Subject-specific lower extremity modeling

Personalization of musculoskeletal models using
medical imaging and functional measurements

Vincenzo Carbone

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SUBJECT-SPECIFIC LOWER EXTREMITY MODELING

PERSONALIZATION OF MUSCULOSKELETAL MODELS USING MEDICAL IMAGING AND FUNCTIONAL MEASUREMENTS

DISSERTATION

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus
prof. dr. H. Brinksma,
on account of the decision of the graduation committee,
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by

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Contents

Summary.....	7
Samenvatting	11
Chapter 1 Introduction.....	15
Chapter 2 Sensitivity of subject-specific models to errors in musculoskeletal geometry	29
Chapter 3 Sensitivity of subject-specific models to Hill muscle-tendon model parameters in simulations of gait	41
Chapter 4 TLEM 2.0 – A comprehensive musculoskeletal geometry dataset for subject-specific modeling of lower extremity	55
Chapter 5 Effect of image-based automatic scaling of musculoskeletal geometry of the lower extremity on model predictions	71
Chapter 6 Effect of global optimization of muscle-tendon parameters of the lower extremity on model predictions	93
Chapter 7 Quantitative validation of subject-specific musculoskeletal models of the lower extremity using FDG-PET	111
Chapter 8 General discussion and recommendations	129
Bibliography	141
Acknowledgements	159
About the author	163

Summary

Musculoskeletal mechanics tries to understand the interaction between muscles, joints and bones that causes all voluntary movements of the skeleton by the application of mechanical principles to human anatomy. In this field, one of the most important research tools are the musculoskeletal models, which are used to understand how the human body works in order to comprehend its functions. In the past decades, musculoskeletal models have been used to calculate non-measurable quantities such as muscle and joint reaction forces, in order to have a better understanding of the basic principles of muscle coordination.

Progress in musculoskeletal mechanics, numerical simulations and image reconstruction, together with advances in computational power, have increased the detail and complexity of musculoskeletal models. Researchers can now use these models to better understand the dysfunctions of the musculoskeletal system, and try to improve the diagnosis and treatment for patients. Hence, the use of musculoskeletal simulations holds significant promise for application in the biomedical industry, and in the near future model predictions are expected to gain a more important role in personalized healthcare. However, at the moment musculoskeletal model results are not considered reliable enough for critical individual applications such as definition of surgical strategies. To face this challenge, work presented in this thesis aims to develop accurate and effective methods to create subject-specific musculoskeletal models of the lower extremity, and to assess whether personalization of model parameters results in improvements in the model predictions, in order to allow for their application in critical scenarios.

An extensive sensitivity analysis was performed to quantify the effect of differences (and potential errors) in musculoskeletal geometry and muscle-tendon parameters on subject-specific model outcomes. Two metrics, namely a Local Sensitivity Index (LSI) and an Overall Sensitivity Index (OSI), allowed to distinguish muscles which make only little contributions to the joint moments from muscles which have an important role during gait, giving an indication on which muscles and which parameters should be estimated most carefully when creating subject-specific models. This analysis showed that small errors in model parameters can have a significant impact on the model force predictions, and that most of the accuracy of the model depends on the estimation of two points (the origin, or pseudo-origin, and the insertion, or pseudo-insertion, attachment sites) and three parameters (tendon slack length, nominal muscle fiber length and maximal isometric muscle force) for each muscle-tendon element. This analysis provided quantitative information to draw up a priority list of the muscles and the parameters that need to be estimated most accurately to create reliable subject-specific musculoskeletal models that satisfy the required accuracy of the specific application.

Then, a new comprehensive dataset of the musculoskeletal geometry of the lower extremity, called Twente Lower Extremity Model 2.0, was created, based on medical imaging data and

dissection measurements performed on one single cadaver specimen. The new TLEM 2.0 dataset represents the first consistent and complete ‘atlas’ model, which includes a set of CT and MRI scans, segmented bone, muscle and subcutaneous fat (including skin) volumes, inertial parameters, coordinates of bony landmarks, muscle and ligaments attachment sites and lines-of-action, and joint centers and axes of rotation. TLEM 2.0 was purposely built to be easily combined with image-based scaling techniques, such as bone surface morphing, muscle volume registration and muscle-tendon path identification, in order to reduce the time and manual intervention required to create subject-specific musculoskeletal models.

TLEM 2.0 represented the starting point of a streamlined modeling workflow that was developed to obtain subject-specific musculoskeletal geometry and muscle-tendon parameters in a semi-automatic way with limited manual intervention. MRI scans were used to segment bone and muscle contours, and to estimate joint geometry and muscle-tendon attachment sites, while dynamometry data were used in a global optimization to estimate values of tendon slack length, nominal muscle fiber length and maximal isometric muscle force. This modeling workflow was applied to ten healthy subjects in order to build a unique set of ten subject-specific musculoskeletal models with limited manual intervention.

Subsequently, a profound analysis of the effect of personalized parameters on the model predictions was performed, comparing generic and subject-specific model. Large differences were found in musculoskeletal geometry parameters, such as body segment size, joint geometry, muscle-tendon attachment sites and muscle-tendon moment arms, resulting in different joint kinematics and net joint moments predicted during gait. Moreover, personalized models presented large differences in the estimated values of tendon slack length, nominal muscle fiber length and maximal isometric muscle force, which significantly affected the predicted muscle forces. These large differences indirectly demonstrated the added value of subject-specific models, since generic models cannot take into account inter-individual anatomical variability, and suggested that subject-specific models are indeed necessary for clinical applications such as surgical planning and clinical decision-making processes.

To verify if predictions by subject-specific models were not only different but also more accurate than generic models, several validation techniques were used. When comparing the measured and the predicted maximum joint torques, each step of the modeling workflow resulted in a significant reduction of the error compared to generic models, hence showing a clear improvement of subject-specific model predictions. Moreover, personalized models resulted in a reduction of the predicted muscle activity to more physiologically realistic values for the most important muscles during gait. However, when comparing the predicted muscle activity with the measured EMG signal, it was not possible to prove any significant improvement, since the personalization affected mostly the magnitude of the muscle activity but not the timing, and likely due to the limitations of EMG as a reliable validation tool.

To further test the subject-specific model predictions, a novel technique of indirect validation was shown by using the positron emission tomography (PET) combined with the radioactive tracer [18F]-Fluoro-deoxy-glucose, which has been used recently to show functional differences in muscle recruitment. When analyzing each individual subject, good to very good correlation was found between muscle metabolism measured using FDG-PET and metabolic energy consumption predicted by generic and subject-specific models. Musculoskeletal models were able to correctly predict very high metabolic energy consumption during walking not only for ankle plantarflexor muscles, as previously indicated in literature, but also for a deep and relatively small muscle like the Gluteus Minimus. These results showed the advantages of FDG-PET technique as a complimentary validation tool to EMG, which is limited to measure only few superficial muscles. Moreover, higher correlation values were found when analyzing results averaged over ten healthy subjects, giving great confidence on the validity of the model outcomes when analyzing muscle coordination during gait. As with the EMG, correlation was slightly higher for subject-specific models compared to generic models, but it was not possible to prove the significance of this improvement, likely due to the fact that FDG-PET is not accurate enough to detect the improvements of personalized models based on healthy subjects. Hence, further validation is essential to gain the reliability necessary for clinical applications.

In conclusion, we have shown that recent advancements in musculoskeletal mechanics, medical imaging and computer science allow today to build a subject-specific model of the lower extremity in an efficient way, and the improvements in the model predictions make the personalization process worth the effort. However, to avoid that these results are fruitless, future research on developing more accurate validation techniques and reducing the dependency of the model on input errors are needed to reach the ambitious goal of application of subject-specific musculoskeletal models to clinical practice on a large scale.

Samenvatting

Het vakgebied van de spier-skelet mechanica onderzoekt de interactie tussen spieren, gewrichten en botten bij diverse lichaamsbewegingen door methoden en technieken uit de klassieke mechanica toe te passen op het menselijk bewegingsapparaat. Computersimulaties met spier-skelet modellen vormen daarbij een belangrijk instrument om te begrijpen hoe het bewegingsapparaat bepaalde lichaamsbewegingen uitvoert. In de afgelopen decennia zijn spier-skelet modellen van de onderste extremiteiten gebruikt om onmeetbare grootheden zoals spier- en gewrichtskrachten te berekenen, met als doel de basisprincipes van spiercoördinatie beter te begrijpen.

Ontwikkelingen in de spier-skelet mechanica, numerieke simulaties en medische beeldvorming hebben - tezamen met de toename in rekencapaciteit van computers - geleid tot meer gedetailleerde en complexere spier-skelet modellen. Deze modellen stellen onderzoekers in staat om afwijkingen in het bewegingsapparaat beter te doorgronden en daarmee de diagnose en behandeling van patiënten te verbeteren. Spier-skelet simulaties hebben daarom grote potentie voor toepassing in de biomedische industrie en het is de verwachting dat in de nabije toekomst modelvoorspellingen een belangrijkere rol zullen spelen in het toespitsen van de zorg aan het individu. Echter, op dit moment zijn uitkomsten van spier-skelet simulaties niet betrouwbaar genoeg voor individuele toepassingen, zoals het bepalen van een patiënt-specifieke operatiestrategie. Om deze uitdaging aan te gaan, wordt in dit proefschrift geanalyseerd welke modelparameters een grote invloed hebben op de uitkomsten van spier-skelet simulaties en wordt een accurate en effectieve methode ontwikkeld om persoon-specifieke spier-skelet modellen van de onderste extremiteit te creëren.

Allereerst is het effect van variaties (en mogelijke fouten) in de geometrie van het spier-skeletmodel en parameters van de spier-peeseenheden op de uitkomsten van een simulatie uitgebreid geanalyseerd en gekwantificeerd. Met twee zelf-gedefinieerde maten, de Local Sensitivity Index (LSI) en de Overall Sensitivity Index (OSI), worden spieren die weinig bijdragen aan de gewrichtsmomenten onderscheiden van spieren die een belangrijke rol spelen in een loopbeweging. Hiermee kan vastgesteld worden welke spieren en welke parameters het meest nauwkeurig bepaald moeten worden om een persoon-specifiek spier-skelet model te ontwikkelen. De analyse toonde aan dat kleine fouten in de modelparameters reeds grote gevolgen kunnen hebben voor de model-voorspelde krachten en dat de nauwkeurigheid van het spier-skelet model grotendeels afhangt van de spieraanhechtingen (de origo of pseudo-origo en de insertie of pseudo-insertie) en drie andere parameters van de spier-peeseenheid (de onbelaste peeslengte, de nominale spiervezellengte en de maximale isometrische spierkracht). Met behulp van deze sensitiviteitsanalyse is op een kwalitatieve manier een prioriteitenlijst opgesteld van spieren en parameters van de spier-peeseenheden

welke zo goed mogelijk geschat dienen te worden om een betrouwbaar persoon-specifiek spier-skelet model te ontwikkelen.

Vervolgens is, op basis van medische beeldvorming en sectie op een kadaver, een nieuwe en uitgebreide dataset van de geometrie van de onderste ledematen ontwikkeld: het zogenaamde Twente Lower Extremity Model 2.0. Deze dataset is het eerste consistente en complete 'atlas' model en bestaat uit een reeks van CT en MRI-scans, gesegmenteerde botten, spieren en onderhuids vet (met inbegrip van de huid), massatraagheidsmoment van elk (model) segment, palpeerbare botmarkeringen, spieraanhechtingen en -werklijnen en gewrichtspunten en -assen. TLEM 2.0 was doelbewust ontwikkeld om gemakkelijk en semiautomatisch aanpasbaar te zijn op basis van medische beeldvorming (intelligent schalen van botoppervlak, automatische registratie van spiervolumes en automatische identificatie van de werklijn van de spier-peeseenheden), zodat het maken van persoon-specifieke spier-skelet modellen minder tijd en handmatige aanpassingen vergt.

TLEM 2.0 was het startpunt van een gestroomlijnde methode voor het verkrijgen van de persoon-specifieke spier-skelet geometrie en parameters van spier-peeseenheden van tien gezonde proefpersonen en wel op een semiautomatische manier met beperkte handmatige interventie. De MRI werd gebruikt om de botten en spieren te segmenteren en de gewrichtsgeometrie en de spier- en peesaanhechtingen te bepalen. De onbelaste peeslengte, de nominale spiervezellengte en de nominale maximale isometrische spierkracht werd bepaald op basis van dynamometrie (krachtmeting) in combinatie met een modelmatige globale optimalisering.

Vervolgens is het effect van het individualiseren van het spier-skelet model bepaald door de uitkomsten van persoon-specifieke en eenvoudigere generieke spier-skeletmodellen te vergelijken. De modellen vertoonden grote geometrische verschillen (zoals de segmentgrootte, gewrichtsgeometrie, spier- en peesaanhechtingen en momentarmen), wat zich uitte in verschillende gewrichtskinematica en gewrichtsmomenten voor eenzelfde gemeten loopbeweging. Bovendien vertoonden de persoon-specifieke modellen grote verschillen in de waarden van de onbelaste peeslengte, de nominale spiervezellengte en de nominale maximale isometrische spierkracht, die de berekende spierkrachten sterk beïnvloeden. Indirect demonstreren deze grote verschillen de toegevoegde waarde van persoon-specifieke modellen, aangezien generieke modellen geen rekening kunnen houden met interindividuele anatomische variabiliteit. Bovendien suggereren de resultaten dat persoon-specifieke modellen inderdaad nodig zijn voor klinische toepassingen, zoals het bepalen van een operatiestrategie.

Om te verifiëren of de uitkomsten van de persoon-specifieke modellen niet alleen anders, maar ook nauwkeuriger zijn dan de uitkomsten van eenvoudigere generieke modellen, zijn verschillende validatietechnieken toegepast. Het vergelijken van de middels dynamometriegemeten en modelbepaalde maximale vrijwillige gewrichtsmomenten toonde

aan dat elke stap in de individualisering van het spier-skeletmodel een significante afname van de fout opleverde ten opzichte van de eenvoudige generieke modellen. Bovendien resulteerde de persoon-specifieke modellen in een verlaagde en fysiologisch meer realistische waarden voor de spieractiviteit voor de meest gebruikte spieren tijdens het lopen. Echter, het vergelijken van de model-voorspelde spieractiviteit met het gemeten EMG-sigitaal leverde slechts een kleine verbetering op, maar niet significant. Dit wordt ondermeer veroorzaakt door de beperkingen van EMG als betrouwbare validatiemethode en doordat het individualiseren van de spier-peeseenheden met name de grootte van de spieractiviteiten niet de timing beïnvloedt.

Om de uitkomsten van de persoon-specifieke modelvoorspellingen verder te valideren, is een nieuwe techniek van indirecte validatie toegepast, bestaande uit positron emissie tomografie (PET) in combinatie met een radioactieve tracer [18F] Fluor-deoxy-glucose. Deze methode is recent gebruikt om functionele verschillen in de spiercoördinatie aan te tonen. Voor elk proefpersoon werd een goede tot zeer goede correlatie gevonden tussen het spiermetabolisme gemeten met behulp van FDG-PET en het metabole energieverbruik voorspeld door simulaties met het spier-skelet model. De spier-skelet modellen bleken in staat niet alleen het hoge metabolisme van kuitspieren tijdens loopbewegingen goed te voorspellen, maar ook het metabolisme van dieper gelegen en relatief kleine spieren zoals de Gluteus Minimus. Dit laatste maakt FDG-PET een nuttige aanvullende validatiemethode naast EMG, dat beperkt is tot het meten van spieren direct onder het huidoppervlak. De analyse van uitkomsten gemiddeld over de tien gezonde proefpersonen leverde nog sterkere correlaties op, wat een groot vertrouwen geeft over de geldigheid van het spier-skelet model bij het analyseren van spiercoördinatie van loopbewegingen. Net als bij de EMG, was de correlatie iets hoger voor de persoon-specifieke modellen ten opzichte van de generieke modellen, maar niet significant. Dit is waarschijnlijk te wijten aan het feit dat FDG-PET niet nauwkeurig genoeg is om de verbetering van gezonde persoon-specifieke modellen aan te tonen. Dus verdere validatie is essentieel om de vereiste betrouwbaarheid te behalen voor klinische toepassingen.

Samengevat hebben we aangetoond dat recente ontwikkelingen in spier-skelet modellen, medische beeldvorming en computertechnologie vandaag de dag toereikend zijn om op een efficiënte manier een persoon-specifiek model van de onderste extremiteit te construeren, en dat de daarmee behaalde verbeteringen van de modeluitkomsten de moeite van het individualiseren van het model waard zijn. Echter, om de beste resultaten te behalen, is vervolgonderzoek noodzakelijk naar het ontwikkelen van accurate validatiemethoden en naar methoden om het model meer onafhankelijk te maken van fouten in de modelparameters. Slechts dan kan de ambitieuze doelstelling worden bereikt: het op grote schaal toepassen van persoons-specifieke spier-skelet modellen in de klinische praktijk.

Chapter 1

Introduction

1.1 Introduction

Humans are able to perform an extraordinary variety of movements, from walking to running 100 meters in less than 10 seconds, from getting up from a chair to jumping higher than 2 meters, from dancing a waltz to climbing the Mount Everest. For every movement, from the simplest to the most complex, the central nervous system is able to choose the most optimal combination of muscle forces to rotate the bones around the joints, in order to move and balance the body and to interact with the external environment.

Musculoskeletal mechanics tries to understand the interaction between muscles, joints and bones that causes all voluntary movements of the skeleton by the application of mechanical principles to human anatomy. In this field, the most important research tools are the musculoskeletal models, which are used to understand how the human body works in order to comprehend its functions. In the past decades, musculoskeletal models of the lower extremity have been used to calculate non-measurable quantities such as muscle and joint reaction forces (Pandy, 2001; Erdemir et al., 2007), in order to have a better understanding of the basic principles of muscle coordination (Zajac, 1993; Zajac et al., 2002) and to deduce the basic role of individual muscles during various tasks such as walking (Neptune et al., 2001; Anderson et al., 2003; Liu et al., 2006), jumping (Pandy et al., 1990; Pandy et al., 1991) or cycling (Neptune et al., 1997; Raasch et al., 1997). Recently, the release of several modeling software packages, such as SIMM (Delp et al., 1995), AnyBody Modeling System™ (Damsgaard et al., 2006), and OpenSim (Delp et al., 2007) has widened the availability of musculoskeletal models to several applications in various fields such as optimization of sport performances (Rasmussen et al., 2012) and ergonomic studies (Wu et al., 2009).

