate system of the femur was defined for all the subjects by fitting a cylinder to the medial and lateral posterior condyles [241]. The origin was placed at the midpoint of the centerline of the cylinder. The medial/lateral axis was defined as the axial direction of the cylinder, whereas the superior/inferior axis was aligned to the posterior line of the femur. The anterior-posterior axis was defined according to the right-handed coordinate system notation. The femoral coordinate system was assigned to tibia and patella at full extension during the knee extension activity.
Figure 4.2: Workflow of the study. TF and PF kinematics from seven subjects performing seated non-weight bearing knee extension and single-leg lunge activities were collected using a high-speed stereo radiography system. Subject-specific and activity-specific knee kinematics were incorporated in a musculoskeletal model in OpenSim. TF and PF kinematics from the model presented by Arnold et al. [15] were also incorporated in the same musculoskeletal model. Moment arms were estimated in OpenSim and compared between subjects and activities. Estimates were also compared to moment arms measured in vitro and estimated with knee passive motion (kinematics from Arnold et al. [15]). Monte Carlo analyses in which uncertainty in muscle attachment locations was modeled as normal distributions with a $5 \text{ mm} \sigma$ were performed to evaluate the robustness of the results. Knee extension moment arms were also estimated with models in which each TF degree-of-freedom was replaced (one at a time) with corresponding passive motion to identify the degree-of-freedom that had the greatest impact on moment arms.
\[ \begin{align*}
\text{Tibiofemoral Kinematics} \\
\text{Flex(-)/Ext(+)} \text{ [deg]} & & \text{Int(+)/Ext(-) Rot [deg]} & & \text{Var(+)/Val(-)} \text{ [deg]} \\
-120 & & 0 & & -6 \\
-100 & & 5 \\
-80 & & 10 \\
-60 & & 15 \\
-40 & & 20 \\
-20 & & 25 \\
0 & & 30 \\
0 20 40 60 80 100 & & 0 20 40 60 80 100 & & 0 20 40 60 80 100 \end{align*} \]

\[ \begin{align*}
\text{Flexion Angle [deg]} & & \text{Lat(+)/Med(-) Transl [mm]} & & \text{Sup(+)/Inf(-) Transl [mm]} & & \text{Ant(+)/Pos(-) Transl [mm]} \\
0 20 40 60 80 100 & & -8 & & -20 & & -30 \\
0 20 40 60 80 100 & & 0 & & 0 & & 0 \\
0 20 40 60 80 100 & & 2 & & 5 & & 2 \\
0 20 40 60 80 100 & & 4 & & 10 & & 5 \\
0 20 40 60 80 100 & & 6 & & 15 & & 3 \\
0 20 40 60 80 100 & & 8 & & 20 & & 3 \\
0 20 40 60 80 100 & & 10 & & 25 & & 5 \\
0 20 40 60 80 100 & & 12 & & 30 & & 6 \\
\end{align*} \]

\[ \begin{align*}
\text{Knee ext} & & \pm \sigma \text{ Knee ext} & & \mu \text{ Lunge} & & \mu \pm \sigma \text{ Lunge} & & \text{Walker 1988} \\
\end{align*} \]

\[ \begin{align*}
\text{Figure 4.3:} & \quad \mu \pm \sigma \text{ TF and PF Kinematics from in vivo measurements for knee extension (dark grey area) and lunge (light grey area) as function of knee flexion, compared to passive cadaveric knee kinematics (red dashed line: TFW and PFA, used in model presented in Arnold et al. [15]).} \\
& \quad \mu \pm \sigma \text{ in vivo kinematics was estimated only within the minimum flexion range common to all the subjects. Statistically significant differences (} p < 0.05 \text{) between knee extension and lunge kinematics were observed for TF internal/external rotation, anterior/posterior translation and PF flexion/extension (*). Differences between in vivo motion and kinematics used in previous models are in TF superior/inferior and anterior/posterior translations, and in PF anterior/posterior translation.} \\
\end{align*} \]
Figure 4.4: Moment Arms estimated with *in vivo* kinematics and passive motion from Arnold et al. [15] compared to *in vitro* measurements [29]. Blue and green areas represent $\mu \pm \sigma$ moment arms across subjects for knee extension and lunge activities, respectively. Differences between moment arms estimated with *in vivo* kinematics and with passive motion can be seen in most of the muscles. Statistically significant differences ($p < 0.05$) between mean moment arms for knee extension and lunge are shown (*).
Figure 4.5: Average RMSD and correlation $r$ between moment arms of the same subject during knee extension and lunge activities. RMSD and $r$ values averaged across Monte Carlo instances in which muscle attachment locations were perturbed (light blue bars) were within 1.6% and 8.5% of baseline values for every muscle except $r$ for biceps femoris long head. Error bars represent one $\sigma$ calculated across Monte Carlo instances.
Figure 4.6: Examples of (a) Monte Carlo 5-95% confidence bounds; (c) degrees-of-freedom changed one at a time from knee extension to TFW [251] kinematics.
Figure 4.7: RMSD and $r$ between moment arms with knee extension kinematics and moment arms with models in which each degree-of-freedom was in turn changed to the corresponding degree-of-freedom from TFW [251] kinematics. Large RMSD and small $r$ indicate that the altered degree-of-freedom has a large influence on the difference between moment arms estimated for different kinematics. Error bars represent one $\sigma$ calculated across subjects. The degree-of-freedom that had the greatest impact on moment arms were superior/inferior translation for all the muscles, internal/external rotation for the hamstrings, and anterior/posterior translation for gastrocnemius and patellar tendon.
Chapter 5

Subject-specific modeling of muscle force and knee contact in total knee arthroplasty

5.1 Abstract

Understanding the mechanical loading environment and resulting joint mechanics for activities of daily living in TKA is essential to continuous improvement in implant design. While survivorship of these devices is good, a substantial number of patients report dissatisfaction with the outcome of their procedure. Knowledge of in vivo kinematics and joint loading will enable improvement in pre-clinical assessment and refinement of implant geometry. The purpose of this investigation was to describe the mechanics of total knee arthroplasty during a variety of activities of daily living. Estimates of muscle forces, tibial contact load, location, and pressure distribution was performed through a combination of mobile fluoroscopy data collection,
musculoskeletal modeling and finite element simulation. For the activities evaluated, joint compressive load was greatest during walking down stairs, however the highest contact pressure occurred during chair rise/sit. The joint contact moment in the frontal plane was mainly varus for gait and walking down stairs, while it was valgus during chair rise/sit. Excursion of the center of pressure on the tibial component was similar during each activity and between the medial and lateral sides. The main determinants of center of pressure location were internal-external rotation, joint load, and tibial insert conformity.

5.2 Introduction

Pre-clinical evaluation of prospective TKA implants is critical to improve component design and predict in vivo performance. Although survivorship is high for most current knee replacements [144], a significant percentage of patients still report dissatisfaction with their procedure [179] and the revision rate for TKA is currently the highest of all joint replacements [94]. About 700,000 knee replacements are performed in the US each year (2011) and this number is projected to grow to roughly 3.5 million procedures by 2030 [143]. As the number of TKA grows, there is a concomitant increase in the number of TKA revision surgeries. Common causes of revision surgery are instability and polyethylene wear, with established links to aseptic loosening and osteolysis [94]. Complications due to wear and instability are dependent on relative motion and local contact between articulating surfaces. Both joint stability and polyethylene wear are determined by a combination of joint load and TF implant conformity [149, 170]. These variables are influenced by characteristics that are specific to each patient, namely implant design, component alignment [38, 82],
passive soft-tissue balance [130], active muscle forces [161], and movement strategies [112]. Taken together these characteristics suggest that the TF contact mechanics of the implanted knee are likely subject and activity dependent, yet few studies have shown this in vivo.

in vivo TKA component contact mechanics are difficult to measure, particularly for common activities of daily living. As a result, in vivo contact location has been estimated using a variety of methods that combine measurement of subject kinematics with the geometry of knee. For example, some researchers have relied on calculation of the ‘lowest point’ (LP) from measured knee kinematics using dynamic or static radiography [33, 218, 219]. LP was used in these studies as a surrogate measure of tibial contact and assumes that contact between the tibial and femoral components occurs at the point of the femoral geometry that is closest to the tibial tray. However, LP estimates do not include the conforming geometry of the polyethylene tibial insert [34], which is normally not visible in x-ray. As a result, others have used dynamic radiography combined with knowledge of knee geometry to estimate contact location as the centroid of the intersection area between the two articulating surfaces [33, 152, 153]. However, joint load correspondence to the estimated contact location is needed to quantify contact pressure on the tibial insert, which is an important determinant of polyethylene wear. Matched contact location and joint load require combined radiography and force-sensing telemetric implants [59, 87], and rarely have these been combined to investigate both contact loading and contact mechanics [219, 248]. Research subjects with telemetric implants are very rare (these studies always include limited numbers of subjects) and do not necessarily exhibit the knee mechanics of patients with other widely available knee components. As an alternative, computational modeling can be used to estimate joint load and, when
combined with radiography measurements, estimate contact center of pressure (CP) on TKA implants [34, 83, 86, 266].

Knee function following TKA is a multiscale problem because joint level complications that influence survivorship and stability interact with strength and movement adaptations at the limb and whole-body scales. Following TKA, the great majority of patients experience substantially reduced pain along with increased ability to perform daily activities [42]. Even so, patients often exhibit adaptations in their movement patterns and kinetics during basic functional tasks such as walking and sit-to-stand even one year after surgery [173, 233]. In addition, patients after TKA have reported limitations in other functional tasks such as navigating stairs and pivoting and in more advanced tasks such as kneeling and deep squats [37, 185]. These adaptations have been attributed to quadriceps strength and activation deficits, and may be enacted to enhance stability in the reconstructed knee [185]. Thus there is a continuing need for evaluations of TKA mechanics that link the knee and whole-body scales through integration of patient-specific measurements and simulation.