Progress in musculoskeletal mechanics, numerical simulations and image reconstruction, together with advances in computational power, have increased the detail and complexity of musculoskeletal models (Viceconti et al., 2006), so that researchers can now also use these models to better understand the dysfunction of the musculoskeletal system, and try to improve the diagnosis and treatment for patients. In fact, accurate knowledge of muscle forces could provide relevant insight in the cause of musculoskeletal disorders (Paul et al., 2005; Higginson et al., 2006; van der Krogt et al., 2013), and holds high promise for orthopedic applications such as the design and assessment of total joint replacements (Brand et al., 1994; Andriacchi et al., 1997). Moreover, detailed musculoskeletal models would be fundamental to predict the biomechanical consequences of alterations in the anatomy introduced by orthopedic interventions, such as osteotomies and muscle-tendon transfers (Cohen et al., 2003; Reinbolt et al., 2009) or joint replacements (Piazza et al., 2001), and could therefore be used to assist clinicians to determine the optimal surgical strategy.

It is clear that the use of musculoskeletal simulations holds significant promise and enormous challenges in biomedical industry, and that model predictions will gain a central role in personalized healthcare in the near future. Recently, the Avicenna Alliance – Association for

Predictive Medicine, has defined the *in silico clinical trials* as “The use of individualized computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention. It is a subdomain of *in silico medicine*, the discipline that encompasses the use of individualized computer simulations in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of disease.”, and has declared that they will transform the biomedical industry (Viceconti et al., 2016).

However, product development and decision-making processes in biomedical industry are still predominantly founded on experimental approaches, driving the healthcare costs to unprecedented levels. The reason for this delay is that musculoskeletal model results are not considered reliable enough for critical individual applications such as definition of surgical strategies. This raises the important issue of how reliable personalized musculoskeletal models can be developed, and how they can be validated and sufficiently proven accurate in order to reach a justified confidence in their predictions.

1.2 Research framework - TLEMsafe project

The research work presented in this thesis was part of the TLEMsafe project (Verdonschot et al., 2012), funded by the Seventh Framework Programme (FP7) of the European Union, and coordinated by the University of Twente. Goal of the TLEMsafe project, which ran from March 2010 till Augustus 2014, was to create a patient-specific surgical navigation system, based on innovative ICT tools, for training, pre-operative planning and execution of complex musculoskeletal surgery, in order to help the surgeon to safely reach the optimal functional result for the patient (Figure 1.1).

Figure 1.1 - TLEMsafe system: a patient-specific surgical navigation system to help the surgeon to safely reach the optimal functional result for the patient after surgery.

The TLEMsafe project involved two technical universities (University of Twente, Enschede, the Netherlands and Warsaw University of Technology, Warsaw, Poland), one university medical center (Radboud University Medical Center, Nijmegen, the Netherlands), one small-medium enterprise (AnyBody Technology A/S, Aalborg, Denmark) and two large industrial partners (Brainlab AG, Munich, Germany and Materialise N.V., Leuven, Belgium). This research consortium had been created to capitalize on the expertise of each partner, including complex musculoskeletal surgery, modeling know-how, medical imaging, virtual reality and surgical navigation.

To reach their goal, the TLEMsafe partners designed a six-step patient workflow (Figure 1.2) in order to support surgeons in providing excellent surgical treatments. The first step was the collection of medical images, including X-rays and MRI scans, and functional measurements of hip-dysplasia and sarcoma patients treated at the Radboud University Medical Center. Then, essential individual details, such as exact bone contours, joint geometry, muscle volumes and muscle attachment sites, were extracted from the MRI scan using innovative algorithms purposely developed by Materialise. As third step, all these data were integrated by the University of Twente into the modeling system provided by AnyBody Technology, in

[1] Medical images (X-rays and MRI) and functional measurements of the lower extremity of the patient are collected.

[2] Patient-specific data (bone surfaces, joint geometry, muscle-tendon attachment sites and muscle volumes) are extracted from MRI.

[3] Patient-specific musculoskeletal model is created to simulate daily living activities (walking, stair climbing, sitting down)

[4] Surgeon can virtually operate on the patient-specific model and select the best strategy to reach optimal functionality after surgery.

[5] Surgical navigation system allows the surgeon to exactly and safely reproduce the selected operative plan.

[6] Optimal functional result is reached, decreasing risks of complication and improving the quality of life for the patient.

Figure 1.2 - TLEMsafe patient-specific workflow depicted for a hip dysplasia patient.

order to build patient-specific models capable of accurately simulating daily living activities, such as walking at various speeds, ascending and descending stairs or sitting down and getting up from a chair. The musculoskeletal model was then loaded into an innovative pre-planning system, developed by the Warsaw University of Technology, which allowed the surgeon to conduct virtual operations on the patient, predict the functional effects of different surgical options, and choose the optimal surgical plan. Finally, a surgical navigation system, developed by Brainlab, guided the surgeon in the operating theatre to exactly reproduce the planned surgical treatment, so that the optimal functional result for the patient was reached. At the core of the TLEMsafe project was the Twente Lower Extremity Model (Klein Horsman et al., 2007), a state-of-the-art comprehensive and consistent musculoskeletal anatomical dataset based on a single cadaver specimen. The role of the Laboratory of Biomechanical Engineering of the University of Twente was to further improve the TLEM model, in order to build personalized musculoskeletal models and to predict the functional outcome of surgical operations on patients. The research presented in this thesis focuses on the subject-specific lower extremity modeling, to create personalized models in an automatic way using medical imaging and functional measurements, and on the validation of subject-specific model predictions in healthy subjects.

1.3 Musculoskeletal models of the lower extremity

A musculoskeletal model is a simplified mathematical description of the anatomy and physiology of muscles, joints and bones that compose the human musculoskeletal system. Models are usually composed of two major components: *musculoskeletal geometry*, to describe the skeletal bones, joint articulations and line-of-action of muscle-tendon actuators, together with a *muscle-tendon model* to describe the force-generating characteristics of each muscle-tendon actuator.

1.3.1 Musculoskeletal geometry

Depending on their application, models contain a less or more detailed (2D or 3D) representation of musculoskeletal anatomy. Mechanical characteristics of body segments, such as dimensions, mass, and inertia, are represented by rigid bodies. Segments are connected by mechanical joints with multiple degrees of freedom, whose geometry describes the center of rotation and direction of axis of rotation. Each muscle-tendon actuator is connected to two or more bones, crossing at least one joint. Muscle-tendon lines-of-action are described by origin and insertion attachment sites and, if appropriate, by via points and wrapping surfaces. In the most complex cases, the mechanical effect of muscle-tendon actuators with large attachment sites is described by multiple muscle-tendon elements (van der Helm et al., 1991). Joint geometry and muscle-tendon line-of-action allow to calculate the moment arms and thus the moment-generating characteristic of each muscle-tendon element with respect to the anatomical joints.

1.3.2 Muscle-tendon model

A muscle-tendon model is a description of the mechanical interactions of the different components within the muscle-tendon actuator. The most used model in literature is the phenomenological model proposed by Hill (1938), which represents the dynamic properties of muscle contractions to different length, loading and stimulation conditions (based on experimental observations), without describing the complex mechanobiological process of muscle fiber contraction. The extended version of the Hill-type muscle-tendon model proposed by Zajac (1989) (Figure 1.3A) consists of a force-generating muscle, represented by an active contractile element CE, in parallel with a passive element PE, representing the passive stiffness of connective tissue, and in series with an elastic tendon T, modeled as a nonlinear spring.

Forces produced by each muscle-tendon element depend on the physiological boundaries imposed by force-length and force-velocity characteristics of the contractile element CE, and the elasticity of the passive element PE and of the tendon T. In particular, the force in the muscle is expressed as:

$$F^M = F^{CE} + F^{PE} = \overline{F^M} * F_l(L_f) * F_v(\dot{L}_f) * a + F_p(L_f)$$

where $\overline{F^M}$ denotes the maximal isometric muscle force, F_l , F_p and F_v denote the active and passive force-length, and the force-velocity relationships (Figure 1.3B), and a denotes the muscle activity. For each muscle-tendon element, $\overline{L_f}$ represent the nominal muscle fiber length, which is the length at which the muscle can produce the maximal isometric force $\overline{F^M}$. The effective operating range of the muscle begins at roughly $0.5 \overline{L_f}$ and ends at $1.5 \overline{L_f}$. In addition, the muscle starts producing passive force when it is stretched to lengths greater than $\overline{L_f}$. When a muscle fiber is within its force-generating range, in order to transmit force

Figure 1.3 – A: Schematic representation of the three-elements Hill-type muscle-tendon model proposed by Zajac (1989). The MT element consists of an active muscle, represented by a contractile element CE in parallel with a passive element PE, in series with an elastic tendon T, modeled as a nonlinear spring. B: Active force-length relationship F_l , passive force-length relationship F_p and force-velocity F_v relationship.

to a body segment the tendon must be strained beyond its slack length L_T^s , such that the force in the tendon F^{MT} is equal to the summed force in the muscle fibers F^M adjusted by pennation angle γ between the muscle fiber and the tendon:

$$F^{MT} = F^M \cos \gamma$$

$\overline{F^M}$ is assumed to be proportional to physiological cross-sectional area (PCSA), which can be approximated from muscle volume Vol_M and nominal muscle fiber length $\overline{L_f}$ (Lieber et al., 2000), and maximum muscle stress σ_0 :

$$\overline{F^M} = PCSA * \sigma_0 = \frac{Vol_M}{\overline{L_f}} * \sigma_0$$

Hence, given the state of a muscle-tendon element, i.e. the muscle fiber length L_f , muscle fiber velocity $\dot{L}_f$, and pennation angle γ , and knowing the muscle-tendon moment arm based on musculoskeletal geometry, it is possible to calculate the maximum torque that a muscle-tendon element can generate around a joint.

1.3.3 Inverse dynamics and muscle recruitment problem

In gait analysis, position and orientation of body segments are usually measured using video-based motion capture technique systems which track the 3D positions of optical markers placed on the skin at bony landmarks, while force platforms are used to measure ground reaction forces and moments during foot contact. Then, following the so-called inverse dynamics approach, measured movement and external forces are applied to the traditional Newton-Euler equations of motion, in conjunction with the musculoskeletal geometry characteristics of the model, in order to calculate the net joint moments necessary to reproduce the measured movement (Erdemir et al., 2007)

Once the net joint moments are calculated, individual muscle-tendon forces that have produced these joint moments need to be predicted. However, musculoskeletal models are redundant systems, since several muscle-tendon elements cross each joint, hence multiple combinations of muscle activity could result in the predicted net joint moments. To solve this indeterminacy, a muscle recruitment problem is then solved, where an optimal combination of muscle forces is calculated by minimizing a cost function related to physiological quantities, for example muscle stress, muscle activity, or muscle energy (Pedotti et al., 1978; Crowninshield et al., 1981; Rasmussen et al., 2001; Praagman et al., 2006).

1.3.4 Musculoskeletal datasets of the lower extremity

The accuracy of model predictions depends on the quality of musculoskeletal geometry and muscle-tendon parameters used to describe the anatomy of the human part being represented. Collection of these parameters from cadaver specimens has challenged researchers in the past decades. Several anatomical studies have been published in the past, containing values of musculoskeletal geometry (Brand et al., 1982; White et al., 1989; Lengsfeld et al., 1994; Duda et al., 1996; Kepple et al., 1998) and muscle-tendon parameters (Wickiewicz et al.,

1983; Friederich et al., 1990; Spoor et al., 1991; Ward et al., 2009) of different parts of the lower extremity. However, most of these studies were not complete, and the extended datasets constructed by merging these existing sources (Pierrynowski et al., 1985; Delp et al., 1990; Arnold et al., 2010) resulted in inconsistent anatomical configurations that never existed.

The Twente Lower Extremity Model (Klein Horsman et al., 2007) was created to bypass this inconsistency, and was based on an extensive cadaver study, where all model parameters were measured in one single specimen. TLEM consists of 12 body segments, 11 joints and 21 degrees of freedom, each leg containing 56 muscle-tendon parts whose mechanical effect is described by 159 three-element Hill-type muscle-tendon elements (Figure 1.4), and represents the first complete and consistent anatomical dataset of the lower extremity available in literature. Starting point for all research data shown in this thesis was the TLEM musculoskeletal model implemented in the AnyBody Modeling System™ (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006).

Figure 1.4 - Twente Lower Extremity Model (Klein Horsman et al., 2007) implemented in the AnyBody Modeling System™ (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006). A: TLEM consists of 12 body segments (Head-Arms-Trunk, pelvis, and right and left femur, patella, tibia, talus and foot), 11 joints (L5S1 and left and right hip, knee, patella/femur, talocrural and subtalar) and 21 degrees of freedom. B: Each leg contains 56 muscle-tendon parts whose mechanical effect is described by 159 three-element Hill-type muscle-tendon elements.

1.4 Subject-specific modeling

In recent years, musculoskeletal models of the lower extremity have been used to explore biomechanical problems in several disparate disciplines, such as in orthopedic surgery to simulate the effects of joint replacements (Delp et al., 1994; Piazza et al., 2001) and tendon transfers (Piazza et al., 2003; Reinbolt et al., 2009); in neurology to model the effects of a stroke (Higginson et al., 2006), disorders of the central nervous system (Steele et al., 2012; van der Krogt et al., 2013), and spinal cord injuries (Paul et al., 2005; To et al., 2005); in sport to optimize athletes performances (Pandy et al., 1990; Rasmussen et al., 2012), and

analyses and prevent injuries (McLean et al., 2003; Manal et al., 2005); or in ergonomics for prevention of work-related musculoskeletal disorders (Wu et al., 2009).

To represent different subjects, generic models, which are based on one or more cadaver specimens (Delp et al., 1990; Klein Horsman et al., 2007; Arnold et al., 2010), are usually linearly scaled by fitting the anthropometry of the subject to the relative position of the measured optical markers (Andersen et al., 2010). However, these scaling procedures cannot account for inter-individual anatomical variability in musculoskeletal geometry due to differences in age, height, and gender (White et al., 1989; Duda et al., 1996; Kepple et al., 1998). Also muscle-tendon parameters have been shown to vary between subjects based on age and physical activity (Brand et al., 1981; Friederich et al., 1990; Blazevich et al., 2003) and to not correlate with bone dimensions (Ward et al., 2005; Ward et al., 2007). Hence, it is likely that generic models have limited capacity to differentiate between subjects. Hence, for individual applications, an accurate description of the musculoskeletal system is required (Scheys et al., 2008; Lenaerts et al., 2009).

Constructing subject-specific models without intensive manual intervention represents a significant challenge (Blemker et al., 2007). Musculoskeletal parameters were usually measured on cadaver specimens, but recent advancements in medical imaging such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound have opened new possibilities for *in vivo* measurements. Indeed, several recent studies have focused on developing subject-specific models based on imaging or functional measurements (Koo et al., 2002; Scheys et al., 2005; Hainisch et al., 2012). However, these techniques can be computationally intensive and the extensive manual intervention required makes these approaches costly and labor-intensive. Development of accurate, automatic, time-effective and cost-effective methods to obtain subject-specific musculoskeletal models is crucial for their application in clinical scenarios on a large scale. But on which parameters should researcher focus when creating subject-specific models? And will the personalization of the model parameters result in more accurate predictions?

1.4.1 Sensitivity of model predictions

When using detailed state-of-the-art models such as TLEM, it is clear that personalization of all parameters for all muscles is not feasible, hence it is fundamental to clarify which muscles need to be described with greater detail. Unfortunately, it is not clear yet which parameters and which muscles are most sensitive to potential measurement errors.

Previous sensitivity studies have found a critical parameter in the muscle-tendon moment arms (Hoy et al., 1990; Out et al., 1996; Maganaris, 2004), whose estimation depends on the identification of MT line-of-action (Rohrle et al., 1984; Pal et al., 2007) and joint geometry (Martelli et al., 2015; Valente et al., 2015). Moreover, most studies that looked at muscle-tendon parameters have shown that model predictions are most sensitive to changes in tendon slack length, followed by nominal muscle fiber length and maximal isometric muscle force. Unfortunately, these analyses used simplified models (Hoy et al., 1990), reported results

averaged over all muscles analyzed (Scovil et al., 2006), or focused only on a single joint (Out et al., 1996; De Groote et al., 2010) or on a small group of representative muscles (Redl et al., 2007; Xiao et al., 2010; Ackland et al., 2012).

To our knowledge, no extensive sensitivity analysis has been performed on complex and detailed models to study individual sensitivity in muscles to musculoskeletal geometry and muscle-tendon parameters perturbations. This sensitivity analysis would give quantitative information about which parameters and which muscles need to be estimate most accurately, and could be used to define suitable measurements protocols, in order to create detailed subject-specific models in an efficient way.

1.4.2 Subject-specific modeling techniques

Once it is clear which parameters and which muscles need to be estimated with most precision, it is essential to develop accurate and effective methods to estimate subject-specific parameters. Recent studies have demonstrated the potential of using medical imaging data to describe bone geometry (Smith et al., 1989; Viegas et al., 1993), to detect muscle-tendon attachment sites (Scheys et al., 2009) and to determine muscle-tendon moment arms (Arnold et al., 2000; Scheys et al., 2011b). However, those methods can be computationally intensive, time consuming and cost-ineffective, because of the extensive manual intervention required to segment bone and muscles contours. An interesting approach to reduce the processing time was introduced by Scheys et al. (2009) with an atlas-based method to register a previously built template to the medical images of the subject. However, no existing musculoskeletal model in the literature has been accompanied by detailed medical images and post-processing data. Even the TLEM model (Klein Horsman et al., 2007), that represents so far the most complete and consistent dataset of the lower extremity, lacks of detailed medical images of the cadaver specimen used during measurements, requiring significant improvements in order to make it suitable for image-based subject-specific scaling techniques.

Previous studies have presented methods to measure muscle-tendon parameters using non-invasive modality such as ultrasound (Maganaris et al., 1998; Maganaris et al., 2006; Albracht et al., 2008) or medical images (Galbán et al., 2004; Heemskerk et al., 2005; Yuen et al., 2006; Hainisch et al., 2012), however these quantities are very difficult to measure in living subjects, even when non-invasive techniques are used. Hence, these methods are still laborious and not feasible to create a personalized model of the complete lower extremity. One option is to optimize muscle-tendon parameters taking into account subject-specific muscle strength and moment-angle relationship based on dynamometry data (Hatze, 1981; Koo et al., 2002; Garner et al., 2003; van Campen et al., 2014), however no feasible application of these methods have been shown yet.

1.4.3 Validation of model predictions

Once a subject-specific model is built, it is crucial to quantify the effect of the personalization on the model outcomes, and to assess the differences in the force predicted by the subject-

specific and the generic models. However, the most important question is whether predictions by subject-specific models are better than generic models. Validation of musculoskeletal model predictions represents a crucial problem in musculoskeletal mechanics (Lund et al., 2012), since it is essential to have a justified confidence in model outcomes before their application in critical decision-making processes, such as surgery planning.

Direct validation of model outcomes requires a comparison between a model output of interest with an experimental measurement of the same quantity. However, in-vivo measurement of muscle and joint reaction forces requires special circumstances, such as use of optic-fiber technique (Finni et al., 2000), in situ buckle-type force transducers (Gregor et al., 1991), or instrumented joint replacements (Bergmann et al., 2001; Fregly et al., 2012). For these reasons, direct validation of musculoskeletal models is inherently difficult, costly and ethically problematic to perform.

The inability to measure forces directly leaves the researcher with the option to focus on other model outcomes that are easier to measure experimentally. Comparison of electromyography (EMG) measurements with predicted muscle activity represent an example of indirect validation of models prediction (Giroux et al., 2013). Unfortunately, EMG signals are known to be sensitive to the placement of the electrodes on the surface of the skin above muscles (De Luca, 1993). Also, electromechanical delay has been reported to be dependent on several factors, such as muscle-tendon stiffness (Grosset et al., 2008), the type of muscular contraction (Cavanagh et al., 1979; Zhou et al., 1995), the age (Grosset et al., 2005) and gender (Winter et al., 1991) of the subject. All these factors are likely to affect the reliability of EMG measurements for quantitative validation, as suggested by Lund et al. (2012).

Next to EMG, measurement of local oxygen consumption of muscle tissue, reflecting the energy consumption process, through near infrared spectroscopy (NIRS) has been proposed as a validation tool for musculoskeletal models (Praagman et al., 2003). Although both EMG and NIRS represent a convenient and non-invasive technique for indirect validation of musculoskeletal models, they share important limitations, such as the number of muscles that can be measured at the same time is restricted, deep-lying muscles cannot be measured, and adipose tissue and crosstalk from other muscles represent important confounding factors.

Positron emission tomography (PET) combined with the radioactive tracer [^{18}F]-Fluoro-deoxy-glucose (FDG) has been recently employed to measure the intensity of muscular activity of the lower extremity during aerobic activities such as walking (Oi et al., 2003), being able to distinguish the relative contributions of individual muscles to joint moments (Pappas et al., 2001; Masood et al., 2014), hence to indirectly ascertain the functional differences in the muscle recruitment process. Moreover, unlike EMG and NIRS, FDG-PET can be used to estimate activity in all muscles of the lower extremity, including the deep muscles, in a single session (Kolk et al., 2015). However, its feasibility as a validation tool for musculoskeletal models has not been proved.

1.5 Aim and outline of thesis

The main goal of this thesis is to develop accurate and effective methods to create subject-specific musculoskeletal models of the lower extremity, and to assess whether personalization of model parameters results in improvements in the model predictions, in order to allow for their application in critical scenarios such as clinical decision making. The research results are shown in the following chapters:

Chapter 2 and **Chapter 3** present an extensive sensitivity analysis to quantify the effect of potential errors in musculoskeletal geometry and muscle-tendon parameters on subject-specific model outcomes. Two metrics, namely a Local Sensitivity Index (LSI) and an Overall Sensitivity Index (OSI), are used to distinguish the effect of the perturbation on the perturbed muscles and on all the remaining muscles, respectively. The results provide quantitative information to draw up a priority list of muscles and parameters that should be estimated most accurately, in order to create detailed and reliable subject-specific musculoskeletal models that satisfies the required accuracy of the specific application.

Chapter 4 presents an updated version of the Twente Lower Extremity Model, called TLEM 2.0, a new comprehensive dataset of the musculoskeletal geometry of the lower extremity, which is based on new medical imaging data and dissection measurements performed on one single cadaver specimen. The new TLEM 2.0 dataset represents the first consistent and complete ‘atlas’ model, which includes a set of CT and MRI scans, segmented bone, muscle and subcutaneous fat (including skin) volumes, inertial parameters, coordinates of bony landmarks, muscle and ligaments attachment sites and lines-of-action, bony wrapping surfaces, and joint centers and axes of rotation. TLEM 2.0 is purposely built to be easily combined with image-based scaling techniques, such as bone surface morphing, muscle volume registration and muscle-tendon path identification, in order to obtain subject-specific musculoskeletal models in a quick and accurate way.

In **Chapter 5**, TLEM 2.0 is combined with novel image-based scaling methods to obtain personalized musculoskeletal geometry of the lower extremity of ten healthy subjects with limited manual intervention. Then, the differences between generic and subject-specific musculoskeletal geometry are quantified, and the effect of the personalized parameters are assessed by comparing predictions by generic and subject-specific models.

Subsequently, in **Chapter 6**, the modeling workflow presented in Chapter 5 is expanded with additional methods for estimating muscle-tendon parameters from MRI and dynamometry data, in order to build ten personalized musculoskeletal models with increasing details. Again, the differences between generic and subject-specific muscle-tendon parameters are quantified, and the effect of the personalized parameters are assessed by comparing predictions by generic and subject-specific models.

In **Chapter 7**, the novel technique of positron emission tomography (PET) combined with the radioactive tracer [18F]-Fluoro-deoxy-glucose is used as an indirect validation tool for musculoskeletal models. The activity of all muscles of the lower extremity during walking, measured on the ten healthy subjects using FDG-PET, is compared with the metabolic energy consumption predicted by the corresponding personalized models built in Chapter 6, in order to determine whether subject-specific models provide better predictions than generic models.

Finally, **Chapter 8** presents a general discussion, where the added value and limitations of the subject-specific lower extremity modeling proposed in this thesis are discussed, and future work is suggested for further improvements.

Chapter 2

Sensitivity of subject-specific models to errors in musculoskeletal geometry

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Abstract

Subject-specific musculoskeletal models of the lower extremity are an important tool for investigating various biomechanical problems, for instance the results of surgery such as joint replacements and tendon transfers. The aim of this study was to assess the potential effects of errors in musculoskeletal geometry on subject-specific model results. We performed an extensive sensitivity analysis to quantify the effect of the perturbation of origin, insertion and via points of each of the 56 muscle-tendon parts contained in the model. We used two metrics, namely a Local Sensitivity Index (LSI) and an Overall Sensitivity Index (OSI), to distinguish the effect of the perturbation on the predicted force produced by only the perturbed muscle-tendon parts and by all the remaining muscle-tendon parts, respectively, during a simulated gait cycle. Results indicated that, for each muscle-tendon part, only two points show a significant sensitivity: its origin, or pseudo-origin, point and its insertion, or pseudo-insertion, point. The most sensitive points belong to those muscle-tendon parts that act as prime movers in the walking movement (insertion point of the Achilles Tendon: LSI=15.56%, OSI=7.17%; origin points of the Rectus Femoris: LSI=13.89%, OSI=2.44%) and as hip stabilizers (insertion points of the Gluteus Medius Anterior: LSI=17.92%, OSI=2.79%; insertion point of the Gluteus Minimus: LSI=21.71%, OSI=2.41%). The proposed priority list provided quantitative information to improve the predictive accuracy of subject-specific musculoskeletal models.

2.1 Introduction

Accurate knowledge of lower limb muscle and joint reaction forces is fundamental to explore several biomechanical problems. Musculoskeletal (MS) models have previously been used to simulate the effects of surgery such as joint replacements (Delp et al., 1994; Piazza et al., 2001) and tendon transfers (Piazza et al., 2003; Reinbolt et al., 2009). In these cases, subject-specific MS geometry is essential to achieve reliable muscle-tendon (MT) force predictions (Lenaerts et al., 2009). Unfortunately, it remains unclear which parameters and which muscles are most sensitive to potential errors.

Previous analyses on MS geometry focused on the sensitivity of muscle moment arms (Hoy et al., 1990; Out et al., 1996; Maganaris, 2004), whose estimation depends on the identification of MT path (Rohrle et al., 1984; Pal et al., 2007). However, to our knowledge no comprehensive analysis has been performed on complex, multi-segment MS models.

The aim of this study was to assess the potential effects of errors in MS geometry on subject-specific model outcomes. We performed an extensive sensitivity analysis to quantify the effect of perturbation of muscle origin, insertion and via points on the model force predictions during gait. The results provided quantitative information to draw up a priority list of the points that need to be estimated most accurately, in order to obtain more reliable subject-specific MS models.

2.2 Methods

We used the Twente Lower Extremity Model (TLEM) (Klein Horsman et al., 2007) implemented in the AnyBody Modeling System™ ver. 4.2.1 (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006) (Figure 2.1A). The model consisted of 12 body segments, 11 joints, and 21 degrees of freedom. Each leg contained 56 MT parts whose mechanical effect was described by 159 three-element Hill-type MT elements (Zajac, 1989). Each MT element was described by the origin and insertion points on the corresponding segments. In case of surrounding structures, such as retinacula and tendon sheaths, via points were defined (Delp et al., 1990). The most distal via point on the proximal segment, if present, was defined as pseudo-origin. Similarly, the most proximal via point on the distal segment, if present, was defined as the pseudo-insertion.

Inverse dynamics simulations were based on 3D motion analysis and force-plate data recorded during a trial of walking on a level walkway. Age, height and mass of the one male subject were 26 years, 1.73 m and 63 kg respectively. The model was linearly scaled in order to match the anthropometry of the subject, derived from the marker positions relative to each other. A static optimization problem was solved, minimizing the sum of the cubes of muscle activity at each time step (Crowninshield et al., 1981).

For each MT part, origin, insertion and via points were perturbed from their nominal position. For each point, 6 perturbations were applied: +1 cm and -1 cm along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) directions of the local segment coordinate

systems (Wu et al., 2002). MT parts sharing a common point were perturbed simultaneously (Figure 2.1B). For reasons of symmetry, only the MT parts in the right leg were perturbed. In total, 55 origin points, 39 insertion points and 39 via points (including pseudo-attachment points) were perturbed from their nominal position, for a total of $(55+39+39) \times 6 = 798$ perturbations.

Figure 2.1 – A: TLEM model implemented in the AnyBody Modeling System™ ver. 4.2.1 (AnyBody Technology A/S, Aalborg, Denmark). It consisted of 12 body segments: HAT (Head, Arms and Trunk), pelvis, and right and left femur, patella, tibia, talus and foot. The fibula was considered as one unit in combination with the tibia. The model comprised 11 joints: L5S1 and left and right hip, knee, patella/femur, talocrural and subtalar. The L5S1 and hip joints were modeled as a ball-and-socket, defined by a rotation center and three orthogonal axes. The knee, talocrural and subtalar joints were defined as a hinge, with a fixed rotation center and axis. The patella could rotate with respect to the femur around a rotation axis with a fixed rotation center. The patellar tendon was defined as a non-deformable element that connected the patella to the tibia. Thus, without introducing an extra degree of freedom (DOF), the orientation and position of the patella depended solely on the knee flexion angle. The orientation and position of the center of mass of the pelvis with respect to a 3D global frame, together with the joint rotations of the L5S1, hip, knee, talocrural and subtalar joints, resulted in a model with 21 DOFs. B: Perturbations of the 3D location of the insertion point of the Achilles Tendon from its nominal position. Perturbations of +1 cm and -1 cm were performed along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) directions of the local coordinate system of the foot.

For each perturbed MT element, tendon slack lengths were automatically recalibrated maintaining the nominal muscle fiber length. Then, a new static optimization problem was solved. Sensitivity of the model was quantified by computing two metrics:

1. Local Sensitivity Index (LSI), to quantify the effect of the perturbation on the predicted force produced only by the perturbed MT parts:

$$LSI = \frac{\sum_{i=pert} \int_0^T |F_{new,i}^{MT}(t) - F_{old,i}^{MT}(t)| dt}{\sum_{i=pert} \int_0^T F_{old,i}^{MT}(t) dt} \cdot 100\% \quad (1)$$

2. Overall Sensitivity Index (OSI), to quantify the effect of the perturbation on the predicted force produced by all the remaining not-perturbed MT parts of the right leg:

$$OSI = \frac{\sum_{i \neq pert} \int_0^T |F_{new,i}^{MT}(t) - F_{old,i}^{MT}(t)| dt}{\sum_{i \neq pert} \int_0^T F_{old,i}^{MT}(t) dt} \cdot 100\% \quad (2)$$

where $F_{old,i}^{MT}(t)$ and $F_{new,i}^{MT}(t)$ are the nominal and perturbed values of force, respectively, produced by the perturbed ($i = pert$) and not-perturbed ($i \neq pert$) MT parts at time step t , and T is the final time of the simulated gait cycle. Pilot results showed that perturbations in the right leg had no influence on predicted forces in the left leg.

For the three origin, insertion and via points that showed the highest OSI values, we also performed perturbation of -1.5 cm, -0.5 cm, +0.5 cm and +1.5 cm along the X, Y and Z directions, in order to check the linearity of the sensitivity values.

2.3 Results

This study indicated that the model predictions were sensitive to small changes in MS geometry. Tables 2.A1, 2.A2 and 2.A3 contained in the Appendix show the complete sensitivity results for perturbations of muscle origin, insertion and via points, respectively.

LSI values, representing the sensitivity of the perturbed MT parts, depended strongly on which point was perturbed and on the direction of the perturbation (Figure 2.2A-B-C). Mean LSI values ranged from a maximum of 39.10% (insertion point of the Obturator Externus Superior (Table 2.A2)) to negligible contributions for the least sensitive points. The maximum LSI value was equal to 80.89% (insertion point of the Obturator Externus Superior - +1 cm along the Y direction (Table 2.A2)).

Similarly, OSI values, representing the sensitivity of the not-perturbed MT parts, depended strongly on which point was perturbed and on the direction of the perturbation (Figure 2.2D). Mean OSI values ranged from a maximum of 7.17% (insertion point of the Achilles Tendon (Table 2.A2)), to negligible contributions for the least sensitive points. The maximum OSI value was equal to 15.47% (insertion point of the Achilles Tendon - +1 cm along the Z direction (Table 2.A2)).

Moreover, LSI and OSI values showed a small Pearson linear correlation coefficient ($r=0.3661$). Hence, the points that showed very high LSI values did not necessarily show very high OSI values (Figure 2.3).

Finally, for the three origin, insertion and via points that were found to be the most sensitive, the OSI values showed a close-to-linear pattern in the range of perturbations between -1.5 cm and +1.5 cm (Figure 2.4).

2.4 Discussion

The purpose of this study was to assess the sensitivity of subject-specific models to potential errors in MS geometry. Similarly to Redl et al. (2007), we quantified the sensitivity of the model by computing two metrics. Local Sensitivity Index (LSI) quantified the reaction of the

Figure 2.2 - Effect of perturbation of muscle points from their nominal position on the predicted MT forces during normal walking. Perturbations of +1 cm and -1 cm were performed along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) directions of the local segment coordinate systems. The black solid lines are the nominal MT forces before the perturbation; the blue, red and green dashed lines are the predicted MT forces after the perturbation along the X, Y Z directions, respectively. A: Force produced by the Rectus Femoris after the perturbation of the origin points of the Rectus Femoris; B: Force produced by the Adductor Longus after the perturbation of the origin points of the Adductor Longus; C: Sum of the forces produced by the Gastrocnemius Lateralis and Medialis, Soleus Lateralis and Medialis, and Plantaris after the perturbation of the insertion point of the Achilles Tendon; D: Sum of the forces produced by all the remaining not-perturbed MT parts after the perturbation of the insertion point of the Achilles Tendon. Local Sensitivity Index (LSI) was calculated by integrating the absolute difference between the nominal and perturbed MT forces over the simulated gait cycle, and then summing these integrated quantities across all the perturbed MT parts (see Eq. (1)). Overall Sensitivity Index (OSI) was calculated by integrating the absolute difference between the nominal and perturbed MT forces over the simulated gait cycle, and then summing these integrated quantities across all the non-perturbed MT parts (see Eq. (2)). Please note that different scales were used for subplots A-B and C-D.

perturbed MT parts to maintain their nominal contribution to the joint moment, and depended mainly on the variation of the moment arms. On the other hand, Overall Sensitivity Index (OSI) quantified the reaction of all the not-perturbed MT parts to balance the different contribution to the joint moments by the perturbed MT parts, especially for biarticular MT parts.

For each MT part (the only exception was the Sartorius), only two points showed significant sensitivity: its origin, or pseudo-origin, and its insertion, or pseudo-insertion. In fact, muscle moment arms were affected only by perturbations of attachment or pseudo-attachment points, while perturbations of any other point would just affect the length of the MT element.

Figure 2.3 - Overall Sensitivity Index (OSI) values of the model to perturbations of muscle points from their nominal position, plotted against their relative Local Sensitivity Index (LSI) values. LSI and OSI values showed a small Pearson linear correlation coefficient ($r=0.3661$). The point that showed the highest LSI value (I: insertion point of the Obturator Externus Superior - +1 cm along the Y direction (Table 2.A2)) differs from the point that showed the highest OSI value (II: insertion point of the Achilles Tendon - +1 cm along the Z direction (Table 2.A2)); III: origin point of the Popliteus - +1 cm along Y direction showed very high LSI value but very low OSI value (Table 2.A1); insertion point of the Achilles Tendon showed the maximum LSI value for perturbation of +1 cm along the X direction (II), while the maximum OSI value for perturbation of +1 cm along the Z direction (IV) (Table 2.A2).

Moreover, points showing high LSI values but low OSI values indicated large relative changes in MT parts contributing only little to the joint moments: the effect of the perturbation was limited to the perturbed MT part only and did not influence the rest of the model. On the contrary, high OSI values indicated MT parts with an important role during the gait and whose perturbation would affect the remaining MT parts.

For these reasons, we decided to use OSI values as an index to draw up a priority list of the points that need to be estimated most carefully to create a more reliable subject-specific MS model (Table 2.1). The most sensitive points belong to the MT parts that act as prime movers in the walking movement (Triceps Surae, Quadriceps Femoris, Hamstrings) and hip stabilizers (Gluteal Muscles, Iliacus, Obturator Internus and Externus, and Piriformis).

Several limitations should be kept in mind before interpreting our results. Firstly, the proposed sensitivity analysis was based on the gait simulation of a single subject. Gait simulations of various healthy subjects are likely to show great similarities in the force predictions. Therefore, the ranking of the most sensitive points is expected to remain similar. Secondly, the sensitivity analysis was applied only to normal walking. Since muscle function strongly depends on the task performed (Liu et al., 2008), results are expected to change based on the movement analyzed (Scovil et al., 2006).

Thirdly, the static optimization problem was solved using a single performance criterion, specifically by minimizing the sum of cubes of muscle activation at each time step. It is likely

Figure 2.4 - Linearity of the model sensitivity to perturbation of muscle points from their nominal position. Perturbations of -1.5 cm, -1 cm, -0.5 cm, +0.5 cm, +1 cm and +1.5 cm were performed along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) directions of the local segment coordinate systems. For each perturbation, Overall Sensitivity Index (OSI) values are plotted. A: OSI values of the three origin points that were found to be most sensitive: Rectus Femoris, Gluteus Medius Anterior, Sartorius; B: OSI values of the three insertion points that were found to be the most sensitive: Achilles Tendon, Gluteus Medius Anterior, Gluteus Minimus; C: OSI values of the three via points that were found to be the most sensitive: Peroneus Longus, Peroneus Brevis, Iliacus. Plots show a close-to-linear pattern in the range of perturbations between -1.5 cm and +1.5 cm.

that sensitivity results depend on the performance criterion used, but the ranking of the most sensitive points could be similar for other criteria (De Groote et al., 2010).