The purpose of this investigation was to quantify joint contact mechanics in patients with TKA performing varied activities of daily living. This was achieved by driving a finite element model of the implants with kinematics measured from a mobile fluoroscopy system and joint loads estimated with a whole-body musculoskeletal model [84]. The finite element model was used to estimate tibial contact load, location and pressure.
5.3 Methods

In overview, six patients with TKA (age 72±8, 179±3 cm, 77.4±5.5 kg) performed three activities (walking on level, down stairs and chair rising) at self-selected speed while video motion capture and ground force data were collected simultaneously with moving fluoroscopy of the involved knee. All the patients were implanted with the same cruciate retaining TKA design (Sigma®, DePuy Synthes). All experimental data collection occurred at the Institute for Biomechanics, ETH Zurich, Switzerland. Each subject signed an informed consent form, in accordance with the research ethics committee of the ETH Zurich. These data were used as input to a musculoskeletal simulation to estimate muscle and joint loads using OpenSim. In turn, estimated joint forces and knee kinematics from fluoroscopy were applied to a finite element model of the subject’s implant to provide TF contact pressure, location, and force (Fig. 5.1).

Marker-based motion capture data were collected by means of a 12 camera video photogrammetric system (Vicon MX system, Oxford Metrics Group, UK). Simultaneous ground forces were recorded using six force plates (Kistler Instrumentation, Switzerland) mounted flush with the floor of the movement analysis laboratory. Two additional force plates were installed in a staircase for the measurement of the stair descent activity. The staircase consisted of a platform at the top and two descending stairs embedded force plates. Single-plane fluoroscopy images were collected with a modified BV Pulsera (Philips Medical Systems, Switzerland) with a field of view of 30.5 cm, pulsed mode of 25 Hz, 8 ms radiation time, 1 ms shutter time and an image resolution of 1000 x 1000 pixels with a grayscale resolution of 12 bit [84]. Fluoroscopy was collected using the moving fluoroscope (Institute for Biomechanics, ETH Zurich,
Switzerland) that maintained the involved knee in the image capture area during the activities [30, 84]. Registration of the implant components was performed by means of matching the CAD-models of the subject’s components to the fluoroscopic images, providing the instantaneous relative location between femoral component and tibial tray. Custom software was used to create a digital-reconstructed radiograph (DRR) of the implants, and then locate its pose in space by sequentially comparing the DRR to the actual x-ray fluoroscopic image. The initial pose was manually adjusted and then refined by means of a least-squares optimization algorithm that adjusted the pose to minimize the difference between gradient magnitudes and gray values in the DRR and fluoroscopic image [30]. Uncertainty of the implant’s pose reconstruction was assessed in a previous study [84]. A total of 63 acquisitions of x-ray images of a similar TKA implant (balanSys®, Mathys) in predefined positions were performed. The positioning of the implant was obtained by means of a three dimensional positioning system composed of an industrial cross table (0.01 mm resolution) and a marking unit (0.01 mm resolution). The pose of both components was reconstructed using the CAD-models of the implant and translational and rotational errors were estimated. Root mean square errors (RMSE) across the 63 measurements can be found in Tab. 5.1 [84].

The musculoskeletal used for the study presented in Chapter 3 was used to estimate muscle and joint loading in OpenSim [51]. The model consisted of 23 degrees-of-freedom and 92 musculotendon units modeled as Hill-type muscles [237]. The anthropometry of the model was scaled to the six subjects with scaling factors obtained by calculating the ratios of the distances between recorded marker trajectories during a static trial and virtual marker locations on the baseline model. The lower limbs included a ball-and-socket hip joint and a revolute ankle joint. In the current
study the knee joint was modified to implement a coupled mechanism (1 degree-of-
freedom) with translations of the tibia and patella prescribed by the knee flexion
angle [56]. Muscle forces were represented by a contractile element with force-length
and force-velocity properties in series with an elastic tendon. The quadriceps geom-
etry of the original OpenSim model was refined to insert on the tibial tubercle with
via points placed on the superior and inferior poles of the patella (Fig. 5.1) [56]. This
enabled resultant quadriceps forces to be properly included in the calculation of TF
contact forces in OpenSim. Via point locations of the quadriceps were adjusted to
guarantee that the moment arm of the musculotendon units replicated measurements
of patellar tendon moment arm [141]. Finally, the path of the two gastrocnemius
musculotendon units (medialis and lateralis) was modified to better match moment
arm measurements from experiment [15, 29].

The marker trajectories and ground forces recorded from the subjects were used as
input to musculoskeletal simulations in OpenSim to estimate muscle and joint loads.
Subject kinematics were calculated from the marker trajectories using OpenSim. To
achieve the pose of the subject, the recorded marker locations are matched to virtual
markers on the kinematic model of the subject. This matching technique is performed
by solving a weighted least squares problem that minimizes marker errors at each
time frame. Net forces and moments at the joints were obtained through the inverse
dynamics solution. Because the number of muscles exceeds the degrees-of-freedom of
the model, muscle forces for each activity were estimated by static optimization that
minimized the summed muscle activations squared at each time frame [12]. With the
muscle forces as input, reaction forces and moments at the knee were calculated in
the coordinate system of the implanted tibia. Resultant TF loads were compared to
in vivo measurements from other patients with instrumented implants for validation [19].

The contact location, force and pressure on the tibial insert were calculated by applying the estimated joint loads and measured kinematics to a finite element model of each subject’s TKA implant. A finite element model of the implant (femoral component, tibial insert and tibial tray) was developed in Abaqus/Explicit (Abaqus, Dassault Systèmes, Vélizy-Villacoublay, France) for each subject. The femoral components and the tibial tray were modeled with rigid triangular elements, while the tibial insert was modeled with deformable eight-noded hexahedral elements (Fig. 5.1). A previously validated plasticity model was used for the elements representing the polyethylene tibial insert [109]. The coefficient of friction between metal and polyethylene was set to 0.04 [97]. The tibial component was fixed to the global coordinate system. Motion and loads were applied to the femoral component along and about the axes of the Grood and Suntay definition [102]. According to this notation the medio/lateral axis is directed relative to the orientation of the femur, the superior/inferior axis is directed relative to the orientation of the tibia and the antero/posterior axis is a floating axis perpendicular to both the medio/lateral and superior/inferior axes. Flexion/extension, antero/posterior translation and internal/external rotation were driven by the kinematics measured from fluoroscopy. Superior/inferior translation was left free and the TF reaction force from the musculoskeletal model calculations along the same direction was applied [83, 86]. Due to the reduced out-of-plane accuracy of single-plane fluoroscopy [262], varus/valgus rotation and medio/lateral translation were left free [86]. Instead, the varus/valgus reaction moment estimated by the musculoskeletal model was applied about
the antero/posterior axis, and relative medio/lateral position was determined by the
applied boundary conditions and component geometry [86].

A total of 18 simulations were performed: three tasks for each of the six sub-
jects. Muscle forces, joint loads, and TF CP and contact pressure were extracted for
each simulation. The ratio between maximum medial and total pressures was also
calculated as

\[
\frac{P_{med}}{P_{med} + P_{lat}}
\]  

(5.1)

where \( P_{med} \) and \( P_{lat} \) are the maximum medial and lateral pressure respectively
(Eq. 1). In addition, the locations of the geometric LP of the femoral component
were calculated relative to the tibial insert for comparison with the location of the
center of pressure. LP results have been frequently used as a surrogate measurement
of CP. LP are defined as the most inferior points on the medial and lateral femoral
condyles with respect to the superior-inferior axis of the tibia at each instant of
time [18]. To evaluate the role of internal/external rotation and internal/external
alignment of the implant on CP location, the angle between the line connecting CP
on medial and lateral plateaus and the medio/lateral line of the tibial component
(CP angle) was calculated. Internal/external TF alignment was identified as the
internal/external angle in correspondence to full extension or the smallest flexion
angle during chair rise/sit (standing phase between rising and sitting). This variable
was compared to the maximum CP angle in each simulation to evaluate its influ-
ence on CP location. Finally, a sensitivity analysis was performed to evaluate the
variability in contact mechanics due to uncertainty in the kinematics measured from
fluoroscopy. Kinematic profiles were shifted by ±0.5 mm in antero/posterior and
±0.5° in internal/external in isolation [86] during stair descent for three subjects that showed substantial inter-subject differences in TF internal/external alignment and CP location, and contact results were compared. RMSE for maximum contact pressure and CP location between baseline and perturbed simulations were calculated. Unpaired samples Student’s t-tests were used to verify if inter-subject differences in CP centroid locations and antero/posterior excursions in antero/posterior directions between subjects were evident despite kinematic uncertainty. CP centroid locations and antero/posterior excursions on medial and lateral sides from the five simulations for each subject (1 baseline + 4 perturbations) were compared to the same results for the other two analyzed subjects. In the results, time was normalized with each activity progressing from 0 to 100%. The gait simulations include the swing phase and begin and end with heel-strike. Similarly, the stair decent activity begins with heel-strike of the involved side on the first descending stair and ends just prior to the next heel-strike of the same foot on the ground. The chair rise/sit simulations begin when the subjects leave the seat, proceed through stance, and end when the subject descends and touches the seat.

5.4 Results

Muscle forces were highest during the chair rise/sit activity. The average peak quadriceps force occurred when the subjects left the chair and was 2172 N (286 %BW) (Fig. 5.2). High quadriceps forces were also estimated for the stair descent at contralateral heel-strike (average peak 256 %BW). Muscle forces during gait were much lower (average peak 93 %BW).
Joint compressive force was highest during walking down stairs (340 %BW), followed by the chair rise/sit (330 %BW) (Fig. 5.3). The chair rise/sit had the greatest range in joint force (excluding swing phase for gait and walking down stairs) from a high of 330 %BW as the subject left the chair, to a minimum of 79 %BW during the moment of standing before the subject moved back into the chair. During level walking, average peak joint force occurred late in stance (225 %BW) as some of the subjects appeared to adopt a gait strategy that avoided early stance phase extensor moment.

Knee kinematics as measured by the fluoroscopy system demonstrated consistent trends across subjects that were particular to each activity. The chair rise/sit produced the highest amount of knee flexion (average peak 81.0°) across all subjects (Fig. 5.4). A noticeable hyperextension of the femoral component was apparent at heel-strike (average peak −11.8° during gait). The chair rise/sit elicited anterior position of the femur during the rising and descending phases of the activity. The posterior position of the femoral component relative to the tibial component was similar between stair descent and gait, only moving posteriorly during swing (Fig. 5.4). The pattern of internal/external rotation of the femur relative to the tibia was unique to each activity. External rotation was present as the subjects entered and returned to the seated position in the chair rise/sit (Fig. 5.4). Gait showed only small rotations during all phases of the gait cycle, whilst stair descent revealed a distinct external rotation as the foot left the step and began swing. Moreover, although the pattern of internal/external rotation is generally consistent among the subjects, each showed a subject-specific TF internal/external alignment at full extension. Three subjects possessed an internal rotation of the femoral component (4.2°, 2.7° and 2.5°), two subjects possessed an external rotation (−1.9° and −2.6°), and one subject was neu-
neutral (−0.1°). These different alignments between patients remained mostly constant at every flexion angle during each activity they performed. For example, two patients that showed respectively 2° of internal rotation and 2° of external rotation at full extension during chair rise/sit, showed 6 and 10° of external rotation at the highest flexion angle, keeping an almost constant alignment difference of 4°. Subjects with an internal alignment of the femoral component at full extension (3.2° on average) showed lower maximum CP angle (2.4° on average) in comparison with subjects with an external femoral alignment (−2.3° on average) that presented large maximum CP angles (16.9° on average).

During all activities, motion of the CP on the tibial component was primarily in the anterior-posterior direction and similar on the medial and lateral sides (Fig. 5.5). Excluding the swing phase, motion of the CP was greatest during gait (average 18.7 mm antero/posterior on the lateral side) and least during the chair rise (average 11.7 mm antero/posterior on the lateral side) (Tab. 5.2). Motion of the CP in the medio/lateral direction was less than 7.5 mm on average across all activities. Average peak antero/posterior motion of LP was 5.8 mm on the medial side, which was much less than motion of the CP (Fig. 5.6).

Antero/posterior joint load estimated by the finite element models was greatest during stair descending in the posterior direction with an average peak of 19.0 %BW (Fig. 5.7). Internal/external joint moment was highest in gait and stair descending with an average peak of 0.6 %BWm in internal rotation (Fig. 5.7). Maximum estimated contact pressure showed a similar pattern to the TF contact force applied along the superior/inferior axis of the tibia (Fig. 5.8). Its peaks occurred when the applied joint reaction force was highest (contralateral heel-strike for gait and stair descent and during the exit and entrance to the chair for the chair rise/sit activity).
The highest contact pressure occurred during the chair rise/sit activity (average peak 26.8 MPa) on the lateral plateau.

The ratio between maximum medial and total pressures was generally higher than 50% during gait and stair descent and it was highest during gait with an average peak of 68% (Fig. 5.8). Conversely, pressure on the lateral side was generally higher than on the medial side during chair rise/sit, with a minimum $M/(M + L)$ ratio of 41%. During walking down stairs a higher contact pressure was estimated at the second contact force peak in comparison to the first peak although similar compressive forces were applied. This happened at higher flexion angles because a reduction in articulating femoral surface geometry causes a decrease of the contact area, and a consequent increase of contact pressure.

No significant differences ($p > 0.1$) were found when antero/posterior excursions of CP on the tibial insert for different activities were compared with paired sample t-tests. In addition, no significant differences ($p > 0.1$) were found when comparing antero/posterior ranges on the medial and lateral plateaus for each activity.

Results from the sensitivity analysis showed that RMSE for CP location and maximum contact pressure were on average 0.4 mm and 2.1 MPa, respectively. In addition, there were significant differences ($p < 0.05$) in CP centroid location and CP excursions in the antero/posterior direction between the three analyzed subjects in 11 of the 12 comparisons (Fig. 5.9). RMSE for antero/posterior and internal/external contact loads were on average 50 N and 0.70 Nm.
5.5 Discussion

A method to estimate contact mechanics in a TKA that links whole body and joint-level scales was developed and used to examine knee joint loading and contact mechanics in TKA patients performing multiple activities of daily living. Subject-specific kinematic and ground force measurements were used as input to a musculoskeletal model to calculate TF joint reaction force at the implanted knee. Combining these joint load data with precise knee kinematics from fluoroscopy, a finite element model of the implant components was used to estimate subject-specific contact mechanics for three activities. Joint load was greatest during contralateral heel-strike walking down stairs, while contact pressure was greatest during the chair rise/sit activity as the subjects exited and entered the seat. However, the resultant excursion of the CP on the tibial component was similar during each activity and between the medial and lateral sides. The main determinants of CP location were internal/external rotation and tibial insert conformity, as indicated by a high correlation between internal/external rotation of the joint and CP angle (0.82 on average), and the significant difference between CP and LP due to the anterior and posterior slopes of the insert. Inter-subject differences in CP location were partly explained by corresponding differences in internal/external TF alignment. In fact, external alignment of the femur with respect to the tibia at full extension resulted in larger CP angles. In all cases, LP calculations underestimated movement of the CP.

There were a number of limitations associated with this investigation. First of all, static optimization was used to estimate muscle forces of the subjects. Although this method is reliable for healthy subjects during gait (muscle forces were comparable in pattern and magnitude to previous reports of muscle forces during walking
[12, 210]), no studies have evaluated its accuracy with TKA subjects performing activities such as walking down stairs and chair rising. Notably, static optimization estimated low quadriceps forces at weight acceptance in patients analyzed in this study that adopted movement strategies with reduced extensor demand relative to their normal limb. In addition, good agreement between measurements of joint loads and our estimates provided confidence that the muscle forces were reasonable. Peak contact forces measured with instrumented implants are between 180 and 280 %BW during walking, and approximately 350 %BW when descending stairs [19, 87, 145], which agrees with our average peaks of 225 and 340 %BW during gait and walking down stairs, respectively. Similarly, studies that calculate contact force by means of musculoskeletal models report peaks of 200-400 %BW during level walking [210, 225, 236]. Only during chair rise/sit did our model appear to overestimate joint reactions when the subjects entered and exited the chair. Studies using instrumented implants report peak forces of 250-260 %BW during chair rise/sit, while we found 330 %BW in our study. Our varus/valgus moment estimates agree with data collected by means of instrumented implants, showing varus peaks during gait and walking down stairs, and valgus moments when the subjects are exiting and entering the chair.

A second limitation was that the analysis required two separate computational models (musculoskeletal whole-body and finite element knee) to estimate subject-specific CP. The two models utilized in this study address two different physical scales and present different complexities. The musculoskeletal model contained a simplified representation of the knee with only one degree-of-freedom. This simplification is often made in whole body models whose main goal is to estimate muscle forces, muscle moment arms or muscle length [12, 13, 210]. Since muscle forces are the
major contributor to joint forces, the joint forces estimated by the musculoskeletal model were applied to detailed 6 degrees-of-freedom finite element models of the TKA implants. Our results for TF contact might be improved if muscle and joint forces, and contact mechanics were calculated in a single modeling framework.

A third limitation was that the finite element model of the TKA implants used in this study did not have the same geometry and boundary conditions utilized in previous validation studies [34, 83, 86, 109]. Provided contact on the medial and lateral condyles of the femoral component, the locations of the centers of pressure on the medial and lateral sides can be spatially determined by the flexion/extension, antero/posterior, internal/external and medio/lateral kinematics of the joint [34]. However, the validation study by Fregly et al. [86] found that estimation of joint contact best matched telemetric implant measurements by not prescribing medio/lateral and varus/valgus kinematics, and instead applying subject-specific superior/inferior and varus/valgus load. Following these recommendations, the finite element model of our study was kinematically driven in flexion/extension, internal/external and antero/-posterior, while medio/lateral remained free, and superior/inferior and varus/valgus loads were applied. In agreement with the conclusions of Fregly [86] and Fitzpatrick [83], the results of the sensitivity analysis showed that use of these boundary conditions provided reliable estimates of contact pressure and location when kinematic uncertainty was considered, whereas contact load estimates were more sensitive to kinematics errors.

A fourth limitation was that TF ligaments were not modeled in the finite element simulations. Therefore, contact pressure may have been slightly underestimated because the contribution of ligament force was not included in the overall joint load. This limitation may have also affected the medial-lateral contact pressure shown in
In addition, the estimated varus/valgus moment for one subject during gait was reduced with a 0.8 scale factor in order to prevent an unnatural lifting of the lateral femoral condyle that was not seen in the fluoroscopy kinematics. Despite this limitation, contact pressure ratios are consistent with results in the literature. In particular, Halder et al. [105] report an average medial load share of 73% at the first axial force peak of gait and 65% at the second axial peak among five patients with instrumented implants. Across individuals medial load share ranged from 55% to 85% at the first peak and 47% to 81% at the second peak. The results of our study present a consistent behavior with average medial pressure ratios of 58% and 67% in correspondence of the two compressive load peaks of the stance phase. To evaluate the impact of varus/valgus moment on contact mechanics, all the simulations were repeated without including the varus/valgus moment at the knee. When varus/-valgus moment was applied, the root mean square difference between medial and lateral contact pressure as a percent of maximum pressure was 28.5, 11.2, and 11.5% for gait, descending stairs and chair rise, respectively. With varus/valgus moment removed, these values dropped by more than half to 13.5, 5.2, and 4.5%. Therefore, contact pressure differences between medial and lateral sides of the insert were explained mainly by the varus/valgus moment estimated by the musculoskeletal model. Prior work has demonstrated that accurate antero/posterior and internal/external joint loads can be estimated from a combination of compressive force and relative TF pose, and are further improved with the inclusion of varus/valgus load [83, 86]. This was illustrated in the current study where estimates of antero/posterior and internal/external joint loads showed magnitudes very similar to instrumented implant data (Fig. 5.7). Temporal trends were similar for gait and for substantial portions of the other activities that were analyzed. Differences with telemetric data
in antero/posterior and internal/external joint loads can be explained by the different geometries between the implants of the patients in the telemetric studies and those measured here. While compressive and varus/valgus joint loads are mainly determined by ground reaction and muscle forces, the antero/posterior and internal/external load directions are strongly influenced by the components geometrical conformity [83, 86].