Table 2.1 - Priority list of the most sensitive attachment, or pseudo-attachment, points to perturbations from their nominal position.

		Local Sensitivity Index (%)				Overall Sensitivity Index (%)			
		X	Y	Z	Mean	X	Y	Z	Mean
Achilles Tendon	I.	24.62	5.60	16.46	15.56	7.17	1.74	12.60	7.17
Gluteus Medius Anterior	I.	15.94	28.39	9.43	17.92	3.31	3.62	1.42	2.79
Rectus Femoris	O.	18.89	10.70	12.08	13.89	2.72	1.74	2.86	2.44
Gluteus Minimus	I.	28.65	22.89	13.59	21.71	4.08	1.74	1.40	2.41
Gluteus Medius Posterior	I.	53.43	32.57	11.78	32.60	4.08	1.93	0.69	2.23
Obturator Internus	I.	21.08	37.22	6.65	21.65	1.51	3.92	0.88	2.10
Iliacus	I.	5.98	2.19	6.87	5.01	1.39	1.34	3.00	1.91
Quadriceps Femoris	I.	15.06	14.24	7.82	12.37	1.85	1.88	1.16	1.63
Peroneus Longus	P.O.	1.26	20.66	12.08	11.33	0.29	2.76	1.41	1.49
Obturator Externus Superior	I.	32.55	72.84	11.90	39.10	1.36	2.27	0.51	1.38
Gluteus Medius Anterior	O.	6.94	2.91	1.58	3.81	2.05	1.20	0.39	1.21
Peroneus Brevis	P.O.	3.38	26.61	12.90	14.29	0.21	2.06	0.99	1.09
Sartorius	O.	2.56	1.31	2.62	2.16	1.53	0.63	1.02	1.06
Adductor Longus	O.	53.37	21.46	18.19	31.01	1.54	0.63	0.74	0.97
Piriformis	I.	14.59	22.67	5.00	14.09	0.55	1.55	0.67	0.92
Iliacus	P.O.	11.76	6.11	8.60	8.82	1.20	0.44	1.08	0.91
Gluteus Minimus Anterior	O.	20.68	2.12	3.10	8.63	1.56	0.38	0.53	0.82
Biceps Femoris	I.	24.53	15.47	10.58	16.86	1.08	0.79	0.51	0.79
Obturator Externus Superior	P.O.	25.68	19.46	9.87	18.34	1.01	1.00	0.33	0.78
Tibialis Anterior	P.I.	24.06	2.13	7.19	11.13	0.81	0.42	1.08	0.77
Obturator Internus	P.O.	3.82	5.05	2.77	3.88	0.56	1.06	0.29	0.64
Sartorius	I.	2.37	1.30	0.80	1.49	0.95	0.55	0.34	0.61
Soleus Medialis	O.	0.98	0.65	0.85	0.83	0.90	0.28	0.64	0.60
Semitendinosus	P.I.	16.22	13.27	7.34	12.28	0.85	0.51	0.36	0.57
Semimembranosus	I.	29.52	18.57	13.29	20.46	0.76	0.45	0.35	0.52
Soleus Lateralis	O.	0.62	0.61	1.21	0.81	0.78	0.20	0.50	0.50
Peroneus Tertius	P.O.	4.92	28.72	13.67	15.77	0.20	0.74	0.43	0.46
Flexor Hallucis Longus	P.O.	33.46	6.25	5.68	15.13	0.89	0.25	0.21	0.45
Biceps Femoris Caput Longum	O.	13.28	9.39	14.42	12.36	0.35	0.24	0.74	0.44
Tibialis Posterior Medialis	P.O.	9.38	45.71	5.64	20.24	0.23	0.90	0.17	0.44
...	...	...	...	...	...	...	...	...	...

Perturbations of +1 cm and -1 cm were performed along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) direction of the local segment coordinate systems. For each point, mean values of Local Sensitivity Index (LSI) and Overall Sensitivity Index (OSI) over X, Y and Z direction and over the six perturbations are indicated. Cell shading (blue for LSI, red for OSI) is directly proportional to the sensitivity values. O., P.O., I. and P.I. indicate if the point represents an origin, pseudo-origin, insertion or pseudo-insertion, respectively.

In conclusion, this study showed that small errors in MS geometry can have a significant impact on muscle force predictions, and provided quantitative information to improve the predictive accuracy of MS models. An expansion of the proposed sensitivity analysis to several subjects and tasks, different performance criterion and other model parameters related to MS geometry and MT architecture could help to improve our understanding of the vulnerability of subject-specific model outcomes to potential measurement errors.

Appendix

Tables 2.A1, 2.A2 and 2.A3 contain the complete sensitivity results for perturbations of muscle-tendon origin, insertion and via points, respectively.

Table 2.A1 - Sensitivity of the model to perturbations of muscle-tendon origin points from their nominal position.

		Local Sensitivity Index (%)						Overall Sensitivity Index (%)							
		X		Y		Z		Mean	X		Y		Z		Mean
		-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm		-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	
Adductor Brevis Distal	Pe	13.10	12.26	3.86	3.72	3.96	4.92	6.97	0.07	0.05	0.04	0.03	0.03	0.03	0.04
Adductor Brevis Mid	Pe	12.60	13.73	3.02	3.50	5.40	6.14	7.40	0.06	0.06	0.04	0.04	0.03	0.03	0.04
Adductor Brevis Proximal	Pe	27.29	29.53	7.66	8.93	12.35	21.24	17.83	0.11	0.14	0.08	0.08	0.05	0.10	0.09
Adductor Longus	Pe	66.98	39.76	24.99	17.94	10.10	26.28	31.01	1.47	1.60	0.79	0.47	0.56	0.93	0.97
Adductor Magnus Distal	Pe	17.12	45.55	8.68	9.14	16.76	14.17	18.57	0.22	0.46	0.09	0.11	0.23	0.20	0.22
Adductor Magnus Mid	Pe	6.05	7.42	9.64	8.17	10.82	11.41	8.92	0.05	0.06	0.03	0.03	0.08	0.08	0.05
Adductor Magnus Proximal	Pe	33.18	22.90	4.18	6.44	8.26	9.79	14.13	0.10	0.09	0.03	0.03	0.04	0.04	0.06
Biceps Femoris Caput Breve	Fe	5.96	6.74	0.88	0.82	0.96	0.86	2.70	0.08	0.08	0.01	0.01	0.01	0.01	0.03
Biceps Femoris Caput Longum	Pe	12.04	14.52	8.71	10.07	14.39	14.45	12.36	0.32	0.38	0.22	0.25	0.70	0.78	0.44
Extensor Digitorum Longus	Ti *	0.04	0.02	0.78	0.79	0.08	0.10	0.30	0.00	0.00	0.01	0.01	0.00	0.00	0.01
Extensor Hallucis Longus	Ti *	0.27	0.20	0.99	1.00	0.08	0.15	0.45	0.00	0.00	0.01	0.01	0.00	0.00	0.01
Flexor Digitorum Longus	Ti *	0.16	0.25	1.98	1.99	0.12	0.02	0.75	0.00	0.00	0.01	0.01	0.00	0.00	0.00
Flexor Hallucis Longus	Ti *	0.00	0.07	1.14	1.15	0.20	0.27	0.47	0.00	0.00	0.02	0.02	0.00	0.01	0.01
Gastrocnemius Lateralis	Fe	0.96	1.05	0.57	0.71	1.84	2.00	1.19	0.11	0.19	0.06	0.06	0.39	0.42	0.20
Gastrocnemius Medialis	Fe	1.86	0.73	0.78	0.75	3.05	3.04	1.70	0.37	0.20	0.16	0.15	0.76	0.82	0.41
Gemellus Inferior	Pe	2.32	3.08	10.03	8.38	1.40	1.51	4.45	0.10	0.13	0.25	0.24	0.07	0.07	0.15
Gemellus Superior	Pe	3.03	3.02	4.56	3.77	2.32	2.89	3.27	0.06	0.07	0.09	0.07	0.04	0.04	0.06
Gluteus Maximus Inferior	Pe	4.05	4.23	4.81	4.84	3.40	3.58	4.15	0.14	0.15	0.14	0.14	0.16	0.17	0.15
Gluteus Maximus Superior	Pe *	0.04	0.01	0.39	0.39	0.09	0.06	0.16	0.00	0.00	0.01	0.01	0.00	0.00	0.01
Gluteus Medius Anterior	Pe	6.71	7.16	3.12	2.70	1.70	1.46	3.81	2.10	2.00	1.30	1.09	0.42	0.35	1.21
Gluteus Medius Posterior	Pe	3.35	3.86	1.80	1.22	5.56	5.05	3.47	0.46	0.50	0.11	0.08	0.47	0.43	0.34
Gluteus Minimus Anterior	Pe	18.76	22.59	2.33	1.92	3.27	2.92	8.63	1.37	1.75	0.41	0.34	0.54	0.52	0.82
Gluteus Minimus Mid	Pe	9.99	9.99	2.56	2.38	3.18	3.04	5.19	0.66	0.60	0.20	0.18	0.29	0.29	0.37
Gluteus Minimus Posterior	Pe	8.81	11.93	2.37	2.22	2.81	2.57	5.12	0.63	0.67	0.17	0.15	0.31	0.32	0.37
Gracilis	Pe	0.75	1.15	0.41	0.43	0.67	0.81	0.70	0.53	0.58	0.15	0.11	0.60	0.55	0.42
Iliacus Lateralis	Pe *	0.02	0.01	0.25	0.26	0.09	0.11	0.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Iliacus Medialis	Pe *	0.09	0.07	0.19	0.20	0.05	0.04	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Iliacus Mid	Pe *	0.15	0.11	0.35	0.36	0.02	0.06	0.17	0.00	0.00	0.01	0.01	0.00	0.00	0.00
Obturator Externus Inferior	Pe	15.97	11.83	9.04	11.14	3.20	2.89	9.01	0.08	0.09	0.06	0.07	0.02	0.02	0.06
Obturator Externus Superior	Pe *	0.44	0.60	0.31	0.14	1.03	0.99	0.58	0.01	0.02	0.01	0.00	0.03	0.03	0.02
Obturator Internus	Pe *	0.66	0.69	0.07	0.20	0.14	0.03	0.30	0.06	0.06	0.01	0.02	0.01	0.00	0.02
Pectineus	Pe	14.42	14.14	5.13	6.59	8.74	11.81	10.14	0.11	0.13	0.08	0.08	0.07	0.10	0.09
Peroneus Brevis	Ti *	0.02	0.02	0.54	0.54	0.02	0.07	0.20	0.01	0.01	0.03	0.03	0.01	0.01	0.02
Peroneus Longus	Ti *	0.01	0.01	0.33	0.33	0.02	0.03	0.12	0.01	0.01	0.04	0.04	0.01	0.00	0.02
Peroneus Tertius	Ti *	0.09	0.07	0.42	0.42	0.01	0.04	0.18	0.01	0.01	0.02	0.02	0.01	0.01	0.01
Piriformis	Pe	2.87	2.72	4.53	3.74	0.76	0.91	2.59	0.24	0.24	0.31	0.26	0.08	0.09	0.20
Plantaris	Fe	14.52	20.72	10.40	6.85	1.61	1.46	9.26	0.10	0.11	0.05	0.04	0.02	0.02	0.06
Popliteus	Pe	21.78	12.67	27.36	56.71	1.36	1.48	20.23	0.07	0.07	0.19	0.14	0.02	0.02	0.08
Quadratus Femoris	Pe	24.49	24.11	12.93	15.68	7.66	8.37	15.54	0.34	0.34	0.30	0.31	0.11	0.12	0.25
Rectus Femoris	Pe	15.75	22.02	9.60	11.80	11.38	12.77	13.89	2.65	2.79	1.65	1.82	2.81	2.91	2.44
Sartorius	Pe	2.92	2.19	1.27	1.36	2.94	2.31	2.16	1.59	1.47	0.64	0.61	1.04	1.00	1.06
Semimembranosus	Pe	12.10	11.53	10.78	9.45	14.92	11.61	11.73	0.28	0.29	0.25	0.24	0.41	0.42	0.32
Semitendinosus	Pe	8.25	9.14	7.12	6.62	8.68	7.14	7.82	0.31	0.33	0.25	0.24	0.41	0.41	0.32
Soleus Lateralis	Ti	0.55	0.69	0.61	0.61	1.16	1.26	0.81	0.77	0.80	0.20	0.20	0.51	0.50	0.50
Soleus Medialis	Ti	0.96	1.00	0.66	0.65	0.74	0.95	0.83	0.88	0.92	0.28	0.27	0.65	0.62	0.60
Tensor Fasciae Latae	Pe	7.50	8.58	3.56	3.58	1.62	1.62	4.41	0.32	0.40	0.11	0.11	0.29	0.29	0.25
Tibialis Anterior	Ti *	0.00	0.00	0.11	0.11	0.00	0.00	0.04	0.00	0.00	0.01	0.01	0.00	0.00	0.00
Tibialis Posterior Lateralis	Ti *	0.06	0.19	1.82	1.85	0.46	0.58	0.83	0.00	0.00	0.01	0.01	0.00	0.00	0.01
Tibialis Posterior Medialis	Ti *	0.10	0.17	1.65	1.66	0.07	0.15	0.63	0.00	0.00	0.02	0.02	0.00	0.00	0.01
Vastus Intermedius	Fe	2.11	1.67	1.49	1.54	1.25	1.71	1.63	0.03	0.03	0.02	0.02	0.02	0.02	0.02
Vastus Lateralis Inferior	Fe	2.48	2.10	3.87	4.00	0.99	1.28	2.45	0.01	0.01	0.01	0.01	0.00	0.00	0.01
Vastus Lateralis Superior	Fe	0.35	0.27	0.54	0.55	0.61	0.69	0.50	0.05	0.05	0.05	0.05	0.03	0.03	0.05
Vastus Medialis Inferior	Fe	12.20	13.95	10.81	20.37	17.72	13.15	14.70	0.03	0.03	0.03	0.05	0.05	0.04	0.04
Vastus Medialis Mid	Fe	6.80	5.29	1.32	1.06	1.26	2.89	3.10	0.04	0.11	0.07	0.07	0.08	0.05	0.07
Vastus Medialis Superior	Fe	2.16	1.42	1.09	1.57	0.80	1.55	1.43	0.05	0.09	0.08	0.07	0.08	0.06	0.07

Perturbations of +1 cm and -1 cm were performed along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) direction of the local segment coordinate systems. For each perturbation, Local Sensitivity Index (LSI) and Overall Sensitivity Index (OSI) values are indicated. For each point, mean LSI and OSI values over the six perturbations are indicated. Cell shading (blue for LSI, red for OSI) is directly proportional to the sensitivity values. The body segment where each origin point was located is indicated: Pe=Pelvis, Fe=Femur, Ti=Tibia. * indicates MT parts having also a pseudo-origin point.

Table 2.A2 - Sensitivity of the model to perturbations of muscle-tendon insertion points from their nominal position.

		Local Sensitivity Index (%)						Overall Sensitivity Index (%)					
		X		Y		Z		X		Y		Z	
		-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm
		Mean						Mean					
		-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm
Achilles Tendon	Fo	18.60	30.64	5.75	5.45	17.01	15.91	15.56	5.69	8.64	1.82	1.65	9.74
Adductor Brevis Distal	Fe	5.44	5.78	0.67	0.70	1.79	1.56	2.66	0.04	0.04	0.01	0.01	0.01
Adductor Brevis Mid	Fe	4.79	5.64	0.71	0.84	2.12	2.07	2.70	0.04	0.04	0.01	0.01	0.02
Adductor Brevis Proximal	Fe	26.68	13.43	2.28	3.40	7.08	6.54	9.90	0.17	0.10	0.04	0.05	0.06
Adductor Longus	Fe	12.46	14.26	2.02	2.00	4.75	3.40	6.48	0.49	0.50	0.05	0.06	0.22
Adductor Magnus Distal	Fe	4.52	3.23	1.13	1.03	3.24	4.01	2.86	0.05	0.04	0.01	0.01	0.05
Adductor Magnus Mid	Fe	1.39	1.56	0.39	0.39	5.43	5.82	2.50	0.01	0.01	0.00	0.00	0.04
Adductor Magnus Proximal	Fe	11.26	12.42	0.99	0.71	5.57	5.13	6.01	0.04	0.04	0.00	0.01	0.01
Biceps Femoris	Ti	24.91	24.14	16.23	14.71	10.22	10.94	16.86	1.30	0.86	0.82	0.77	0.47
Extensor Digitorum Longus	Fo *	0.66	0.67	0.30	0.25	0.01	0.06	0.33	0.01	0.01	0.01	0.00	0.00
Extensor Hallucis Longus	Fo *	0.90	0.90	0.33	0.27	0.02	0.04	0.41	0.01	0.01	0.00	0.00	0.00
Flexor Digitorum Longus	Fo *	1.81	1.81	0.03	0.12	0.17	0.26	0.70	0.01	0.01	0.00	0.00	0.00
Flexor Hallucis Longus	Fo *	1.07	1.07	0.02	0.09	0.11	0.03	0.40	0.02	0.02	0.00	0.00	0.00
Gemellus Inferior	Fe	13.08	12.20	56.23	23.95	6.31	5.10	19.48	0.29	0.24	0.89	0.51	0.22
Gemellus Superior	Fe	40.76	33.94	40.56	52.95	7.39	9.46	30.84	0.23	0.13	0.32	0.47	0.11
Gluteus Maximus Inferior	Fe	6.42	6.34	7.05	8.39	8.32	6.95	7.25	0.14	0.14	0.27	0.35	0.41
Gluteus Maximus Superior	Fe	6.60	7.31	2.27	2.91	6.57	6.60	5.38	0.17	0.18	0.07	0.09	0.32
Gluteus Medius Anterior	Fe	11.76	20.11	36.34	20.44	10.58	8.28	17.92	2.63	3.99	4.47	2.77	1.57
Gluteus Medius Posterior	Fe	38.54	68.33	34.05	31.09	13.49	10.07	32.60	3.06	5.10	1.95	1.92	0.75
Gluteus Minimus	Fe	20.14	37.15	25.54	20.24	15.71	11.47	21.71	3.03	5.14	2.07	1.40	1.52
Gracilis	Ti *	0.03	0.05	0.19	0.17	0.03	0.10	0.10	0.00	0.00	0.00	0.00	0.00
Iliacus	Fe	5.31	6.65	1.93	2.44	6.23	7.51	5.01	1.44	1.33	1.17	1.50	3.13
Obturator Externus Inferior	Fe	29.24	14.82	9.83	20.79	5.44	5.84	14.33	0.25	0.13	0.07	0.13	0.04
Obturator Externus Superior	Fe	36.72	28.38	64.79	80.89	12.53	11.27	39.10	1.70	1.02	1.95	2.59	0.58
Obturator Internus	Fe	27.67	14.49	59.06	15.37	7.08	6.22	21.65	2.07	0.95	5.49	2.35	1.02
Pectineus	Fe	7.96	5.96	1.72	2.09	3.77	3.81	4.22	0.10	0.07	0.03	0.04	0.05
Peroneus Brevis	Fo *	0.47	0.48	0.18	0.10	0.03	0.11	0.23	0.03	0.03	0.02	0.01	0.01
Peroneus Longus	Fo *	0.29	0.30	0.09	0.03	0.00	0.07	0.13	0.03	0.03	0.02	0.01	0.01
Peroneus Tertius	Fo	1.47	1.25	5.31	6.90	2.52	3.18	3.44	0.05	0.05	0.21	0.25	0.11
Piriformis	Fe	14.11	15.08	22.05	23.29	4.97	5.02	14.09	0.50	0.59	1.40	1.69	0.78
Popliteus	Fo *	1.72	2.02	2.70	2.39	0.41	0.13	1.56	0.01	0.01	0.01	0.01	0.01
Quadratus Femoris	Fe	26.08	23.91	27.67	36.07	8.12	7.18	21.50	0.58	0.43	0.40	0.53	0.19
Quadriceps Femoris	Fe	16.38	13.74	13.19	15.29	8.23	7.42	12.37	1.74	1.97	1.67	2.08	1.11
Sartorius	Ti	2.34	2.39	1.19	1.40	0.83	0.76	1.49	0.95	0.95	0.51	0.59	0.34
Semimembranosus	Ti	18.18	40.86	13.39	23.76	16.10	10.48	20.46	0.71	0.82	0.42	0.48	0.37
Semitendinosus	Ti *	0.02	0.03	0.05	0.04	0.01	0.00	0.03	0.00	0.00	0.00	0.00	0.00
Tensor Fasciae Latae	Ti	6.58	5.42	3.26	3.06	1.88	2.00	3.70	0.38	0.29	0.18	0.16	0.14
Tibialis Anterior	Fo *	0.09	0.10	0.04	0.02	0.04	0.02	0.05	0.01	0.01	0.00	0.00	0.00
Tibialis Posterior	Fo *	0.97	1.25	0.44	0.16	1.16	0.79	0.79	0.02	0.02	0.01	0.00	0.02