Excursion of the CP on the tibial insert was similar across activities. Student’s t-Tests were performed to compare the mean of antero/posterior ranges for different activities and no significant differences ($p > 0.1$) were found. This finding is consistent with that of Catani et al. who calculated CP locations with fluoroscopy imaging for 16 patients performing stair-climbing, chair rise/sit and step-up/down [33]. Their calculated antero/posterior excursions are consistent with ours presenting an average of 8.9 mm on the medial plateau and 15.6 mm on the lateral plateau. However, unlike Catani et al., we found no significant differences ($p > 0.1$) comparing antero/posterior ranges on the medial and lateral plateaus. While most other investigations found antero/posterior and medio/lateral ranges on the lateral plateau similar to our results, excursions on the medial plateau are shown to be smaller than those on the lateral side [153, 248]. This might be explained by differences in the articulating geometry of the tibial insert between the studies. Some TKA geometries are designed to elicit less translation on the medial side, similar to some results shown for the natural knee [152].

While excursion of the CP on the tibial component was similar across subjects, the CP location was dependent on subject specific internal/external rotation and by the geometrical conformity of the two articulating components. Partly for this reason, CP calculations did not correspond to the location of the LP. In particular,
the angle between the line that connects the estimated CP and the medio/lateral axis of the tibial component (see Fig. 5.6) closely followed the internal/external rotation of the knee. The angle of the CP line was most often magnified relative to the internal/external rotation angle of the knee because the contact occurred on the anterior or posterior upslope of the tibial insert.

Activities that generated greater joint load did not have lower excursion. This contradicts the common expectation that as axial joint load is increased the CP location is pushed closer to the LP of the insert by the conforming geometry of the implant [34]. For example, our results showed that the average antero/posterior motion of the CP on the lateral plateau was highest during gait, which is the activity with the lowest compressive load. However, the difference was not statistically significant because a high standard deviation among subjects was also observed.

The combination of experimental data and simulation used in this study is a significant contribution because it enables subject-specific estimation of TKA contact mechanics and its interactions with joint loads during activities of daily living, for a large population not restricted to patients with instrumented implants. Further understanding of interactions between activities, joint loading, and knee component mechanics may lead to improvements in pre-clinical testing of devices and, ultimately, in TKA survivorship and functional performance.
Table 5.1: RMSE of the registration algorithm for the two implant components. X and y directions are the horizontal and vertical direction of the x-ray image, respectively (approximately antero/posterior and superior/inferior axes of the joint for the performed activities), while z is the out-of-plane direction (approximately medio/lateral axis) [84].

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<th>Femoral component</th>
<th>Tibial component</th>
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<td><strong>Translations</strong> (mm)</td>
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<td>y</td>
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<td>z</td>
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<td><strong>Rotations</strong> (°)</td>
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<td>x</td>
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Figure 5.1: The workflow of this study consisted of three steps: First, motion capture data, ground reaction forces, and fluoroscopy images were collected for walking on level ground, walking down stairs, and chair rise/sit activities for six subjects (left figures). Knee joint loads were calculated from subject-specific simulations in OpenSim using a musculoskeletal model that was modified to transmit forces of the quadriceps through the patella to the tibia (center figures). Estimated knee loads were combined with knee kinematics measured using fluoroscopy and then applied to a finite element model of the subject’s TKA implants to determine contact mechanics (right figures).
Figure 5.2: Calculated muscle forces spanning the knee ($\mu \pm \sigma$) during level walking, walking down stairs, and chair rise/sit. Events for gait and stair descent: Heel-strike at 0% and 100% of cycle, toe-off at 60 – 65% of cycle, contralateral heel-strike at 50 – 55% of cycle.
Figure 5.3: Calculated TF joint compressive force and varus/valgus contact moment \((\mu \pm \sigma)\) during level walking, walking down stairs, and chair rise/sit. The varus/valgus moment is represented as positive (negative) when the femur generates a contact force on the lateral (medial) plateau of the insert. Values estimated in this study are compared to instrumented implant data of two representative patients from the literature. Events for gait and stair descent: Heel-strike at 0% and 100% of cycle, toe-off at 60 – 65% of cycle, contralateral heel-strike at 50 – 55% of cycle.
Figure 5.4: Femoral kinematics with respect to the tibia ($\mu \pm \sigma$). (a) flexion/extension, antero/posterior, and internal/external are measured from mobile single-plane fluoroscopy and used as input to the finite element models. (b) Varus/valgus, medio/lateral, and superior/inferior were not kinematically driven in the finite element models and result from applied loads and geometrical conformity of the implant. Events for gait and stair descent: Heel-strike at 0% and 100% of cycle, toe-off at 60 – 65% of cycle, contralateral heel-strike at 50 – 55% of cycle.
Figure 5.5: Sample TF CP for two of the subjects. The gray dots represent the CP location during swing phase. Both subjects #2 and #5 have right knee implants.
Figure 5.6: (a) Sample comparison of LP and CP estimates for gait of two subjects. The gray dots represent the CP location during swing phase. Both subjects #2 and #5 have right knee implants. (b) Line connecting the CPs (red) compared to the line connecting the lowest points of the femoral component (blue) at a given flexion angle. The CP angle (a) between the CP line (red) and the ML axis of the tibial component (dashed black) is also shown.
Figure 5.7: Estimates of antero/posterior contact force and internal/external contact moment ($\mu \pm \sigma$) acting on the tibia compared to reported measurements using instrumented implants. Events for gait and stair descent: Heel-strike at 0% and 100% of cycle, toe-off at 60 – 65% of cycle, contralateral heel-strike at 50 – 55% of cycle.
Figure 5.8: Top: Maximum and mean contact pressure on the medial and lateral sides ($\mu \pm \sigma$). Bottom: $M/(M+L)$ ratio of maximum contact pressures ($\mu \pm \sigma$). M and L are maximum medial and lateral contact pressures, respectively. The dashed vertical line in the two figures on the right divides the figure into chair exit (0-50% of the cycle) and chair entrance (50–100% of the cycle). Events for gait and stair descent: Heel-strike at 0% of stance cycle, toe-off at 100% of stance cycle, contralateral heel-strike at 80–85% of stance cycle.
Figure 5.9: Results for stair descent of a representative subject included in the sensitivity analysis. Left: CP estimates when antero/posterior measured kinematics was shifted of 0.5 mm in anterior (top) and posterior (bottom) direction. Right: Maximum contact pressure on the lateral side of the insert (top) and antero/posterior contact load (bottom) estimates with baseline and perturbed (± 0.5 mm) kinematics.
### Medio/Lateral Excursion (mm)

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Table 5.2: Excursion of the medial and lateral CP on the tibial component in the medio/lateral and antero/posterior directions. Excursions in gait and walking down stairs do not include swing phase.
Chapter 6

Closed loop muscle control of a finite element musculoskeletal model of the lower limb

6.1 Abstract

Musculoskeletal simulations can provide important insight into human body motion interaction with internal variables, such as muscle and contact forces, and can perform what if studies that predict the behavior of tissues in conditions not testable experimentally. The current state-of-the-art whole body musculoskeletal models include simplified joints (e.g. hinge at the knee) and lack sophisticated soft tissue representations for computational efficiency. More complex models can represent local tissue deformation (e.g. finite element models), but they rarely include whole body neuromuscular control, which is commonly estimated with computationally expensive optimization techniques. However, concurrent modeling across these two
scales is necessary to study the inevitable interdependence between them, such as the effect of tissue damage (e.g. osteoarthritis) on neuromotor strategies. The aim of this study was twofold: first, to develop a computationally inexpensive closed-loop muscle force prediction strategy based on PID controllers to track experimental joint motion with a finite element musculoskeletal model of the lower limb, including a deformable knee representation with 12 degrees-of-freedom; and second, to estimate the robustness of this strategy by simulating different motor activities (chair rise and gait) and changing the geometrical and laxity properties of the knee model. The control strategy was able to track experimental hip, knee, and ankle flexion/extension with RMSE below 1°, estimating muscle, contact and ligament forces in good agreement with previous results. The closed-loop control technique developed in study can be used with computationally expensive finite element musculoskeletal models as an alternative to optimization-based strategies to concurrently estimate muscle forces and tissue deformation.

6.2 Introduction

Musculoskeletal modeling and computer simulations can provide important insight into whole body motion and its interaction with the environment, which is of great interest in many fields of science such as medicine, ergonomics, sport and safety [191]. Moreover, musculoskeletal models can provide estimates of internal quantities not measurable in vivo (e.g. muscle, ligament, joint forces) [226] and be used to perform what if studies that predict the behavior of the human body in untested conditions [85, 224]. In many cases, these simulations use a multiscale approach to examine the essential interactions between movement, muscle forces, and tissue
inside the joints. The current state of the art in multiscale musculoskeletal modeling consists of a sequential approach: first, a rigid multibody musculoskeletal model at the whole body level is used to estimate muscle and joint loads, which are subsequently employed as boundary conditions for a second model at the organ or tissue level to estimate internal behavior and deformation (e.g. finite element representation of a single bone). Examples of this sequential approach are the prediction of ligament and contact forces in the natural knee [225], PF joint stress [21], stresses in a total shoulder arthroplasty [121], and bone adaptation in the femur [93].

This sequential approach is motivated by the need to solve the muscle redundancy problem. Optimization strategies that minimize objective functions based on energy expenditure or total muscle stress have often been used to select a single combination of muscle forces among the infinite possibilities that can produce the same body motion [11, 44]. Since optimization-based techniques require a large number of iterations and are highly computationally expensive, they are more rapidly performed with simplified representations of muscles and joints. However, the level of detail of rigid musculoskeletal models does not provide enough insight to analyze organ level mechanics and deformations, introducing the need for a second more detailed model of the joint and tissue of interest.

In a sequential scheme, parameters at the organ and tissue levels are not part of the muscle control strategy because of the model simplifications. In other words, using two separate simulation frameworks introduces a lack of consistency. For example, it was shown that knee contact forces contribute substantially to the net joint torques, even though whole body models with simplified joint definitions ignore contact forces between segments in the inverse dynamics calculation [252]. In principle, models that represent different scales are coupled, and should be solved
simultaneously [250]. Predicting muscle forces in a single multiscale framework can take into account the essential interdependent action of muscles with subject-specific tissues, such as ligament and cartilage [235]. However, the interaction between different scales has been rarely analyzed in a single framework. Attempts to improve the realism of rigid musculoskeletal models were performed including detailed knee joint representations with ligament and contact models for both the natural [150] and implanted case [239]. However, rigid musculoskeletal dynamic simulations do not enable fully deformable representations and complex material property definitions, unlike finite element models. Concurrent simulations that perform muscle optimization with tissue level finite element models have also been implemented [72, 106, 108, 247]. However, since optimization-based strategies usually require many evaluations of a complex and computationally expensive simulation, the significant increase in computational time is currently prohibitive [235].

Real-time automatic control is a potentially powerful alternative to optimization that may allow simulation using complex multiscale models with practical computational time [16]. More recently, strategies based on conventional proportional-integral-derivative (PID) controllers have been used in a finite element framework to predict muscle forces needed to track measured in vivo knee kinematics [81]. Beginning from an initial pose a PID controller minimizes the error between the measured value (e.g. knee flexion angle) and an input target profile. To do so, the controller generates an input to the model (e.g. muscle force) by scaling the kinematics error, its integral over time, and its rate of change with three gains (proportional, integral, and derivative gains, respectively). As applied by Fitzpatrick et al. [81], the PID control required a number of simulations to tune the gains and obtain stable performance satisfying low RMSE between model knee angle and target profile. Tuning
was accomplished with a 30-trial Latin Hypercube algorithm that sampled PID gains to find the optimal combination. In addition, the same set of PID gains was used to simulate the same activity for different loading conditions. However, only the quadriceps and hamstrings were included in the model and these were represented as linear actuators without physiological muscle properties.

The main purpose of this investigation was to evaluate a computationally inexpensive technique to estimate muscle forces that could be used in a multiscale finite element framework as an alternative to optimization-based strategies. For the evaluation, a multiscale finite element musculoskeletal model of the lower limb including a detailed deformable model of the knee and twenty musculotendon units with physiological properties was used to perform muscle driven forward-dynamics simulations of chair rise and walking. A strategy based on PID controllers was used to track experimental kinematics.

6.3 Methods

Marker-based motion capture and ground reaction forces were collected for two subjects (age 60 and 59, 174.0 and 177.2 cm, 74.8 and 74.4 kg) during chair rise and gait activities, respectively. This study was approved by the University of Denver Institutional Review Board and all participants provided informed consent. In addition, dynamic stereo radiographic images were collected at the knee using two matching custom radiography systems (HSSR) with 40 cm image intensifiers positioned at a relative angle of 60°. High-speed, high-definition cameras interfaced with the image intensifiers captured the motion at 100 frames/sec in a ‘low-dose pulsed’ x-ray mode [127]. Tracking of bone motion was performed by optimizing the position
of bone geometry models to the two-dimensional stereo radiographs using Autoscoper (XROMM, Brown University, RI) and relative TF and PF positions were obtained [133, 172]. An inverse kinematics analysis was performed in OpenSim on a rigid body model with the same segment dimensions and joint definitions of the finite element model. Joint motion at the ankle and hip was obtained from experimental marker location, whereas the twelve degrees-of-freedom at the knee were driven from HSSR measurements, after they were synchronized to marker location. The kinematics of the subjects were reduced to 10-46% of the gait cycle, and to a portion of chair rise between 20 and 80° of knee flexion, according to the images available from HSSR images.

A finite element musculoskeletal model of the lower limb was created in Abaqus/Explicit (Abaqus, Dassault Systèmes, Vélizy-Villacoublay, France) [124] (Fig. 6.1). The model included a 1 degree-of-freedom hinge-joint at the ankle, a 3 degrees-of-freedom ball-joint at the hip, and a 12 degrees-of-freedom joint at the knee. The knee joint included specimen-specific bone and cartilage geometries (femur, tibia and patella), and TF and PF ligaments calibrated against specimen-specific in vitro laxity and knee extension tests [7, 115]. Two lower limb models were created using calibrated specimen-specific knee models (S1 and S2 in Harris et al.). These two knees were chosen because their laxity behavior presented in Harris et al. showed substantial intersubject variability. Twenty musculotendon units of the lower extremity were represented as 1D connector elements. Some muscles were modeled with via points to model a non-linear path, while other muscles could wrap around wrapping surfaces at the knee, bone and cartilage geometries. Specifically, the following muscles were included in the model: soleus, gastrocnemius (medialis and lateralis), tibialis anterioris, vastus medialis (3 fiber boundles), vastus intermedius, vastus lateralis (2 fiber

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boundles), rectus femoris, semimembranosus, semitendinosus, biceps femoris short and long head, gluteus maximus (3 fiber boundles), iliacus and psoas. Each muscu-
lotendon unit was modeled as a Hill-type muscle with force-length and force-velocity
properties. Hill-type model parameters were calibrated using maximum isometric
extension and flexion torques recorded from healthy subjects [124].

A closed-loop scheme was defined to track experimental motion (Fig. 6.2): three
PID controllers were used to track ankle flexion/extension and hip flexion/extension
from inverse kinematics, and knee flexion/extension from HSSR. The error between
target kinematics and model kinematics was used as input to the PID controllers
to produce muscle activations (see below). The muscles present in the model were
separated into 6 groups according to their functions: flexors and extensors of ankle,
knee and hip. Biarticular muscles belonged to two groups according to their function
in the lower limb.

Simulation of each activity was performed in two steps. A first control step found
the activations necessary to hold the model in the initial position of either gait or
chair rise with the corresponding ground reaction forces applied at the foot. This
first step provided initial activations for a second control step, in which a profile of
ground reaction forces was applied to the foot throughout the activity and real-time
muscle activations were calculated to track the subject kinematic profiles at the hip,
knee, and ankle. Each PID controlled the motion of one joint providing the change in
activation Δa_g(t) necessary to the muscle group g to track the reference kinematics
of that joint:

\[
a_m(t) = a_m(0) + \Delta a_g(t) = k^p_g \cdot e_g(t) + k^i_g \cdot \int_{t_0}^{t} e_g(t) dt + k^d_g \cdot \frac{de_g(t)}{dt}
\]

(6.1)
where \((k_g^p, k_g^i, k_g^d)\) is the triplet of PID gains (proportional, integral, and derivative, respectively) for the joint angle controlled by muscle group \(g\), and \(e_g(t)\) is the error between model joint angle and target profile. Since PID controllers introduce an inevitable delay between target kinematics and produced muscle forces, the excitation-activation dynamics of skeletal muscles that accounts for the shift in time between electrical signal and actual muscle contraction was not modeled to avoid additional delay in the kinematics tracking.

The change in activation was positive for agonist muscles (e.g. knee flexors, since flexion was considered positive) and negative for the antagonist muscles (e.g. knee extensors). In addition, a recruitment strategy that privileges the activation of muscles with larger physiological cross sectional area (PCSA) was employed to reduce the muscle effort to perform the two activities:

\[
\begin{align*}
    a_m(t) &= a_m(t_0) + \Delta a_n(t) = a_m(t_0) + \frac{n_g \cdot PCSA_m}{\sum_{i=1}^{n_g} PCSA_i} \cdot \Delta a_g(t) \\
    0.02 < a_m(t) < 1.00
\end{align*}
\] (6.2)

where \(a_m(t)\) is the activation of muscle \(m\) at time \(t\), \(\Delta a_g(t)\) is the output of the controller for muscle group \(g\), \(a_m(t_0)\) is the initial activation of muscle \(m\) calculated in the first control step, \(n_g\) is the number of muscles belonging to group \(g\), \(PCSA_m\) is the PCSA of muscle \(m\). Since biarticular muscles belong to two different groups and can generate motion at two different joints, their activation accounted for the outputs from the two corresponding PIDs:

\[
\begin{align*}
    a_m(t) &= a_m(t_0) + \Delta a_{m1}(t) + \Delta a_{m2}(t) \\
    0.02 < a_m(t) < 1.00
\end{align*}
\] (6.3)
The gains of the PID controller in equation 1 were adjusted until the RMSE between the experimental and simulation kinematics of the chair rise was less than 1 for each controlled degree-of-freedom. In a PID controller the proportional and integral gains are responsible for the tracking of the input (throughout the simulation and at steady-state, respectively), but they can cause low frequency oscillations in the response (overshoot). Therefore, the proportional and integral terms were increased until RMSE in the response smaller than 1° was achieved. On the other hand, the derivative gain acts as a damper on low frequency oscillations such as initial overshoot, but it can produce high frequency oscillations when it is too large. Therefore, the derivative gain was increased to reduce overshoot in the response. The gait simulation did not require additional tuning since RMSE smaller than 1° were produced for each controlled degree-of-freedom with the same gains tuned for chair rise. Both chair rise and gait were performed with both $S1$ and $S2$ knee models.