Perturbations of +1 cm and -1 cm were performed along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) direction of the local segment coordinate systems. For each perturbation, Local Sensitivity Index (LSI) and Overall Sensitivity Index (OSI) values are indicated. For each point, mean LSI and OSI values over the six perturbations are indicated. Cells shading (blue for LSI, red for OSI) is directly proportional to the sensitivity values. The body segment where each insertion point was located is indicated: Fe=Femur, Pa=Patella, Ti=Tibia, Fo=Foot. * indicates MT parts having also a pseudo-insertion point.

Table 2.A3 - Sensitivity of the model to perturbations of muscle-tendon via points from their nominal position.

		Local Sensitivity Index (%)							Overall Sensitivity Index (%)						
		X		Y		Z		Mean	X		Y		Z		Mean
		-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm		-1 cm	+1 cm	-1 cm	+1 cm	-1 cm	+1 cm	
Extensor Digitorum Longus	1 Ti P.O.	16.21	16.99	14.93	11.56	3.29	5.93	11.49	0.07	0.09	0.15	0.06	0.25	0.27	0.15
Extensor Digitorum Longus	2 Fo P.I.	2.88	1.84	2.45	2.06	4.34	6.23	3.30	0.02	0.02	0.03	0.03	0.12	0.12	0.06
Extensor Hallucis Longus	1 Ti	0.03	0.28	0.00	0.03	0.10	0.22	0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Extensor Hallucis Longus	2 Ti P.O.	16.48	12.10	13.04	6.65	7.05	11.67	11.16	0.05	0.06	0.07	0.05	0.11	0.11	0.07
Extensor Hallucis Longus	3 Fo P.I.	12.84	7.55	6.49	5.48	5.41	3.77	6.92	0.07	0.04	0.06	0.08	0.12	0.13	0.08
Flexor Digitorum Longus	1 Ti	0.41	0.52	0.30	0.09	0.22	1.08	0.44	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Flexor Digitorum Longus	2 Ti P.O.	17.30	21.44	3.74	2.75	1.82	2.29	8.22	0.17	0.15	0.03	0.02	0.02	0.02	0.07
Flexor Digitorum Longus	3 Fo P.I.	11.17	9.81	2.16	2.34	7.12	9.67	7.05	0.06	0.06	0.01	0.01	0.06	0.09	0.05
Flexor Hallucis Longus	1 Ti	0.56	0.02	0.12	0.01	0.29	0.25	0.21	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Flexor Hallucis Longus	2 Ti P.O.	23.51	43.41	7.84	4.66	6.58	4.78	15.13	0.97	0.82	0.29	0.22	0.23	0.19	0.45
Flexor Hallucis Longus	3 Fo P.I.	14.49	15.54	6.79	9.89	12.49	16.49	12.62	0.23	0.23	0.11	0.16	0.31	0.42	0.24
Gluteus Maximus Superior	1 Pe P.O.	7.96	10.03	12.74	13.20	12.35	12.53	11.47	0.16	0.21	0.19	0.20	0.56	0.65	0.33
Gracilis	1 Ti P.I.	15.32	20.76	7.52	9.77	6.37	5.56	10.88	0.23	0.25	0.12	0.13	0.08	0.08	0.15
Gracilis	2 Ti	0.11	0.21	0.12	0.26	0.19	0.03	0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Iliacus	1 Pe P.O.	13.29	10.24	6.32	5.90	7.55	9.65	8.82	1.13	1.27	0.40	0.48	1.15	1.00	0.91
Obturator Externus Superior	1 Pe P.O.	24.75	26.61	15.17	23.75	8.84	10.90	18.34	0.87	1.15	0.94	1.06	0.29	0.37	0.78
Obturator Internus	1 Pe P.O.	3.46	4.18	4.95	5.14	2.68	2.86	3.88	0.51	0.62	1.09	1.04	0.28	0.30	0.64
Peroneus Brevis	1 Ti P.O.	3.78	2.97	19.45	33.77	8.98	16.82	14.29	0.20	0.22	1.79	2.34	0.98	0.99	1.09
Peroneus Brevis	2 Fo P.I.	1.20	1.10	13.05	7.07	3.92	1.74	4.68	0.09	0.07	0.61	0.52	0.29	0.17	0.29
Peroneus Longus	1 Ti P.O.	1.18	1.34	27.60	13.71	16.33	7.82	11.33	0.25	0.32	2.92	2.60	1.74	1.09	1.49
Peroneus Longus	2 Fo P.I.	0.74	0.61	3.07	8.54	2.46	1.74	2.86	0.09	0.07	0.43	0.75	0.27	0.18	0.30
Peroneus Tertius	1 Ti P.O.	4.80	5.04	39.24	18.20	17.05	10.28	15.77	0.19	0.21	0.81	0.67	0.48	0.38	0.46
Popliteus	1 Ti P.I.	3.89	3.62	3.43	4.38	2.47	2.67	3.41	0.01	0.01	0.02	0.02	0.01	0.01	0.01
Sartorius Distal	1 Fe	2.94	3.30	0.74	0.61	1.00	1.03	1.60	0.55	0.63	0.25	0.22	0.18	0.17	0.33
Sartorius Proximal	1 Fe	2.39	2.13	0.60	0.67	1.69	1.95	1.57	0.46	0.46	0.13	0.14	0.37	0.39	0.32
Sartorius Proximal	2 Fe	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Sartorius Proximal	3 Fe	0.01	0.00	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Sartorius Proximal	4 Fe	0.01	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Sartorius Proximal	5 Fe	2.55	2.86	0.27	0.24	0.44	0.42	1.13	0.49	0.51	0.06	0.06	0.08	0.08	0.21
Semitendinosus	1 Ti P.I.	10.05	22.40	10.40	16.13	8.68	6.00	12.28	0.75	0.94	0.48	0.54	0.38	0.34	0.57
Semitendinosus	2 Ti	0.02	0.01	0.01	0.02	0.03	0.02	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Tibialis Anterior	1 Ti P.O.	4.11	2.25	0.88	0.46	1.20	2.93	1.97	0.44	0.42	0.17	0.11	0.28	0.27	0.28
Tibialis Anterior	2 Fo P.I.	30.26	17.86	1.73	2.53	8.24	6.15	11.13	0.98	0.64	0.36	0.47	1.04	1.12	0.77
Tibialis Posterior	3 Fo P.I.	8.58	4.80	18.21	23.26	8.57	7.65	11.85	0.28	0.14	0.42	0.57	0.17	0.19	0.30
Tibialis Posterior Lateralis	1 Ti	1.13	0.98	1.83	0.05	1.12	0.89	1.00	0.01	0.01	0.01	0.00	0.01	0.01	0.01
Tibialis Posterior Lateralis	2 Ti P.O.	9.94	12.38	46.06	64.30	6.65	7.37	24.45	0.14	0.23	0.72	0.71	0.10	0.15	0.34
Tibialis Posterior Medialis	1 Ti	1.01	0.83	1.65	0.00	0.86	0.97	0.89	0.01	0.01	0.02	0.00	0.01	0.01	0.01
Tibialis Posterior Medialis	2 Ti	1.37	1.13	0.04	1.64	1.19	1.29	1.11	0.02	0.01	0.00	0.02	0.01	0.01	0.01
Tibialis Posterior Medialis	3 Ti P.O.	8.31	10.44	36.51	54.92	5.26	6.01	20.24	0.18	0.29	0.88	0.93	0.13	0.22	0.44

Perturbations of +1 cm and -1 cm were performed along the posterior/anterior (X), distal/proximal (Y) and medial/lateral (Z) direction of the local segment coordinate systems. For each perturbation, Local Sensitivity Index (LSI) and Overall Sensitivity Index (OSI) values are indicated. For each point, mean LSI and OSI values over the six perturbations are indicated. Cells shading (blue for LSI, red for OSI) is directly proportional to the sensitivity values. For each MT part, via points are sorted from the most proximal to the most distal. The body segment where each via point was located is indicated: Pe=Pelvis, Fe=Femur, Ti=Tibia, Fo=Foot. P.O. and P.I. indicate via points that represent a pseudo-origin or a pseudo-insertion, respectively.

Chapter 3

Sensitivity of subject-specific models to Hill muscle-tendon model parameters in simulations of gait

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Abstract

Subject-specific musculoskeletal (MS) models of the lower extremity are essential for applications such as predicting the effects of orthopedic surgery. We performed an extensive sensitivity analysis to assess the effects of potential errors in Hill muscle-tendon (MT) model parameters for each of the 56 MT parts contained in a state-of-the-art MS model. We used two metrics, namely a Local Sensitivity Index (LSI) and an Overall Sensitivity Index (OSI), to distinguish the effect of the perturbation on the predicted force produced by the perturbed MT parts and by all the remaining MT parts, respectively, during a simulated gait cycle. Results indicated that sensitivity of the model depended on the specific role of each MT part during gait, and not merely on its size and length. Tendon slack length was the most sensitive parameter, followed by maximal isometric muscle force and nominal muscle fiber length, while nominal pennation angle showed very low sensitivity. The highest sensitivity values were found for the MT parts that act as prime movers of gait (Soleus: mean OSI=5.27%; Rectus Femoris: mean OSI=4.47%; Gastrocnemius: mean OSI=3.77%; Vastus Lateralis: mean OSI=1.36%; Biceps Femoris Caput Longum: mean OSI=1.06%) and hip stabilizers (Gluteus Medius: mean OSI=3.10%; Obturator Internus: mean OSI=1.96%; Gluteus Minimus: mean OSI=1.40%; Piriformis: mean OSI=0.98%), followed by the Peroneal muscles (mean OSI=2.20%) and Tibialis Anterior (mean OSI=1.78%), some of which were not included in previous sensitivity studies. Finally, the proposed priority list provides quantitative information to indicate which MT parts and which MT parameters should be estimated most accurately to create detailed and reliable subject-specific MS models.

3.1 Introduction

Musculoskeletal (MS) models of the lower extremity represent a promising tool to explore complex biomechanical problems, such as predicting the functional outcome of orthopedic surgery (Piazza et al., 2003; Reinbolt et al., 2009; Taddei et al., 2012). For these applications, subject-specific models are essential to achieve reliable model predictions (Lenaerts et al., 2009; Scheys et al., 2011b; Gerus et al., 2013). In particular, muscle-tendon (MT) parameters, which greatly affect model outcomes (Brand et al., 1986; Hoy et al., 1990; Out et al., 1996), are difficult to measure directly, and are known to vary with age, gender and activity (Friederich et al., 1990).

Developing efficient methods that allow estimating subject-specific MT parameters represents a significant challenge (Garner et al., 2003; Winby et al., 2008; van Campen et al., 2014). However, when using detailed state-of-the-art models (Klein Horsman et al., 2007; Arnold et al., 2010; Modenese et al., 2011), it is fundamental to clarify which muscles need to be described with greater detail, and what the required accuracy of the measurement techniques should be. Previous studies have investigated the sensitivity of MS model predictions to variations in MT parameters, unfortunately these analyses used simplified models (Hoy et al., 1990), reported results averaged over the muscles analyzed (Scovil et al., 2006), or focused only on a single joint (Out et al., 1996; De Groote et al., 2010) or on a small group of representative muscles (Redl et al., 2007; Xiao et al., 2010; Ackland et al., 2012). To our knowledge, the only extensive sensitivity studies of MS model predictions analyzed uncertainties in MS geometry parameters (Carbone et al., 2012; Valente et al., 2014), but no comprehensive analysis has been performed to study individual sensitivity in muscles to MT parameters perturbations.

The aim of this study was to assess the sensitivity of a detailed state-of-the-art MS model to potential errors in Hill MT model parameters. We performed an extensive analysis to quantify the effect of perturbations on tendon slack length, nominal muscle fiber length, maximal isometric muscle force and nominal pennation angle for each muscle present in the model. The results provided quantitative information to indicate which MT parameters for which muscles should be estimated most accurately to create a reliable subject-specific MS model that satisfies the required accuracy of the specific application.

3.2 Methods

We used the Twente Lower Extremity Model (TLEM) (Klein Horsman et al., 2007) implemented in the AnyBody Modeling System™ ver. 4.2.1 (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006) (Figure 3.1A). The model consisted of 12 body segments, 11 joints, and 21 degrees of freedom. To describe accurately the functionality of the MS system, each leg contained 56 MT parts whose mechanical effect was described by 159 three-element Hill-type MT elements (Zajac, 1989) (Figure 3.1B).

Figure 3.1 - A: TLEM model implemented in the AnyBody Modeling System™ ver. 4.2.1 (AnyBody Technology A/S, Aalborg, Denmark). It consisted of 12 body segments: HAT (Head, Arms and Trunk), pelvis, and right and left femur, patella, tibia, talus and foot. The fibula was considered as one unit in combination with the tibia. The model comprised 11 joints: L5S1 and left and right hip, knee, patella/femur, talocrural and subtalar. The L5S1 and hip joints were modeled as a ball-and-socket, defined by a rotation center and three orthogonal axes. The knee, talocrural and subtalar joints were defined as a hinge, with a fixed rotation center and axis. The patella could rotate with respect to the femur around a rotation axis with a fixed rotation center. The patellar tendon was defined as a non-deformable element that connected the patella to the tibia. Thus, without introducing an extra degree of freedom (DOF), the orientation and position of the patella depended solely on the knee flexion angle. The orientation and position of the center of mass of the pelvis with respect to a 3D global frame, together with the joint rotations of the L5S1, hip, knee, talocrural and subtalar joints, resulted in a model with 21 DOFs. B: Schematic representation of three-elements Hill-type muscle-tendon element. The MT element consists of an active muscle, represented by a contractile element CE in parallel with a passive element PE, in series with an elastic tendon T, modeled as a nonlinear spring. L_f is the muscle fiber length, L_T is the tendon length, γ is the pennation angle between the muscle fiber and the tendon. L_{MT} is the total length of the MT element, which is equal to the sum of tendon length L_T and muscle fiber length L_f adjusted by pennation angle γ : $L_{MT} = L_T + L_f \cos \gamma$. Force in the tendon F^{MT} is equal to the summed force in the muscle fibers F^M adjusted by pennation angle γ : $F^{MT} = F^M \cos \gamma$.

Inverse dynamics simulations were based on 3D motion analysis and force-plate data recorded during a gait trial on a level walkway. Age, height and mass of one male subject were 26 years, 1.73 cm and 63 kg respectively (AnyBody Managed Model Repository™ ver. 1.3). The model was linearly scaled to match the anthropometry of the subject, based on the relative position of the optical markers. A static optimization problem was solved to calculate MT forces, minimizing the sum of the cubes of muscle activity at each time step (Crowninshield et al., 1981). MT forces were constrained to the dynamic equilibrium equations, taking into account for each MT element the physiological bounds imposed by force-length and force-velocity characteristics of the contractile element CE, and the elasticity of the passive element PE. The effect of the elasticity of the tendon T was approximated by allowing the length and the force of the tendon to vary with the muscle activity. Assuming relatively small tendon elongations, the tendon force dependency on muscle activity was approximated with a linear relationship that could be incorporated efficiently into the muscle recruitment solver implemented in the AnyBody Modeling System™.

Our sensitivity analysis focused on four MT parameters that can be potentially measured in vivo (Narici et al., 1996; Fukunaga et al., 1997) or estimated (Garner et al., 2003; van Campen et al., 2014) when creating a subject-specific model: tendon slack length L_T^s , nominal muscle fiber length $\bar{L}_f$, maximal isometric muscle force $\bar{F}^M$ and nominal pennation angle $\bar{\gamma}$. For each MT part and each of the four MT parameters, two perturbations from its nominal value were applied, based on the average anatomical variability calculated by Ward et al. (2009): specifically, +20% and -20% for L_T^s , $\bar{L}_f$ and $\bar{F}^M$, and +10° and -10° for $\bar{\gamma}$ (only +10° for not-pennated MT elements).