A sensitivity analysis was performed on the gait simulation to evaluate how sensitive the results were to the PID gains. Six more instances of the simulation were run with Proportional, Integral, and Derivative gains increased and decreased by 50%, respectively.

Finally, to test the impact of the PCSA recruitment strategy in Eq. 6.2, a simulation of gait in which the same change in activation $\Delta a_g(t)$ was assigned to all the muscles belonging to the same group (no PCSA-based recruitment ratios) was also performed:

$$
\begin{align*}
    a_m(t) &= a_m(t_0) + \delta a_g(t) \\
    0.02 < a_m(t) < 1.00
\end{align*}
$$

(6.4)
The performance of the two recruitment strategies was compared \textit{a posteriori} with a muscle stress based criterion \cite{44}

\[ U_1(t) = \sqrt[3]{\sum_{i=1}^{n} \left( \frac{F_i(t)}{PCSA_i} \right)^3} \]  

(6.5)

where \( n \) is the total number of muscles in the model and \( F_i(t) \) is the force generated by muscle \( i \) at time \( t \), and an activation based cost function \cite{12}

\[ U_2(t) = \sum_{i=1}^{n} a_i^2(t) \]  

(6.6)

to verify that the PCSA-based recruitment strategy reduces total muscle stress and activation.

Lastly, an open-loop simulation of gait in which the model was forward-driven with muscle forces previously predicted with the closed-loop control strategy was performed to quantify the computational cost added by the PID control technique to the finite element simulation.

\section*{6.4 Results}

Simulations of chair rise and gait required 632 and 438 minutes, respectively, using a single Intel\textsuperscript{\textregistered} Xeon\textsuperscript{\textregistered} 3.60 GHz processor on a desktop computer with 16.0 GHz of memory. The muscle-driven simulation of gait in which the closed-loop algorithm was not implemented required 420 minutes.

The tracking produced RMSE below 1\degree for every simulation (Fig. 6.3) (Tab. 6.1). The PID gain triplets calibrated for the chair rise simulation were (120-120-2) (P-I-D,
respectively) for the hip, (120-120-1) for the knee, and (120-120-0.2) for the ankle. These gains produced RMSE below 1° for both activities and with both knee models S1 and S2. Tracking with the S1 and S2 knee models produced similar results.

Quadriceps forces dominated the chair rise, starting from a peak of 2641/2670 N for S1/S2, respectively, and decreasing throughout the activity (Fig. 6.4). Soleus and gastrocnemius were active throughout the activity with a peak in the soleus of 1009/1051 N. Hamstrings and gluteus maximum presented a similar decreasing profile with a total initial peak of 2066/2150 N for S1 and S2, respectively. Iliacus and psoas were also active, and their force increased throughout the activity, reaching a peak of 503/529 N. Substantial differences between S1 and S2 were not observed.

The vasti were active only during the weight acceptance portion of the stance phase of gait, reaching a peak of 458/365 N (Fig. 6.4). The rectus femoris was active both at the beginning and at the end of the stance phase. Soleus and gastrocnemius generated forces during the second part of the stance phase with a combined peak at contralateral heel strike (CHS) of 2434/2469 N. The soleus was the muscle that exerted the highest force during gait, with a peak of 1375/1313 N. Iliacus and psoas were active at the end of the stance phase with a peak of 321/352 N. The hamstrings muscle that generated the largest force during gait was the biceps femoris short head with a peak of 252/289 N. The main inter-specimen differences during gait were that peak quadriceps force was 26% higher and mean hamstrings force was 14% lower for S1.

TF compressive forces (along the superior/inferior axis of the tibial coordinate system) predicted by the model presented a single peak at chair exiting (444/472 % BW) in correspondence of the quadriceps force peak (Fig. 6.5), and presented an increasing trend during gait from 232/227 %BW at contralateral toe off (CTO) to
352/368 %BW at CHS (Fig. 6.5). Mean compressive load on the medial compartment of the tibia was 27% greater during chair rise and 29% greater during gait for S2.

During chair rising, the posterior cruciate ligament (PCL), medial collateral ligament (MCL), and popliteofibular (PFL) carried load for both S1 and S2 with respective peak of 472/643 N, 364/474 N, and 180/135 N at chair exit (Fig. 6.6). During gait, the ACL and MCL constrained the motion for S1, with peaks of 110 N at CTO (ACL), and of 123 N at maximum knee extension (approximately 38% of the gait cycle) (MCL) (Fig. 6.6). PCL and MCL were active for S2, with peaks of 38 N and 246 N, respectively, at maximum knee extension.

RMSE between model and target kinematics from the sensitivity analysis were always below 1° (Tab. 6.2). Average RMS differences between baseline muscle forces and forces estimated by the sensitivity analysis simulations peaked at 11.5 N (5% of peak muscle force) (Tab. 6.2).

The comparison between the performance of the simulations with and without PCSA-based recruitment strategy showed that the activation-based cost function averaged across time was 18% higher when no ratios were used ($\bar{U}_2 = 0.90$ and 1.07 with and without ratios, respectively). The muscle stress-based cost function was also lower in the case without ratios ($\bar{U}_1 = 30.8$ and 31.2 N/cm² with and without ratios, respectively).

6.5 Discussion

A computationally efficient muscle prediction algorithm based on closed-loop kinematics tracking was developed and tested with a finite element multiscale musculoskeletal model of the lower limb to simulate chair rise and gait. Muscle forces
were calculated simultaneously with joint and tissue level variables in a single forward integration. Two different specimen-specific knee models with calibrated TF and PF ligaments were implemented in the lower limb model to investigate differences between muscle force predictions and verify the robustness of the closed-loop approach.

The main advantage of the closed-loop approach presented in this study is that, given a calibrated combination of PID gains for hip, knee and ankle, it solves the muscle redundancy problem in a single simulation, without requiring multiple iteration as for optimization-based techniques. Previous studies that performed muscle optimizations with a musculoskeletal model including a deformable finite element model of the foot reported computational times of 10-14 days [106] and 4 weeks [108]. Although a single simulation in the present study took a relatively long time (10 and 7 hours for chair rise and gait, respectively) in comparison to muscle force estimations with rigid multibody models that can take less than a minute, it was substantially more efficient than methods used with models of similar complexity. This computational efficiency allowed a level of detail in terms of deformability and personalization that is not compatible with optimization-based force prediction strategies. Therefore, forces that are usually ignored in the muscle force calculation, such as contact and soft tissue forces, where accounted for. Another relevant finding was that a difference of only 18 minutes in computational time was observed when the closed-loop algorithm was implemented. Therefore, 96% of the time required by the closed-loop simulation (420 minutes out of 438) is due to the computational cost of the finite element method and does not depend on the control algorithm.

Predicted muscle forces were in good agreement with previous computational studies [11, 222] and with average EMG signals collected for the two activities with
healthy subjects [57, 119, 206] (Fig. 6.4). Anderson and Pandy [11] simulated a gait cycle with a muscle-driven optimization-based forward simulation and predicted quadriceps force peaking at CTO (1200 N vs. 793/706 N in this study), and greatest forces in the plantarflexor muscles at CHS (2800 N vs. 2434/2469 N in this study). Shelburne et al. [222] simulated a rising activity and reported muscle force peaks at 80° of knee flexion for quadriceps (2800 N vs. 2641/2670 N in this study), gluteus maximus (1250 N vs. 1198/1231 N) and hamstrings (600 N vs. 868/918 N).

Additional confidence in the predicted muscle forces is provided by the TF contact forces estimated by the model. Specifically, predicted contact force magnitudes compared favorably to telemetric measurements in TKR patients [19] (Fig. 6.5). Although the two typical distinct peaks in TF compressive load during gait are not predicted, load estimates were within the upper limit of experimental measurement bounds (µ ± 2σ from 6 subjects reported in Bergmann et al. 2014) at both CTO (232/227 %BW) and CHS (352/368 %BW) (Fig. 6.5). Even though measurements from instrumented implants are the only available in vivo data in terms of joint contact loads, differences between healthy and TKR subjects motivated by nonequivalent articular surfaces and ligament behavior can be expected. TF contact loads predicted for chair rise presented a decreasing trend starting from a peak of 444/472 %BW for the two knee models. Although the upper bound of telemetric experimental data from 7 subjects is lower (428 %BW), predicted loads decrease in the first 5% of the task cycle and are within telemetric bounds for most of the activity (Fig. 6.5).

Ligament forces are generally in good agreement with estimates from previously published data. Specifically, ligament forces during the chair rise activity were dominated by the PCL for both S1 and S2 (peaking at 472/643 N) (Fig. 6.6). Shelburne and Pandy [222] also simulated a rising movement and estimated highest PCL force
in deep knee flexion (peak at 660 N at 80° of flexion), and turning off at 30°, as observed in the present study. The ACL dominated shear forces in S1 during gait and its peak at CTO (110 N) is supported by results previously reported [113, 176, 223], even though these studies observed larger peak forces (411 N in Harrington 1976, 156 N in Morrison 1970, 303 N in Shelburne et al. 2004). The ligaments of S2 presented an unexpected behavior during gait: the ACL did not carry force throughout the stance phase, whereas some posterior shear force present at the knee during weight acceptance was resisted by the PCL.

Differences in force estimates for the two knee models were observed. Although the same skeletal anthropometry, muscular properties, external forces and target kinematics were used for both knee models S1 and S2, the simulations predicted different quadriceps, hamstrings and contact forces. Specifically, peak quadriceps force and mean hamstrings force for S1 during gait were 26% higher and 14% lower than for S2, respectively. TF contact force on the medial plateau was also influenced by the knee model, presenting greater mean values for S2 in both activities (27% and 29% greater for chair rise and gait, respectively). These differences may be caused by a combination of joint contact geometry [229] and ligament behavior [228]. Different kinematics in the secondary degrees-of-freedom of the knee may have also influenced muscle moment arms and the corresponding contribution to joint torque. A future application of the closed-loop control strategy is the evaluation of force differences predicted after the simulation of a surgical procedure such as TKR implantation. More significant changes in load prediction are expected in that case.

A number of limitations were present in this study. First, simulations with our PID-based technique can be performed only if a target signal (in our case, joint kinematics) is available. In contrast, forward dynamics simulations that predict muscle
forces, body kinematics, and external forces given the goal of the motor activity (e.g. maximum height jump) have been successfully presented in the literature [3, 61, 194]. Since the closed-loop strategy presented in this study requires a target to track, the simulations cannot be used to predict new movements. In addition, the accuracy of the predictions depends on the accuracy of the tracked data. Despite this limiting factor, an advantage of the closed-loop technique is that the target does not have to be necessarily a kinematics profile. For instance, Fitzpatrick et al. [81] used a similar PID control strategy to track knee joint load measures from a telemetric implant. This feature potentially allows the tracking of any available experimental data and provides further flexibility to the control solution. In addition, a development that would improve the technique is to model the contact between foot and ground, and compare estimated ground reaction forces to experimental values to further validate model predictions.

A second limitation is that the closed-loop control used in this study does not solve the muscle redundancy problem minimizing an objective function as optimization or optimal control strategies do [11, 44]. Muscle recruitment strategies that reduce energy expenditure or total muscle stress have been shown to produce realistic joint kinematics and muscle coordination for gait in healthy conditions [11, 12]. This limitation was addressed in the present study by privileging the on-line recruitment of muscles with larger PCSA, which consequently can produce larger forces. The performance of this recruiting strategy in terms of muscle stress and activations was more efficient than the case that did not distinguish between muscles belonging to the same group.

The purpose of this investigation was to address the tradeoff between computational efficiency and model detail that is inevitable in musculoskeletal simulations.
The control technique presented in the current study was shown to be robust to changes in knee model and in simulated activity, since the PID gains used for the two specimens were the same and produced RMSE under 1° for both activities. Finally, the sensitivity analysis demonstrated that the control technique is also not sensitive to changes in PID gains. In conclusion, a computationally efficient muscle prediction strategy was developed to perform muscle-driven forward simulations of gait and chair rise with a finite element musculoskeletal model of the lower limb. The similarity between results presented in this study and in previous investigations suggests that the closed-loop strategy proposed is a viable alternative to computationally expensive optimization-based approaches, which are prohibitive with complex deformable representations.
Table 6.1: RMSE between target kinematics and model motion for hip, knee, and ankle flexion/extension degrees-of-freedom for chair rise and gait simulated with knee models $S_1$ and $S_2$.

<table>
<thead>
<tr>
<th>DoF</th>
<th>Chair</th>
<th>Gait</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$S_1$</td>
<td>$S_2$</td>
</tr>
<tr>
<td>Hip</td>
<td>0.36</td>
<td>0.38</td>
</tr>
<tr>
<td>Knee</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.08</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Table 6.2: Sensitivity analysis results. RMSE between target kinematics and model motion for hip, knee, and ankle flexion/extension for gait simulated with knee model $S_1$ are shown on top. Baseline indicates the simulation that used baseline PID gains (see text for details). $P_+ = $ Proportional gains +50%; $P_- = $ Proportional gains -50%; $I_+ = $ Integral gains +50%; $I_- = $ Integral gains -50%; $D_+ = $ Derivative gains +50%; $D_- = $ Derivative gains -50%. Average RMS differences between muscle forces predicted with baseline PID gains and with the sensitivity analysis simulations are shown on the bottom. RMS differences are expressed both in N and in % of the peak force for each muscle.

<table>
<thead>
<tr>
<th>DoF</th>
<th>Baseline</th>
<th>$P_+$</th>
<th>$P_-$</th>
<th>$I_+$</th>
<th>$I_-$</th>
<th>$D_+$</th>
<th>$D_-$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>0.59</td>
<td>0.59</td>
<td>0.61</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
</tr>
<tr>
<td>Knee</td>
<td>0.30</td>
<td>0.22</td>
<td>0.43</td>
<td>0.25</td>
<td>0.35</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.22</td>
<td>0.17</td>
<td>0.29</td>
<td>0.18</td>
<td>0.29</td>
<td>0.22</td>
<td>0.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle forces</th>
<th>Baseline</th>
<th>$P_+$</th>
<th>$P_-$</th>
<th>$I_+$</th>
<th>$I_-$</th>
<th>$D_+$</th>
<th>$D_-$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>10.0 N</td>
<td>11.5 N</td>
<td>2.0 N</td>
<td>2.3 N</td>
<td>5.6 N</td>
<td>8.5 N</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>4.3%</td>
<td>5.0%</td>
<td>0.7%</td>
<td>0.8%</td>
<td>2.1%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
Figure 6.1: The lower limb finite element model used in the current study included twenty musculotendon units represented as linear connectors that could generate contraction force. Some muscles were modeled with via points, whereas other muscles could wrap around bone and cartilage surfaces. A 12 degrees-of-freedom knee model was included. Two different specimen-specific knee models (S1 and S2) with TF and PF soft tissue response calibrated on in vitro experiments were used [7, 115].
Figure 6.2: The closed-loop control system developed in this study consisted of three PID controllers that tracked experimental kinematics from inverse kinematics for hip and ankle, and stereo-radiography for the knee. The error between input and model motion was the input to three controllers, which produced the changes in muscle activation ($\Delta a_g(t)$) needed to follow the target. Changes in activation calculated in this fashion were added to initial conditions and scaled according to a recruitment strategy that privileged muscles with larger $PCSA$. Muscle forces were calculated with the input activations in Hill-type muscle models, which were applied to the finite element musculoskeletal model. The motion of the model was forward integrated and given back to the error calculation.
Figure 6.3: Hip, knee and ankle flexion/extension kinematics were tracked by three PID controllers to simulate chair rise (a) and gait (b). Tracked kinematics obtained from inverse kinematics (hip and ankle) and stereo-radiography (knee) is shown with a black solid line. Dashed red and orange lines represent the model kinematics for the two specimen-specific knees $S1$ and $S2$, respectively. All the simulations produced RMSE between tracked motion and model kinematics below $1^\circ$ using the same PID gains.
Figure 6.4: Muscle forces predicted by the model for chair rise (a) and gait (b). Force estimates were in good agreement with average EMG signals for the two activities [57, 119] and with previous musculoskeletal simulations [11, 193]. The quadriceps were mostly active at contralateral toe off, whereas gastrocnemius and soleus peaked at contralateral heel strike. Peak quadriceps force and mean hamstrings force for $S_1$ during gait were 26% higher and 14% lower than for $S_2$, respectively.
Figure 6.5: TF contact forces along the superior/inferior axis of the tibia predicted for chair rise (a) and gait (b). The sum of medial and lateral contact forces was compared to measurements from knee telemetric implants [19]. TF compressive force on the medial plateau was influenced by the knee model, presenting greater mean values for S2 in both activities (27% and 29% greater for chair rise and gait, respectively).
Figure 6.6: Ligament forces calculated for the chair rise (a) and gait (b) activities. Ligaments not shown in the figure (lateral collateral and posterior capsule) did not generate any force during the two activities. PCL, MCL and PFL were mainly active during chair rise for both knee models (a), whereas during gait ACL and MCL generated force for S1, and PCL and MCL were active for S2 (b).
Chapter 7

Conclusions and recommendations

The overall objective of this dissertation was to contribute to the evolution of computational musculoskeletal modeling in order to foster its utilization for informing design and decision making in orthopaedics. Even though many advancements still need to be achieved, this dissertation contributed to addressing three of the main issues that currently limit the potential of state-of-the-art computational modeling in orthopaedics: validation, personalization, and multiscale complexity. These limitations of musculoskeletal models are not independent of each other. The relationship between them is complex and they cannot be addressed separately. Model personalization and multiscale complexity are necessary, along with novel experimental instrumentation for measuring of internal variables, to provide a detailed representation of reality that can be validated at different levels.

Specific contributions of this research were to first quantify the scope of currently used musculoskeletal models, improve their personalization by including subject-specific joint representations, and develop state-of-the-art simulations that would describe the interaction between whole-body and joint scales in a single framework.
Specifically, Chapter 3 analyzed the reliability of the predictions of a musculoskeletal model developed in OpenSim and commonly used in the literature to perform simulations of movement. A global probabilistic analysis was employed to estimate the impact of model parameters’ uncertainty on muscle force and knee joint load predictions. The comparison of knee load 5-95% confidence bounds to subject-specific instrumented implant measurements validated the model and, consequently, quantified the reliability of its predictions, given the input variability. Although joint load experimental measurements were within estimated 5-95% confidence bounds for most of the stance phase, it was shown that the input uncertainties of the generic model produced large variability in output predictions.

Chapter 4 contributed to the same goal by assessing the dependence of muscle moment arms predicted by a similar musculoskeletal model to variability of knee kinematics. Since moment arms map muscle forces into joint torques, their correct estimation is crucial to accurately model the interaction between internal forces and joint motion. Even though the variability of moment arm estimates due to muscle geometry uncertainty has been previously analyzed [189], joint motion variability had never been taken into account. The results presented in Chapter 4 contribute to quantifying the reliability of generic musculoskeletal models because they show that moment arms estimated with generic passive motion implemented in many generic models [15, 200, 251] are substantially different from estimates obtained with in vivo joint motion. In addition, Chapter 4 represents an example of musculoskeletal model personalization, since subject- and activity-specific knee kinematics measured with a biplane stereo-radiography system were utilized. Inter-activity and inter-subject differences were observed, demonstrating that knee joint kinematics personalization
in musculoskeletal models is necessary to correctly describe the relation between muscle function and joint torque.