After each perturbation, a new static optimization problem was solved to compute the corresponding changes in the predicted MT forces. For reasons of symmetry, perturbations were performed only in the right leg. Consistently with our previous sensitivity analysis on MS geometry (Carbone et al., 2012), we calculated the sensitivity of the model by using two metrics:

1. Local Sensitivity Index (LSI), to quantify the effect of the perturbation on the force produced by the perturbed MT part:

$$LSI = \frac{\sum_{i=pert} \int_0^T |F_{new,i}^{MT}(t) - F_{old,i}^{MT}(t)| dt}{\sum_{i=pert} \int_0^T F_{old,i}^{MT}(t) dt} \cdot 100\% \quad (1)$$

2. Overall Sensitivity Index (OSI), to quantify the effect of the perturbation on the force produced by all the remaining MT parts:

$$OSI = \frac{\sum_{i \neq pert} \int_0^T |F_{new,i}^{MT}(t) - F_{old,i}^{MT}(t)| dt}{\sum_{i \neq pert} \int_0^T F_{old,i}^{MT}(t) dt} \cdot 100\% \quad (2)$$

where $F_{old,i}^{MT}(t)$ and $F_{new,i}^{MT}(t)$ are the nominal and perturbed values of force, respectively, produced by the perturbed ($i = pert$) and not-perturbed ($i \neq pert$) MT parts at time step t , and T is the final time of the simulated gait cycle.

Finally, Pearson product-moment correlation coefficients r were calculated to assess if the model was most sensitive to potential errors in MT parts presenting the largest L_T^s , $\bar{L}_f$, $\bar{F}^M$ and $\bar{\gamma}$, respectively; to assess if the MT parts that showed the highest LSI values tended to show the highest OSI values too; and to assess if the most sensitive MT parts tended to show the highest sensitivity values for all four MT parameters perturbed. Pearson's r were classified as follows, based on Altman (1990): poor correlation for $|r| < 0.20$, fair correlation for $0.21 < |r| < 0.40$, moderate correlation for $0.41 < |r| < 0.60$, good correlation for $0.61 < |r| < 0.80$, very good correlation for $0.81 < |r| < 1.00$.

3.3 Results

Sensitivity of the MS model predictions to potential errors in Hill MT model parameters presented large variability. Detailed results for all perturbations performed are presented in Table 3.A1 contained in the Appendix.

LSI values, representing the sensitivity of the perturbed MT parts, depended strongly on the MT part and the MT parameter perturbed (Figure 3.2A-B). L_T^s was the most sensitive parameter (mean LSI=93.83%; max LSI=899.89% for Vastus Lateralis Inferior; min LSI=0.77% for Pectineus), followed by $\bar{F}^M$ (mean LSI=23.08%; max LSI=30.36% for Gemellus Superior; min LSI=5.90% for Tibialis Anterior), $\bar{L}_f$ (mean LSI=13.93%; max LSI=53.93% for Vastus Medialis Inferior; min LSI=0.76% for Pectineus) and $\bar{\gamma}$ (mean

Figure 3.2 - Effect of perturbation of MT parameters on the predicted MT forces during gait. The black solid lines are the nominal MT forces before the perturbation; the blue, red, green and yellow lines are the predicted MT forces after the perturbation of tendon slack length L_T^s , nominal muscle fiber length $\bar{L}_f$, maximal isometric muscle force $\bar{F}^M$, and nominal pennation angle $\bar{\gamma}$, respectively. A: Force produced by the Rectus Femoris after perturbation of MT parameters of the Rectus Femoris; B: Force produced by the Popliteus after perturbation of MT parameters of the Popliteus; C: Sum of the forces produced by all the remaining MT parts after perturbation of MT parameters of the Rectus Femoris; D: Sum of the forces produced by all the remaining MT parts after perturbation of MT parameters of the Popliteus. Local Sensitivity Index (LSI) was calculated by integrating the absolute difference between nominal and perturbed MT forces over the simulated gait cycle, and then summing these integrated quantities across all the perturbed MT parts (see Eq. (1)). Overall Sensitivity Index (OSI) was calculated by integrating the absolute difference between nominal and perturbed MT forces over the simulated gait cycle, and then summing these integrated quantities across all the non-perturbed MT parts (see Eq. (2)). Please note that different scales were used for subplots A-B and C-D.

Figure 3.3 - A-D: Overall Sensitivity Index (OSI) values plotted against the nominal values of the corresponding MT parameter perturbed (to assess if the model was most sensitive to potential errors in MT parts presenting the largest L_T^s , L_f , F^M and $\bar{\gamma}$, respectively). E-H: Overall Sensitivity Index (OSI) values plotted against the corresponding Local Sensitivity Index (LSI) values of the same MT part (to assess if the MT parts that showed the highest LSI values tended to show the highest OSI values too).

Table 3.1 – Correlation between sensitivity values of the MT parameters perturbed.

Correlation between LSI values and nominal values of MT parameter perturbed

L_T^s	$\bar{L}_f$	$\bar{F}^M$	$\bar{\gamma}$
0.21	-0.14	-0.50	0.58

Correlation between OSI values and nominal values of MT parameter perturbed

L_T^s	$\bar{L}_f$	$\bar{F}^M$	$\bar{\gamma}$
0.34	-0.17	0.72	0.67

Correlation between LSI values and OSI values of the same MT parameter perturbed

L_T^s	$\bar{L}_f$	$\bar{F}^M$	$\bar{\gamma}$
0.15	0.26	-0.55	0.40

Correlation between LSI values of different MT parameters perturbed

LSI	L_T^s	$\bar{L}_f$	$\bar{F}^M$	$\bar{\gamma}$
L_T^s	1.00			
$\bar{L}_f$	0.55	1.00		
$\bar{F}^M$	-0.18	0.05	1.00	
$\bar{\gamma}$	0.18	0.07	-0.33	1.00

Correlation between OSI values of different MT parameters perturbed

OSI	L_T^s	$\bar{L}_f$	$\bar{F}^M$	$\bar{\gamma}$
L_T^s	1.00			
$\bar{L}_f$	0.79	1.00		
$\bar{F}^M$	0.91	0.77	1.00	
$\bar{\gamma}$	0.68	0.61	0.80	1.00

Legend

Pearson product-moment correlation coefficients r calculated to measure the linear correlation between Local Sensitivity Index (LSI) or Overall Sensitivity Index (OSI) values and the nominal values of the corresponding MT parameter perturbed (to assess if the model was most sensitive to potential errors in MT parts presenting the largest L_T^s , $\bar{L}_f$, $\bar{F}^M$ and $\bar{\gamma}$, respectively), between LSI and OSI values of the same MT part (to assess if the MT parts that showed the highest LSI values tended to show the highest OSI values too), and between the LSI or OSI values of the same MT part for different MT parameters perturbed (to assess if the MT parts that showed the highest sensitivity values for one MT parameter tended to show the highest sensitivity values for the other MT parameters as well).

LSI=3.33%; max LSI=17.59% for Gastrocnemius Medialis; min LSI=0.29% for Tibialis Anterior).

Similarly, OSI values, representing the sensitivity of all the remaining MT parts, depended strongly on the MT part and the MT parameter perturbed (Figure 3.2C-D). Again, L_T^s was the most sensitive parameter (mean OSI=3.16%; max OSI=21.73% for Gastrocnemius Medialis; min OSI<0.01% for Pectineus), followed by $\bar{F}^M$ (mean OSI=0.64%; max OSI=3.32% for Soleus Lateralis; min OSI=0.03% for Popliteus), $\bar{L}_f$ (mean OSI=0.40%; max OSI=2.95% for

Rectus Femoris; min OSI<0.01% for Adductor Magnus Proximal) and $\bar{\gamma}$ (mean OSI=0.13%; max OSI=1.86% for Rectus Femoris; min OSI<0.01% for Adductor Brevis Mid).

The highest OSI values were found not only for the MT parts that act as prime movers during gait (Triceps Surae, Quadriceps Femoris, Gluteal muscles, Biceps Femoris Caput Longum), considered amongst the most representative muscles, but also for MT parts that are usually excluded from sensitivity studies, such as Peroneus Longus and Brevis, Obturator Internus, Tibialis Anterior and Piriformis.

We found good correlation between OSI values and nominal values of $\bar{F}^M$ ($r=0.72$) and $\bar{\gamma}$ ($r=0.67$), hence stronger and more pennated MT parts showed the highest sensitivity, while only poor to fair correlation was found for L_T^S and $\bar{L}_f$ ($r=0.34$ and $r=-0.17$, respectively) (Figure 3.3A-D). Moreover, we found poor to even negative correlation between LSI and OSI values of the same MT parameter ($-0.55 < r < 0.40$), hence the MT parts that showed the highest LSI values did not necessarily show the highest OSI values (Figure 3.3E-H). Finally, we found moderate to even negative correlation between LSI values of the same MT part for different MT parameters ($-0.33 < r < 0.55$), but good to very good correlation between OSI values ($0.61 < r < 0.91$), indicating that the most sensitive MT parts tended to show the highest OSI values for all four MT parameters perturbed. Detailed results of correlation analysis are presented in Table 3.1.

3.4 Discussion

The purpose of this extensive sensitivity analysis was to assess the effects of potential errors in Hill MT model parameters on the predictions of a detailed state-of-the art MS model of the lower extremity. In accordance with the results of previous investigations (Hoy et al., 1990; Out et al., 1996; Redl et al., 2007), L_T^S was found to be the most sensitive parameter, whose perturbation greatly affected the model force predictions, followed by $\bar{F}^M$ and $\bar{L}_f$, while $\bar{\gamma}$ showed very low sensitivity values. However, sensitivity results depended largely also on the specific function of the MT part perturbed (Figure 3.2), in accordance with Ackland et al. (2012). OSI values were greatly reduced compared to LSI values, indicating that the complex MS system was able to compensate for perturbations better than the perturbed MT part alone, in agreement with Scovil and Ronsky (2006).

Moreover, some MT parts showed very high LSI values but very low OSI values (for example the Popliteus muscle, Figure 3.2B-D), indicating that large relative changes in MT parts contributing only little to joint moments did not influence the rest of the model, similarly to De Groote et al. (2010). On the other hand, high OSI values indicated MT parts with an important role during gait, for which potential errors would affect the remaining MT parts (for example the Rectus Femoris muscle, Figure 3.2A-C). Also, the most sensitive MT parts tended to show the highest OSI values for all four MT parameters perturbed. For these reasons, OSI values were used as an index to draw up a priority list of the MT parameters

and the MT parts that should be estimated most carefully when creating a detailed subject-specific MS model (Table 3.2).

The highest sensitivity values were found for the prime movers of gait (Triceps Surae, Rectus Femoris, Vastus Lateralis, and Biceps Femoris Caput Longum) and hip stabilizers (Gluteal muscles, Obturator Internus, and Piriformis), followed by the Peroneal muscles and Tibialis Anterior. It is important to note that some MT parts, such as Peroneal muscles, Obturator Internus, Tibialis Anterior and Piriformis, which were not included in previous sensitivity studies (Redl et al., 2007; Xiao et al., 2010; Ackland et al., 2012), showed higher sensitivity than other MT parts that are usually considered more representative, such as Iliacus, Adductors, Semitendinosus and Semimembranosus, highlighting the importance of an extensive sensitivity analysis when using a detailed MS model.

Sensitivity results showed strong correlation with nominal values of $\overline{F^M}$ and $\bar{y}$, but poor correlation with L_T^S and $\overline{L_f}$, indicating that the order of the proposed priority list was not merely determined by the size and length of the MT parts. Moreover, high sensitivity values were not directly related to high nominal values of muscle activity, but depended deeply on the specific role of the perturbed MT part during gait, and on the capability of the model to compensate to each specific perturbation.

Differences in MT parameters had an effect on the capacity of the perturbed MT parts to generate force, hence on the distribution of forces predicted by the muscle recruitment problem. For example, perturbations of the Tibialis Anterior, which represents the biggest contributor to ankle dorsiflexion, would require a compensation by other minor dorsiflexor MT parts who act also on the subtalar joint, such as Extensor Hallucis Longus, Extensor Digitorum Longus and Peroneus Tertius. This would result in a redistribution of forces generated by other MT parts acting on the ankle/subtalar joint and, through the Gastrocnemius, on the knee joint too, in order to reproduce the nominal net joint moments and minimize the cost function of the static optimization problem. Perturbations of the Peroneal muscles, which represent the biggest contributors to subtalar eversion, would result in a similar situation. Also, perturbations of the Obturator Internus, which acts only as hip lateral rotator, would require a compensation by other MT parts acting also as hip abductor/adductors, such as Gluteus Maximus Inferior, Piriformis and Quadratus Femoris, resulting again in a new optimal redistribution of muscle forces to reproduce the nominal net joint moments.

Furthermore, sensitivity results could be used as an indication to how much perturbation can be tolerated before normal walking is affected, suggesting that gait is most sensitive to weakness in ankle plantarflexors and hip abductors, and more robust to weakness in other muscles, similarly to what found by van der Krogt et al. (2012).

Table 3.2 - Priority list of the most sensitive MT parts to potential errors in MT parameters.

	Tendon slack length L_T^s		Nominal muscle fiber length $\overline{L_f}$		Maximal isometric muscle force F_M		Nominal pennation angle $\bar{\gamma}$		Mean OSI (%)
	LSI (%)	OSI (%)	LSI (%)	OSI (%)	LSI (%)	OSI (%)	LSI (%)	OSI (%)	
Soleus Lateralis	97.83	17.30	7.15	1.22	17.90	3.11	6.34	1.23	5.72
Gastrocnemius Medialis	113.09	18.43	7.50	1.08	16.63	2.41	9.11	0.12	5.51
Soleus Medialis	91.75	13.69	7.55	1.19	19.23	3.01	8.50	1.43	4.83
Rectus Femoris	68.36	11.33	12.69	2.34	14.36	2.69	9.26	1.53	4.47
Gluteus Medius Anterior	89.13	10.46	17.73	2.09	16.54	1.95	1.19	0.14	3.66
Peroneus Longus	95.94	8.76	7.51	0.66	14.98	1.25	1.63	0.19	2.72
Gluteus Minimus Anterior	162.06	8.44	37.27	1.99	19.96	1.07	1.99	0.11	2.90
Gluteus Medius Posterior	148.89	7.55	23.21	1.32	18.36	1.04	6.31	0.26	2.54
Vastus Lateralis Superior	90.17	7.27	18.76	1.41	16.15	1.16	0.53	0.05	2.47
Gastrocnemius Lateralis	131.12	6.43	8.10	0.39	25.12	1.11	3.81	0.24	2.04
Obturator Internus	88.09	6.01	6.87	0.48	18.18	1.27	1.09	0.08	1.96
Peroneus Brevis	96.51	5.17	7.91	0.46	18.75	0.94	3.97	0.20	1.69
Tibialis Anterior	83.31	6.04	4.89	0.45	6.66	0.59	5.99	0.04	1.78
Biceps Femoris Caput Longum	74.89	2.90	13.76	0.47	16.77	0.54	7.41	0.33	1.06
Piriformis	75.94	2.73	6.79	0.25	25.19	0.90	1.59	0.06	0.98
Gluteus Maximus Superior	76.77	2.07	22.48	0.62	24.03	0.65	1.34	0.04	0.85
Obturator Externus Superior	76.59	2.20	13.15	0.43	22.34	0.65	0.82	0.02	0.83
Tibialis Posterior Medialis	90.40	2.79	10.95	0.12	23.37	0.28	8.61	0.10	0.82
Gluteus Minimus Mid	107.56	2.41	11.77	0.27	22.17	0.51	0.84	0.02	0.80
Flexor Hallucis Longus	126.61	2.61	9.54	0.14	23.63	0.33	10.78	0.13	0.80
Vastus Intermedius	169.61	2.15	42.96	0.50	25.87	0.29	5.52	0.08	0.76
Sartorius Distal	20.03	1.13	3.98	0.22	24.66	1.33	1.55	0.09	0.69
Semitendinosus	85.42	2.09	5.13	0.11	19.87	0.47	1.21	0.03	0.67
Peroneus Tertius	76.27	1.89	8.00	0.15	21.54	0.35	6.27	0.09	0.62
Tensor Fasciae Latae	119.19	2.00	22.59	0.36	20.46	0.34	1.15	0.02	0.68
Sartorius Proximal	17.48	0.81	2.65	0.13	25.56	1.14	1.72	0.08	0.54
Semimembranosus	96.75	1.58	8.85	0.14	21.64	0.34	6.34	0.10	0.54
Tibialis Posterior Lateralis	147.90	1.78	10.19	0.07	23.82	0.20	9.95	0.17	0.55
Vastus Medialis Superior	163.84	1.59	39.05	0.34	26.42	0.22	2.19	0.02	0.54
Gluteus Minimus Posterior	76.81	1.43	5.88	0.12	24.39	0.49	0.67	0.01	0.51
Adductor Magnus Distal	106.47	1.43	15.99	0.22	20.98	0.28	0.73	0.01	0.49
Flexor Digitorum Longus	100.00	1.90	16.20	0.06	20.55	0.08	6.54	0.04	0.52
Extensor Digitorum Longus	120.20	1.38	15.82	0.19	25.48	0.31	6.42	0.03	0.48
Vastus Medialis Mid	170.14	1.30	53.24	0.39	26.94	0.20	5.39	0.04	0.48
Gluteus Maximus Inferior	26.11	0.64	14.71	0.39	25.00	0.55	1.62	0.04	0.41
Iliacus Mid	87.53	1.11	7.95	0.08	27.64	0.36	0.60	0.01	0.39
Adductor Longus	24.97	0.57	18.50	0.41	21.89	0.46	1.72	0.04	0.37
Extensor Hallucis Longus	112.28	0.97	29.65	0.27	26.68	0.24	2.23	0.02	0.37
Quadratus Femoris	61.59	0.91	12.35	0.19	24.50	0.35	0.69	0.01	0.36
Gemellus Inferior	68.40	0.92	6.30	0.09	27.47	0.37	1.74	0.02	0.35
Gracilis	64.90	0.72	6.93	0.08	26.28	0.29	1.39	0.02	0.28
Vastus Lateralis Inferior	499.94	0.92	33.19	0.05	21.17	0.04	2.73	0.00	0.25
Adductor Magnus Mid	91.32	0.46	20.87	0.11	26.56	0.13	1.22	0.01	0.18
Plantaris	242.64	0.58	13.29	0.03	24.79	0.05	1.37	0.00	0.17
Biceps Femoris Caput Breve	53.10	0.34	6.83	0.04	26.88	0.21	1.69	0.01	0.15
Iliacus Medialis	52.40	0.32	4.92	0.03	28.79	0.18	1.47	0.01	0.13
Gemellus Superior	64.56	0.31	11.32	0.06	29.11	0.14	1.62	0.01	0.13
Obturator Externus Inferior	32.61	0.19	7.84	0.05	27.61	0.15	1.33	0.01	0.10
Vastus Medialis Inferior	106.59	0.23	34.63	0.07	28.12	0.06	5.89	0.01	0.09
Iliacus Lateralis	33.99	0.15	3.93	0.02	29.08	0.14	4.51	0.06	0.09
Pectineus	0.79	0.01	3.23	0.02	27.58	0.17	1.55	0.01	0.05
Adductor Brevis Mid	8.56	0.04	7.85	0.03	27.80	0.11	0.91	0.00	0.05
Adductor Brevis Proximal	8.05	0.03	7.55	0.03	27.82	0.11	0.95	0.00	0.04
Popliteus	138.89	0.17	12.65	0.01	24.34	0.03	1.29	0.00	0.05
Adductor Brevis Distal	9.90	0.04	6.80	0.03	27.79	0.10	1.02	0.00	0.04
Adductor Magnus Proximal	10.09	0.03	2.65	0.01	27.27	0.08	1.86	0.01	0.03
min	0.79	0.01	2.65	0.01	6.66	0.03	0.53	0.00	
max	499.94	18.43	53.24	2.34	29.11	3.11	10.78	1.53	
mean	93.83	3.16	13.93	0.40	23.08	0.64	3.33	0.13	

For each MT part and each MT parameter, mean values of Local Sensitivity Index (LSI) and Overall Sensitivity Index (OSI) over the two perturbations are indicated. Cell shading (blue for LSI, red for OSI) is directly proportional to the sensitivity values.