The findings of these first two investigations have a number of implications on whole body musculoskeletal modeling. First, modelers and model users are invited to always address the inevitable uncertainty in model parameters. The recent rapid advancements in computational efficiency and public availability of musculoskeletal models, in great part fostered by the release of the open-source software for biomechanical simulations OpenSim [51], facilitated the spread of whole body computational simulations of movement throughout the world. A static optimization simulation to estimate muscle forces during a gait cycle can be performed in less than a minute. This computational efficiency substantially facilitates the use of probabilistic tools such as Monte Carlo analyses to evaluate the impact of input uncertainty on model outputs. A Monte Carlo analysis with 1000 iterations can be performed on a 30 seconds static optimization simulation in less than 9 hours. Therefore, the uncertainty in the outputs of a musculoskeletal simulation performed at the whole body level with conventional publicly available models can be estimated in reasonable time. The utilization of confidence bounds should become a standard practice in the presentation of results from computationally efficient simulation. As already mentioned in Chapter 2, stating the limits to the applicability and the errors of a model is fundamental. The scientific community can certainly benefit from a clear description of the reliability of model predictions presented in the literature, according to the uncertainty in the inputs. Other probabilistic tools already utilized in biomechanics to describe the variability across a population, such as statistical shape models and principal component analyses, can also be further developed to have a direct impact on musculoskeletal simulations. For instance, a statistical shape
model of the femur was created to predict the shape of the whole bone given only a specific region [265]. This technique can be used for subject-specific scaling of generic musculoskeletal models [74]. A promising principal component approach that leverages relationships between specimen-specific TF and PF kinematics and anatomy has been proposed [229]. A potential development of the study presented in Chapter 3 is to implement in the musculoskeletal model knee kinematics inferred from joint anatomy, and verify whether moment arm estimates replicate the results obtained with kinematics measured in vivo better than generic passive cadaveric motion.

A second implication revealed by the studies presented in Chapter 3 and Chapter 4 is the need for publicly available repertoires of anthropometrical and functional parameters that can be accessed to refine the accuracy of computational models. Ideally, future technological advancements will provide non-invasive experimental instrumentation to instantaneously access subject-specific parameters in vivo. An example of a promising technology that enhances our knowledge of internal parameters is a minimally invasive wearable microscope that can measure sarcomere length of individual motor units in vivo [208] that was used to quantify changes in vastus lateralis sarcomere lengths with knee flexion [36]. This sort of technology combined with medical imaging can significantly contribute to our knowledge of muscle functioning and to model identification. However, as long as parameter uncertainty remains a limitation of musculoskeletal investigations, the availability of comprehensive datasets that quantify the variability of certain parameters across a population is crucial. Limited examples are already available: muscle properties from 21 cadavers [253] and image-based measurements of muscle PCSA from 35 lower limbs [111] were presented in the literature. Our knowledge of the complex internal behavior of some muscles such as the vasti [25, 118] would also benefit from cadaveric measurements that map the
variability of sarcomere length within a single human muscle as shown in a study performed on two rat muscles [186].

Chapter 5 proceeded in the effort taken for model personalization and started addressing multi-scale complexity. Knee joint loads were predicted for three daily living activities (gait, walking down stairs, chair rise/sit) with a generic musculoskeletal model scaled on subject-specific dimensions for 6 TKR patients. Load estimates were used, along with fluoroscopy-measured implant motion, to drive a finite element model of the TKR geometries to assess subject-specific contact mechanics. This multiscale sequential approach (whole-body musculoskeletal model with simplified joint representation followed by a detailed finite element model of the subject-specific joint geometry) provided personalized contact mechanics, showing differences between patients in terms of contact location, area and pressure.

Finally, Chapter 6 specifically addresses the lack of consistency between whole-body and organ/joint representations commonly present in multiscale sequential studies. Muscle driven simulations of gait and chair rise were performed with a musculoskeletal model of the lower limb developed in a finite element framework. The model included a detailed representation of the knee with specimen-specific geometries and ligament properties tuned and validated on in vitro experiments. Therefore, this final study represents one of the first examples of concurrent simulation of whole-body muscle force prediction and joint level deformation analysis. Specifically, the study focused on developing a muscle recruitment strategy based on tracking of experimental kinematics with a number of PID controllers. This method was shown to be robust to changes in knee model and PID gains, and succeeded for both gait and chair rise simulations. The main advantage of the developed recruitment strategy
is its computational efficiency when compared to computationally more expensive optimization-based techniques used with models of similar complexity [106, 108].

Chapter 5 and Chapter 6 represent state-of-the-art modeling platforms that can be used to investigate the complex and unknown relationships between neuromuscular control and local deformation. These two studies revealed that computational cost is still a significant obstacle and, at the same time, investigated possible solutions to address the issue. The two main computational bottlenecks are the selection of a single solution to the muscle redundancy problem (multiple combinations of muscle forces produce the same joint motion), and the calculation of local strain with the finite element method. Although the effort to reduce the cost of complex simulations should be continuously addressed, the computational burden should not be considered an insuperable obstacle. Two decades ago significant advancements in musculoskeletal modeling were obtained when optimal control and dynamic optimization strategies were employed for the first time with three-dimensional rigid whole body representations [11, 193, 194]. Even though these simulations could appear excessively time consuming (convergence to an optimal solution took multiple weeks), advancements in computer performance and convergence methods in the past few years took computational time down to few hours [198, 246]. Therefore, it is reasonable to assume that the efficiency of optimization strategies and finite element solutions will significantly increase. The two investigations presented in Chapter 5 and Chapter 6 represent an attempt to address this current limitation. While in the study presented in Chapter 5 a sequential approach was used to reduce computational burden (joint loads and local strain were predicted in separate simulations at different scales), the closed-loop technique proposed in Chapter 6 has the specific goal to estimate muscle forces and local strain concurrently in a single simulation,
with no need to perform multiple iterations. To fully understand the accuracy and efficiency of this control strategy a traditional muscle optimization should be performed with the same lower limb finite element model and compared to the findings presented in Chapter 6. An additional advantage of the closed-loop control developed in the study is its relative simplicity in comparison to optimization techniques. PID controllers are often used in the industrial setting because of their simplicity and adaptability to very diverse processes. In addition, the adapting nature of a PID controller can be seen as a surrogate for the plasticity of the human neuromotor system to investigate neuromuscular adaptations to changes in the physical system such as a total joint replacement. Although there is certainly room to improve this technique in the future by improving its robustness and muscle performance, other control strategies that could be applied to the same sophisticated finite element model should be investigated. As mentioned in Chapter 6, a limitation of the closed-loop technique is that some target experimental kinematics need to be tracked and, consequently, novel movements cannot be predicted. However, so far only optimal control and dynamic optimization strategies have shown the potential to be fully predictive, and they require a high number of iterations to find an optimal solution. A promising option is to reduce computational cost of the simulations by identifying the computational bottlenecks in the model (e.g. contact) and using surrogate representations, which are able to significantly reduce the simulation time [71, 156].

Finally, a note on model validation is necessary. The effort to increase complexity of models and muscle recruitment strategies, and reduce computational burden is only meaningful if a concurrent work towards validation accompanies it. The proliferation of publicly available experimental datasets represents a key opportunity for
the evolution of musculoskeletal modeling. Blind prediction of experimental measurements has revealed great potential in fostering modeling attempts. The ideal dataset should be progressively shared allowing modelers to gradually refine their predictions and assess the reliability of each detail level when more information is available. The most popular example of blind predictions in biomechanics is the series of Knee Grand Challenge Competitions that shared motion data of a number of subjects with telemetric knee implants [87]. This initial attempt should be expanded with a larger set of data and imitated for different types of experiment. For example, the same approach can be utilized with in vitro experiments that evaluate the behavior of a cadaveric joint under several loading conditions to encourage detailed specimen-specific modeling to recreate the experiment.

In conclusion, the research topics presented in this dissertation contribute to evolve musculoskeletal computational modeling with the purpose of improving its reliability and trustworthiness. Specifically, the four studies focused on addressing the need for model validation, personalization, and multiscale complexity. Future work is certainly needed to proceed along the same path and foster the informed use of musculoskeletal modeling as a design and decision-making tool in orthopaedics. In summary, future efforts should particularly focus on in vivo parameters identification, collection of comprehensive datasets to describe the variability within different populations, spread of probabilistic methods to report model output uncertainty and to inform subject-specific musculoskeletal models, development of novel computationally efficient techniques to solve the muscle redundancy problem concurrently to the estimation of local tissue deformation. A common effort in this direction will promote the use of musculoskeletal modeling in a clinical setting.
Bibliography


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tion can prevent posterior edge loading of hip replacements. *J Orthop Res*,
31(8):1172–9, 2013.

efficient musculoskeletal simulation and optimal control. *Procedia IUTAM*,

[247] Antonie J van den Bogert and Ahmet Erdemir. Concurrent simulations of
musculoskeletal movements and tissue deformations. In *ASME 2007 Summer
Bioengineering Conference*, pages 5–6. American Society of Mechanical Engi-
neers.

vivo contact kinematics and contact forces of the knee after total knee arthro-
plasty during dynamic weight-bearing activities. *J Biomech*, 41(10):2159–68,
2008.

[249] M. Viceconti, F. Taddei, L. Cristofolini, S. Martelli, C. Falcinelli, and
E. Schileo. Are spontaneous fractures possible? an example of clinical applica-
tion for personalised, multiscale neuro-musculo-skeletal modelling. *J Biomech*,

[250] Marco Viceconti, Debora Testi, Fulvia Taddei, Saulo Martelli, GORDON J
CLAPWORTY, and SERGE VAN SINT JAN. Biomechanics modeling of
the musculoskeletal apparatus: Status and key issues. *Proceedings of the IEEE*,

hinge design and placement on joint mechanics. *J Biomech*, 21(11):965–74,

tibiofemoral joint contact to net loads at the knee in gait. *J Orthop Res*,


Appendix A

Related publications