Since this study was based on the same MS model and metrics used for our previous extensive sensitivity analysis on MS geometry (Carbone et al., 2012), it is possible to directly compare the two priority lists. L_T^S represented the most sensitive parameter, while perturbations of MT attachment sites showed sensitivity values similar to $\overline{F^M}$ and $\overline{L_f}$. However, it is important to note that MS geometry has a direct effect on the total length of MT elements and, consequently, on their force-generating characteristics. Therefore, we suggest that both MS geometry and MT parameters should be taken into account in order to obtain a reliable and detailed subject-specific model. Moreover, even though the two studies were based on the same model, some MT parts like Iliacus and Adductor Longus presented a relatively high sensitivity to MS geometry but low sensitivity to MT parameters, while other MT parts like Gluteus Maximus showed opposite characteristics. This difference in the ranking is ascribable to the fact that perturbations of MT parameters only affected the force-generating characteristics of the perturbed MT parts, while perturbations of MT attachment sites affected the moment arms and functions of the perturbed MT parts, and consequently their torque-generating characteristics. This indicates how extensive sensitivity analyses of different parameters are very important indeed to better understand the complexity of MS models.

It is furthermore important to note that this study was applied only to normal gait, and that sensitivity results are expected to change when analyzing different movements like slow and fast gait, and running, as shown before by Scovil and Ronsky (2006). Moreover, this study was based on the gait simulation of a single healthy subject using a generic model, with parameter perturbations based on anatomical variability between healthy subjects. Gait simulations using subject-specific models are expected to show great similarities in the ranking of the most sensitive MT parts, however results could be different when analyzing patients suffering from pathologies affecting their MS system and their movements. Finally, although sensitivity depends on the method used to predict MT forces, the ranking is expected to be similar when using dynamic optimization or forward dynamics instead of static optimization, as indicated by De Groote et al. (2010).

In conclusion, this study showed that potential errors in Hill MT model parameters, within the anatomical variability measured in literature, can have a significant impact on MT force predictions, depending on the specific role of the perturbed MT part. Therefore, it is necessary to acquire a good estimate of the most sensitive MT parameters for the most sensitive MT parts, through accurate measurements and detailed optimization, to obtain reliable model outcomes. The proposed priority list provided quantitative information that, combined with our previous extensive sensitivity analysis on MS geometry (Carbone et al., 2012), could be used to define suitable measurement protocols, in order to create detailed subject-specific models that meet the required accuracy of the specific application.

Appendix

Table 3.A1 contains the complete sensitivity results for perturbations of MT parameters.

Table 3.A1 - Sensitivity of the model to perturbations of MT parameters from their nominal value.																									
	Tendon slack length L_{T_0}						Nominal muscle fiber length $\bar{L}_f$						Maximal isometric muscle force $\bar{F}_0$						Nominal pennation angle $\bar{\gamma}$						
	Local Sensitivity Index (%)			Overall Sensitivity Index (%)			Local Sensitivity Index (%)			Overall Sensitivity Index (%)			Local Sensitivity Index (%)			Overall Sensitivity Index (%)			Local Sensitivity Index (%)			Overall Sensitivity Index (%)			
	-20%	+20%	Mean	-20%	+20%	Mean	-20%	+20%	Mean	-20%	+20%	Mean	-20%	+20%	Mean	-20%	+20%	Mean	-20%	+20%	Mean	-20%	+20%	Mean	
Adductor Brevis Distal	11.64	8.16	9.90	0.05	0.03	0.04	8.27	5.34	6.80	0.03	0.02	0.03	26.88	28.70	27.79	0.10	0.11	0.10	-	1.02	1.02	-	0.00	0.00	
Adductor Brevis Med	9.13	7.99	8.56	0.04	0.03	0.04	9.28	6.41	7.85	0.04	0.03	0.03	26.95	28.65	27.80	0.11	0.12	0.11	-	0.91	0.91	-	0.00	0.00	
Adductor Brevis Proximal	8.57	7.54	8.05	0.04	0.03	0.03	9.00	6.10	7.55	0.04	0.03	0.03	26.94	28.70	27.82	0.11	0.12	0.11	-	0.95	0.95	-	0.00	0.00	
Adductor Longus	22.25	27.68	24.97	0.51	0.63	0.57	19.22	17.79	18.50	0.44	0.39	0.41	22.05	21.73	21.89	0.46	0.46	0.46	-	1.72	1.72	-	0.04	0.04	
Adductor Magnus Distal	11.12	98.82	106.47	0.46	0.44	0.45	18.46	13.51	15.99	0.25	0.19	0.22	21.82	20.14	20.98	0.29	0.27	0.28	-	0.73	0.73	-	0.01	0.01	
Adductor Magnus Med	13.52	100.00	126.61	0.76	0.76	0.76	11.49	9.54	10.51	0.11	0.11	0.11	21.43	22.86	22.14	0.33	0.33	0.33	-	1.61	1.61	-	0.01	0.01	
Adductor Magnus Proximal	7.71	12.47	10.09	0.03	0.04	0.03	3.99	1.32	2.65	0.01	0.00	0.01	26.46	28.05	27.27	0.08	0.09	0.08	-	1.82	1.82	-	0.01	0.01	
Adductor Pollicis	40.85	62.45	53.10	0.23	0.44	0.34	0.01	5.57	6.83	0.05	0.00	0.04	26.26	27.49	26.88	0.21	0.21	0.21	-	1.69	1.69	-	0.01	0.01	
Biceps Femoris Caput Breve	75.99	73.78	74.89	3.28	2.51	2.90	15.63	11.89	13.76	0.54	0.41	0.47	17.56	15.97	16.77	0.57	0.52	0.54	7.43	7.40	7.41	0.24	0.42	0.33	
Biceps Femoris Caput Longum	140.40	100.00	120.20	1.59	1.18	1.38	17.19	14.45	15.82	0.21	0.18	0.19	24.88	26.09	25.48	0.30	0.32	0.31	1.20	11.64	6.42	0.01	0.05	0.03	
Extensor Digitorum Longus	124.55	100.00	112.28	1.07	0.87	0.97	30.33	28.77	29.65	0.27	0.26	0.27	26.26	27.16	26.68	0.28	0.25	0.24	1.46	3.01	2.23	0.01	0.03	0.02	
Extensor Hallucis Longus	100.00	100.00	100.00	3.41	0.39	1.90	19.79	12.60	16.20	0.07	0.04	0.06	21.09	20.02	20.55	0.08	0.07	0.08	8.54	4.53	6.54	0.03	0.05	0.04	
Flexor Digitorum Longus	135.23	100.00	126.61	0.76	0.76	0.76	11.49	9.54	10.51	0.11	0.11	0.11	21.43	22.86	22.14	0.33	0.33	0.33	9.13	12.44	10.78	0.11	0.16	0.13	
Flexor Hallucis Longus	126.19	100.00	113.05	0.73	0.53	0.63	9.12	5.88	7.50	0.13	0.03	0.08	17.72	15.53	16.63	0.20	0.23	0.21	0.64	17.59	9.11	0.10	0.15	0.12	
Gastrocnemius Medialis	56.76	80.03	68.40	0.76	1.08	0.92	7.09	5.50	6.30	0.10	0.08	0.09	26.69	28.24	27.47	0.34	0.38	0.37	-	1.74	1.74	-	0.02	0.02	
Gemelli Superior	31.71	97.41	64.56	0.14	0.47	0.31	13.47	9.17	11.32	0.07	0.05	0.06	27.87	30.36	29.11	0.14	0.15	0.14	-	1.62	1.62	-	0.01	0.01	
Gemelli Inferior	22.30	89.61	26.11	0.58	0.71	0.64	18.79	10.64	14.71	0.49	0.29	0.39	24.96	23.03	24.03	0.55	0.55	0.55	-	1.62	1.62	-	0.04	0.04	
Gluteus Maximus Inferior	66.86	26.68	76.77	1.77	2.37	2.07	24.07	11.39	17.73	2.86	1.33	2.09	16.86	16.23	16.54	1.96	1.94	1.95	-	1.34	1.34	-	0.04	0.04	
Gluteus Maximus Superior	137.63	40.63	89.13	16.41	4.51	10.46	24.07	21.86	23.21	1.42	1.22	1.32	19.51	19.21	19.36	1.11	0.96	1.04	3.87	8.74	6.31	0.23	0.28	0.26	
Gluteus Medius Anterior	199.12	98.66	148.99	9.57	5.72	7.55	24.56	21.86	23.21	1.42	1.22	1.32	19.51	19.21	19.36	1.11	0.96	1.04	3.87	8.74	6.31	0.23	0.28	0.26	
Gluteus Medius Posterior	37.63	55.66	46.64	0.51	0.72	0.61	11.49	9.54	10.51	0.11	0.11	0.11	21.43	22.86	22.14	0.33	0.33	0.33	-	1.61	1.61	-	0.01	0.01	
Gluteus Minimus Anterior	175.64	39.46	107.56	3.95	1.85	2.90	24.07	21.86	23.21	1.42	1.22	1.32	19.51	19.21	19.36	1.11	0.96	1.04	3.87	8.74	6.31	0.23	0.28	0.26	
Gluteus Minimus Med	92.90	60.71	76.81	1.64	1.22	1.43	7.00	4.76	5.88	0.14	0.10	0.12	24.09	24.69	24.39	0.49	0.50	0.49	-	0.84	0.84	-	0.01	0.01	
Gluteus Minimus Posterior	51.93	77.87	64.90	0.59	0.86	0.72	8.12	5.73	6.93	0.09	0.07	0.08	25.87	26.70	26.28	0.29	0.30	0.29	-	1.39	1.39	-	0.02	0.02	
Graecilis	28.91	39.08	33.99	0.13	0.17	0.15	4.71	3.15	3.93	0.02	0.01	0.02	27.82	30.35	29.08	0.13	0.14	0.14	8.03	1.00	4.51	0.04	0.09	0.06	
Iliacus Lateralis	48.38	56.42	52.40	0.31	0.33	0.32	5.85	4.00	4.92	0.03	0.02	0.03	27.61	28.51	28.07	0.18	0.19	0.18	-	1.47	1.47	-	0.01	0.01	
Iliacus Medialis	80.00	95.06	87.53	1.03	1.19	1.11	9.17	6.73	7.95	0.09	0.07	0.08	26.77	28.51	27.64	0.34	0.37	0.36	-	0.60	0.60	-	0.01	0.01	
Obturator Internus	30.35	34.87	32.61	0.18	0.21	0.19	9.16	6.52	7.84	0.06	0.04	0.05	26.82	28.41	27.61	0.15	0.16	0.15	-	1.33	1.33	-	0.01	0.01	
Obturator Externus Inferior	76.35	49.94	63.09	1.81	1.35	1.58	18.75	17.21	17.98	0.38	0.37	0.38	19.15	17.21	18.18	1.34	1.19	1.27	-	1.09	1.09	-	0.08	0.08	
Obturator Externus Superior	76.35	49.94	63.09	1.81	1.35	1.58	18.75	17.21	17.98	0.38	0.37	0.38	19.15	17.21	18.18	1.34	1.19	1.27	-	1.09	1.09	-	0.08	0.08	
Obturator Foramen	0.81	0.77	0.79	0.01	0.01	0.01	5.70	0.76	3.23	0.04	0.01	0.02	26.87	28.29	27.58	0.17	0.18	0.17	-	1.55	1.55	-	0.01	0.01	
Pectineus	93.51	99.50	96.51	4.73	5.60	5.17	9.82	5.99	7.91	0.59	0.33	0.46	19.86	17.65	18.75	1.02	0.86	0.94	3.36	4.58	3.97	0.18	0.22	0.20	
Peroneus Brevis	91.88	100.00	95.94	2.39	8.14	8.76	9.17	5.86	7.51	0.81	0.52	0.66	16.88	13.08	14.98	1.42	1.07	1.25	1.85	1.42	1.63	0.16	0.21	0.19	
Peroneus Longus	52.91	99.63	76.27	1.92	1.56	1.89	8.31	7.68	8.00	0.16	0.15	0.15	21.86	21.22	21.54	0.35	0.34	0.35	3.69	8.86	6.27	0.06	0.11	0.09	
Peroneus Tertius	54.69	97.79	75.94	1.92	3.54	2.73	8.14	5.43	6.79	0.30	0.20	0.25	25.05	25.33	25.19	0.90	0.90	0.90	-	1.59	1.59	-	0.06	0.06	
Piriformis	378.38	99.00	145.64	0.94	0.21	0.58	13.52	10.65	13.58	0.04	0.02	0.03	23.08	25.00	24.79	0.05	0.05	0.05	-	1.37	1.37	-	0.00	0.00	
Plantaris	18.15	100.00	100.00	0.13	0.13	0.13	13.52	10.65	13.58	0.04	0.02	0.03	23.08	25.00	24.79	0.05	0.05	0.05	-	1.37	1.37	-	0.00	0.00	
Popliteus	51.89	71.30	61.59	0.74	1.07	0.91	12.76	11.95	12.76	0.19	0.18	0.19	23.77	25.23	24.50	0.34	0.36	0.35	-	0.69	0.69	-	0.01	0.01	
Quadratus Femoris	69.03	67.68	68.36	11.52	1.14	1.23	16.77	8.60	12.69	2.95	1.72	2.34	16.29	12.44	14.36	0.95	2.42	2.69	6.25	12.28	9.26	1.21	1.86	1.53	
Sartorius Distal	14.86	25.20	20.03	0.82	1.44	1.13	4.91	3.06	3.98	0.27	0.17	0.22	24.67	24.66	24.66	1.34	1.31	1.33	-	1.55	1.55	-	0.09	0.09	
Sartorius Proximal	13.75	21.20	17.48	0.61	1.01	0.81	3.23	2.08	2.65	0.16	0.10	0.13	25.36	25.75	25.56	1.41	1.14	1.14	-	1.72	1.72	-	0.08	0.08	
Semimembranosus	93.61	99.59	96.75	1.59	1.56	1.58	9.94	8.06	8.85	0.15	0.12	0.14	22.87	18.86	19.87	0.50	0.44	0.47	-	1.21	1.21	-	0.03	0.03	
Semitenosus	72.55	98.29	85.42	1.83	2.34	2.09	5.99	4.27	5.13	0.13	0.09	0.11	20.87	18.86	19.87	0.50	0.44	0.47	-	1.21	1.21	-	0.03	0.03	
Soleus Anterior	84.28	99.88	97.25	1.58	1.56	1.57	8.97	7.45	8.70	0.14	0.10	0.12	22.92	19.20	21.04	0.32	0.29	0.31	4.92	7.76	6.34	0.88	1.38	1.23	
Soleus Medialis	81.43	123.94	102.69	1.83	2.17	2.00	29.56	15.62	22.59	0.48	0.25	0.36	20.41	20.50	20.46	0.34	0.34	0.34	7.61	1.15	1.15	0.02	0.02	0.02	
Tensor Fasciae Latae	66.62	100.00	83.31	4.54	7.53	6.04	5.71	4.07	4.89	0.47	0.43	0.45	7.41	5.90	6.66	0.60	0.58	0.59	0.29	11.69	5.99	0.03	0.05	0.04	
Thibalis Anterior	195.80	100.00	147.90	2.73	0.84	1.78	12.40	7.97	10.19	0.09	0.06	0.07	23.45	23.82	24.15	0.20	0.20	0.20	15.60	4.29	9.95	0.13	0.20	0.17	
Thibalis Posterior Medialis	80.79	100																							

Chapter 4

TLEM 2.0 – A comprehensive musculoskeletal geometry dataset for subject-specific modeling of lower extremity

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Abstract

When analyzing complex biomechanical problems such as predicting the effects of orthopedic surgery, subject-specific musculoskeletal models are essential to achieve reliable predictions. The aim of this paper is to present the Twente Lower Extremity Model 2.0, a new comprehensive dataset of the musculoskeletal geometry of the lower extremity, which is based on medical imaging data and dissection performed on the right lower extremity of a fresh male cadaver. Bone, muscle and subcutaneous fat (including skin) volumes were segmented from computed tomography (CT) and magnetic resonance imaging (MRI) scans. Inertial parameters were estimated from the image-based segmented volumes. A complete cadaver dissection was performed, in which bony landmarks, attachments sites and lines-of-action of 55 muscle actuators and 12 ligaments, bony wrapping surfaces, and joint geometry were measured. The obtained musculoskeletal geometry dataset was finally implemented in the AnyBody Modeling System™ (AnyBody Technology A/S, Aalborg, Denmark), resulting in a model consisting of 12 segments, 11 joints and 21 degrees of freedom, and including 166 muscle-tendon elements for each leg. The new TLEM 2.0 dataset was purposely built to be easily combined with novel image-based scaling techniques, such as bone surface morphing, muscle volume registration and muscle-tendon path identification, in order to obtain subject-specific musculoskeletal models in a quick and accurate way. The complete dataset, including CT and MRI scans, and segmented volume and surfaces, is made available for the biomechanical community at <http://www.utwente.nl/ctw/bw/research/projects/TLEMsafe>, in order to accelerate the development and adoption of subject-specific models on large scale. TLEM 2.0 is freely shared for non-commercial use only, under acceptance of the TLEMsafe Research License Agreement.

4.1 Introduction

Musculoskeletal models of the lower extremity represent a valuable tool to explore various biomechanical problems, where accurate knowledge of muscle and joint reaction forces is necessary. In the past, musculoskeletal models of the lower extremity have been used in several disparate disciplines, such as in orthopedic surgery to simulate the effects of joint replacements (Delp et al., 1994; Piazza et al., 2001) and tendon transfers (Piazza et al., 2003; Reinbolt et al., 2009); in neurology to model the effects of a stroke (Higginson et al., 2006), disorders of the central nervous system (Steele et al., 2012; van der Krogt et al., 2013), and spinal cord injuries (Paul et al., 2005; To et al., 2005); in sport to optimize athletes performances (Pandy et al., 1990; Rasmussen et al., 2012), and analyses and prevent injuries (McLean et al., 2003; Manal et al., 2005); or in ergonomics for prevention of work-related musculoskeletal disorders (Wu et al., 2009).

Unfortunately, reliability of force predictions is affected by the accurateness of many model inputs. In particular, one of the most sensitive parameters of the musculoskeletal geometry is represented by muscle-tendon moment arms (Hoy et al., 1990; Out et al., 1996), whose estimation depends on the identification of muscle-tendon lines-of-action (Rohrle et al., 1984; Pal et al., 2007); moreover, errors in the estimated position of muscle-tendon attachment sites have been shown to affect model force predictions (Carbone et al., 2016c). To represent different subjects, simple linear scaling laws are usually applied to generic models, which are based on one or more cadaver specimens (Delp et al., 1990; Klein Horsman et al., 2007; Arnold et al., 2010). However, these scaling procedures do not take into account the inter-individual variability present in musculoskeletal geometry (White et al., 1989; Duda et al., 1996). For these reasons, subject-specific models have been shown to be necessary when exploring complex biomechanical problems, such as representing pathologies in the musculoskeletal anatomy and predicting the outcome of orthopedic surgery (Lenaerts et al., 2009; Scheys et al., 2011b; Taddei et al., 2012; van der Krogt et al., 2013). Constructing subject-specific models without intensive manual intervention represents a significant challenge. Indeed, several recent studies have focused on developing such subject-specific models based on medical imaging or functional measurements (Blemker et al., 2007; Scheys et al., 2011b; Hainisch et al., 2012; Hausselle et al., 2014) but their clinical application on a large scale has not been demonstrated.

An interesting approach to obtain subject-specific models is to register or morph the medical images of the subject to a previously built template or atlas, containing muscle-tendon attachment sites and lines-of-action (Pellikaan et al., 2014), or muscle volumes (Carbone et al., 2013b). However, no musculoskeletal model in literature is linked to such a template or atlas. The Twente Lower Extremity Model (Klein Horsman et al., 2007) represents so far the most complete and consistent dataset of the lower extremity, including both musculoskeletal geometry and muscle-tendon architecture based on one single cadaver specimen.

Unfortunately, lack of detailed medical images of that cadaver specimen makes it impossible to apply any image-based subject-specific scaling technique.

The aim of this study was to create a new comprehensive musculoskeletal geometry dataset of the lower extremity, based on medical images and dissection measurements of a single cadaver specimen. This dataset, named Twente Lower Extremity Model 2.0, consists of a coherent set of medical imaging data (CT and MRI), segmented bone, muscle and subcutaneous fat (including skin) volumes, coordinates of muscle-tendon attachment sites and lines-of-action, ligament attachment sites and lines-of-action, wrapping surfaces, and joint centers and axes of rotation. TLEM 2.0 was purposely built to be easily combined with image-based scaling techniques, in an attempt to accelerate the application of subject-specific models. The complete dataset is made freely available to the scientific community at the website <http://www.utwente.nl/ctw/bw/research/projects/TLEMsafe> to be used for non-commercial use only, under acceptance of the TLEMsafe Research License Agreement.

4.2 Methods

4.2.1 Cadaver specimen

Measurements were performed on the right lower extremity of a fresh cadaver (male, white, age 85 years, estimated mass 45 kg), with no clear pathologies affecting the musculoskeletal system. The leg length, measured from the anterior superior iliac spine to the medial malleolus, was 813 mm.

In the specimen we distinguished six segments: pelvis, femur, patella, tibia (including fibula), talus and foot (consisting of hindfoot, midfoot and phalanges). During the whole measurement session, the foot bones were fixed to each other and the foot was fixed to a wooden plate, in order to avoid internal movements.

4.2.2 Medical imaging

Prior to the dissection of the specimen, computed tomography (CT) and magnetic resonance images (MRI) of both lower extremities, from the most proximal extremity of the iliac crest to the most distal tip of the foot, were acquired at the Department of Radiology of the Radboud University Medical Center (Figure 4.1A). For the CT, a Siemens SOMATOM® Sensation 16 Scanner (Siemens AG, Munich, Germany) was used, with voxel size of 0.977 mm x 0.977 mm x 0.75 mm. For the MRI, T1 weighted axial spin echo (SE) scan was taken using a Siemens 3T MAGNETOM® Skyra (Siemens AG, Munich, Germany), with different slice thickness between series covering the joint regions (3 mm) and series covering the shaft of femur and tibia (8 mm), and an in-plane resolution of 1 mm x 1 mm. To improve the quality of the images and avoid crystallization damage of soft tissues, the scans were performed before freezing of the cadaver specimen.

Figure 4.1 - Measurements performed on the cadaver specimen. A: CT scan (left) and MRI scan (right) of the lower extremities of the cadaver specimen, from the most proximal extremity of the iliac crest to the most distal tip of the foot. B: Right lower extremity specimen after removal of skin and subcutaneous fat. The specimen was not fixed in a specific position, so that segments and joints could be moved freely (except for the foot being fixed to a wooden plate) in order to facilitate the measurements. C: Dissection session using the Brainlab Kolibri™ image-guided surgery platform (Brainlab AG, Munich, Germany). In this example, a reference frame with retro-reflective markers was attached to the femur, and coordinates of muscle attachment sites were measured in three-dimensional space with respect to the reference frame fixed to the bone. Frame attachment pins remained fixed throughout the measurement.

4.2.3 Cadaver measurements

After thawing of the cadaver, a complete dissection of the lower extremity specimen was performed at the Department of Anatomy of the Radboud University Medical Center. The cadaver was divided at the level of L5, then the two lower extremities were separated. The right lower extremity specimen was not fixed in a specific position, so that segments and joints could be moved freely (except for the foot being fixed to a wooden plate) in order to facilitate the measurements. First, skin and subcutaneous fat were removed (Figure 4.1B). Then, reference frames with retro-reflective markers were attached to the pelvis, femur, patella, tibia and foot segments. The Brainlab Kolibri™ image-guided surgery platform (Brainlab AG, Munich, Germany) was used to measure the position of points in 3D space with respect to the corresponding reference frame fixed to the bones. This navigation system had a spatial accuracy of 0.231 ± 0.137 mm (RMS $\pm$ SD) and an average orientation error of 0.383° (Wiles et al., 2004).

4.2.3.1 Muscle attachment sites, lines-of-action, mass and volume

For each muscle, fat at the intermuscular connection was removed, resulting in muscles that were only connected to the bones at origin and insertion. After the identification, each muscle was excised and contours of its origin and insertion were measured with the Brainlab Kolibri™ system (Figure 4.1C). The number of points measured to define each muscle attachment site depended on its shape and size. In total, 55 muscle actuators were analyzed, and 98 attachment sites were measured. In case of a curvature of the muscle-tendon line-of-action, via points and underlying bone contours were measured. Then, tendon, remaining fat and excessive connective tissue were removed from the dissected muscle. Muscle weight was measured using a scale with an accuracy of 1.0 g. Muscle volumes were measured using the water displacement method, using a scaled cylinder with an accuracy of 1.0 ml.

4.2.3.2 Joint geometry

After removal of all muscles, but with ligaments still intact, geometrical behavior of hip, knee, patellofemoral, talocrural and subtalar joints were measured. Each joint was manipulated by hand, the movement being limited by bone contact or ligaments. Throughout the complete joint range of motion, the position of three points on the bone surface of the distal segment was measured in the reference frame of the proximal segment.

4.2.3.3 Ligament attachment sites and lines-of-action

Similarly to muscles, attachment sites and lines-of-action of five ligaments of the hip joint (ischiofemoral, iliofemoral medial, iliofemoral lateral, pubofemoral and ligament of the head of the femur) and five ligaments of the knee joint (tibial collateral, fibular collateral, anterior cruciate, posterior cruciate and patellar ligament) were measured.

4.2.3.4 Bony landmarks and bone surfaces

After all the ligaments and remaining soft tissues had been removed, the bones were separated and 22 bony landmarks were measured on the bone surface, based on the definition by the Standardization and Terminology committee of the International Society of Biomechanics (Wu et al., 2002). Finally, at least 100 additional registration points were collected on the complete surface of each bone, in order to facilitate accurate registration to segmented bone surface later.

4.2.4 Post processing

4.2.4.1 Image post-processing

Bone surfaces were automatically segmented from CT into STL files and re-meshed to obtain a higher resolution in regions with a high curvature. Muscle volumes were segmented from MRI using a semi-automatic registration technique. Subcutaneous fat and skin volumes were manually segmented from MRI. All the image segmentation processing was performed using Mimics® 17.0 (Materialise N.V., Leuven, Belgium).

4.2.4.2 Registration

To register the cadaver measurements to the CT-based bone surface STL files, the iterative closest point method (Besl et al., 1992) was used to minimize the sum of the squared errors (SSE) between the registration points and the closest points on the faces of the STL:

$$SSE = \sum_{i=1}^n (y_i - \hat{y}_i)^2$$

where y_i represents the registration points, $\hat{y}_i$ represents the closest point on the face of the STL to y_i , and n represents the number of registration points. To improve results, 5% of the worst registration points were rejected after the first 50 iterations. After registration, the measured bony landmarks and muscle attachment points were projected to the closest point on the face of the STL.

4.2.4.3 Local reference frames

For each body segment, the following local reference frames were defined (see Figure 4.2):

- Pelvis
 - O: The origin coincident with the right (or left) hip joint.
 - Z: The line parallel to the line connecting the right and left anterior superior iliac spine, and pointing to the right.
 - X: The line parallel to a line lying in the plane defined by the two anterior superior iliac spines and the midpoint of the two posterior superior iliac spines, perpendicular to the Z-axis and pointing anteriorly.
 - Y: The line perpendicular to both X- and Z-axis, pointing cranially.
- Femur
 - O: The origin coincident with the midpoint between the medial and lateral epicondyles of the femur.
 - Y: The line connecting the origin and the hip joint, pointing cranially.
 - Z: The line lying in the plane defined by the medial and lateral epicondyles of the femur and the hip joint, perpendicular to the Y-axis, pointing to the right.
 - X: The line perpendicular to both Y- and Z-axis, pointing anteriorly.
- Patella
 - O: The origin coincident with the center of mass of the patella.
 - X, Y, Z: Coordinate system parallel to the coordinate system of the femur when the knee joint angle is equal to 0° , with position and orientation of the patella being estimated during cadaver dissection and using MRI.
- Tibia
 - O: The origin coincident with the midpoint between the tips of the medial and lateral malleoli.
 - Y: The line connecting the midpoint between the tips of the medial and lateral malleoli, and the midpoint between the most medial point of the medial condyle of the tibia and the most lateral point of the lateral condyle of the tibia, pointing cranially.
 - Z: The line lying in the plane defined by the most medial point of the medial condyle of the tibia, the most lateral point of the lateral condyle of the tibia and the midpoint between the tips of the medial and lateral malleoli, perpendicular to the Y-axis, pointing to the right.
 - X: The line perpendicular to both Y- and Z-axis, pointing anteriorly.
- Talus
 - O: The origin coincident with the center of mass of the talus.
 - X, Y, Z: Coordinate system parallel to the coordinate system of the tibia when talocrural joint angle is equal to 0° , with position and orientation of the talus being estimated during cadaver dissection and using MRI.

- Foot

O: The origin coincident with the center of the subtalar joint.

Y: The line perpendicular to the plane defined by the contact points of heel, first metatarsal and fifth metatarsal, pointing cranially.

X: The line perpendicular to the Y-axis, pointing toward the contact point of the second metatarsal.

Z: The line perpendicular to both Y- and X-axis, pointing to the right.

Figure 4.2 - Local reference frames of the body segments. A: Pelvis (ASIS: anterior superior iliac spine, PSIS: posterior superior iliac spine). B: Femur and patella (ME: medial epicondyle of the femur, LE: lateral epicondyle of the femur). C: Tibia and talus (MC: most medial point of the medial condyle of the tibia, LC: most lateral point of the lateral condyle of the tibia, MM: medial malleolus, LM: lateral malleolus). D: Foot (HC: heel contact point, 1C: first metatarsal contact point, 2C: second metatarsal contact point, 5C: fifth metatarsal contact point).

4.2.4.4 Inertial parameters

Segment mass, center of mass, principal axes of inertia and principal moments of inertia were calculated for each body segment, based on the segmented bone, muscle and fat volumes, using SolidWorks® 2013 (Dassault Systèmes S.A., Vélizy-Villacoublay, France). The following average density parameters were used: 1500 kg/m^3 for bone, 1060 kg/m^3 for muscle and 900 kg/m^3 for fat. Inertial parameters were calculated with respect to the local reference frames defined above.

4.2.4.5 Modeling of muscle and ligament attachment sites and lines-of-action

To accurately describe their mechanical effect, muscle actuators were divided into a sufficient number of muscle-tendon elements, in accordance with the original TLEM dataset (Klein Horsman et al., 2007). The contours of the measured attachment sites were modeled either as points, straight or curved lines, or areas, as described by Pellikaan et al. (2014); afterwards, all the modeled muscle-tendon attachment sites were projected to the closest node point of the bone surfaces STL.

In case of curved muscle-tendon line-of-action, when the muscle was not free to shift over the underlying structures, via points were defined based on the measured coordinates of the line-of-action, dividing the muscle-tendon element in a series of straight line segments.

When a free shift of the muscle over the underlying structure (usually bone) was possible, cylindrical surfaces were defined to represent the bony contours, based on the measured muscle-tendon line-of-action and CT-based bone surfaces. Such wrapping surfaces were defined for Gluteus Maximus, Iliopsoas, Quadriceps Femoris and Gastrocnemius.

Similarly to the muscle-tendon elements, ligaments were modeled as straight lines and their attachment sites and via points modeled from the cadaver measurements.

4.2.4.6 Estimation of joint geometry

Hip rotation center was calculated based on a spherical fit through the trajectory of the femur with respect to the pelvis. Knee rotation center and axis were calculated based on a cylindrical fit through the trajectory of the tibia-fibula with respect to the femur. Patellofemoral rotation center and axis were calculated based on a cylindrical fit through the trajectory of the patella with respect to the femur. Talocrural rotation center and axis were calculated based on a cylindrical fit through the trajectory of the talus with respect to the tibia-fibula. Subtalar rotation center and axis were calculated based on a cylindrical fit through the trajectory of the foot with respect to the talus. The accuracy of the fitting was assessed with the average root mean squared error (RMSE) of the acquired data points to the fitted sphere or cylinder.

4.2.5 Musculoskeletal model

The obtained musculoskeletal geometry dataset was implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006). The muscle-tendon architecture dataset was adapted from the original TLEM dataset (Klein Horsman et al., 2007): nominal muscle fiber lengths were individually scaled, comparing the total length of the muscle-tendon elements in the original TLEM and in the new TLEM 2.0 dataset; tendon slack length of each muscle-tendon element was then calculated to reproduce the relative sarcomere length as measured in the original TLEM dataset; physiological cross-sectional areas (PCSA) were calculated taking into account the scaled nominal muscle fiber lengths, the nominal pennation angles, and the measured muscle volumes. Finally, the obtained musculoskeletal model of the lower extremity was integrated with the full-body model of the AnyBody Managed Model Repository™ ver. 1.6.4 (AnyBody Technology A/S, Aalborg, Denmark). This integration involved connection to the body segments and muscles of the upper extremity spine model, hereunder a set of morphing methods so that the pelvic geometry of the upper extremity model, arising from a different dataset, could fit with the pelvic geometry of TLEM 2.0.

4.3 Results

The complete list of the measured muscle actuators is presented in Table 4.1. For each muscle actuator, the table contains the number of muscle-tendon elements representing that muscle actuator, the type of path line (straight line, passing through via points or curving around a wrapping surface), how the origin and insertion sites were modeled (point, line, or surface), and the measured mass and volume. The dataset contains in total 55 actuators described by 166 muscle-tendon elements. In a similar way, Table 4.2 contains the list of the measured ligaments.

Table 4.1 - List of muscle actuators analyzed: number of muscle-tendon elements representing the muscle actuator, type of the path line (straight line (S), passing through via points (VP) or curving around a wrapping surface (WS)), type of the origin and insertion sites (Point, Line (order), LineArea (order) or Area), mass (g) and volume (ml).

Muscle	# Elements	Type line	Origin	Insertion	Mass (g)	Volume (ml)
Adductor Brevis Distal	2	S	Line (2)	Line (1)	20	20
Adductor Brevis Mid	2	S	Line (2)	Line (1)	20	20
Adductor Brevis Proximal	2	S	Line (2)	Line (1)	20	20
Adductor Longus	6	S	LineArea (2)	Line (2)	67	66
Adductor Magnus Distal	3	S	Line (2)	Point	183	181
Adductor Magnus Mid	6	S	Line (2)	Line (2)	106	102
Adductor Magnus Proximal	4	S	Line (2)	Line (1)	30	30
Biceps Femoris Caput Breve	3	S	Line (2)	Point	61	60
Biceps Femoris Caput Longum	1	S	Point	Point	116	111
Extensor Digitorum Longus	4	VP	Line (2)	Point	36	35
Extensor Hallucis Longus	3	VP	Line (3)	Point	17	16
Flexor Digitorum Longus	4	VP	LineArea (3)	Point	26	25
Flexor Hallucis Longus	3	VP	Line (2)	Point	30	30
Gastrocnemius Lateralis	1	WS	Point	Point	54	54
Gastrocnemius Medialis	1	WS	Point	Point	111	107
Gemellus Inferior	1	S	Point	Point	2	-
Gemellus Superior	1	S	Point	Point	2	-
Gluteus Maximus Inferior	6	WS	Area	Line (1)	336	316
Gluteus Maximus Superior	6	WS	Area	Line (1)	134	130
Gluteus Medius Anterior	6	S	Area	Area	77	75
Gluteus Medius Posterior	6	S	Area	Area	154	150
Gluteus Minimus Anterior	2	S	Area	LineArea (2)	26	26
Gluteus Minimus Mid	2	S	Area	LineArea (2)	26	26
Gluteus Minimus Posterior	2	S	Area	LineArea (2)	26	26
Gracilis	2	S	Line (1)	Point	58	58
Iliacus Lateralis	2	WS	Area	LineArea (2)	30	29
Iliacus Medialis	2	WS	Area	LineArea (2)	30	29
Iliacus Mid	2	WS	Area	LineArea (2)	30	29
Obturator Externus Inferior	2	VP	Line (3)	Point	15	-
Obturator Externus Superior	3	VP	LineArea (1)	Point	26	-
Obturator Internus	6	VP	Area	Point	32	31
Pectineus	4	S	Line (2)	Line (3)	38	37
Peroneus Brevis	3	VP	Line (3)	Point	20	19
Peroneus Longus	3	VP	Line (3)	Point	43	42
Piriformis	1	S	Point	Point	26	25
Plantaris	1	WS	Point	Point	6	5
Popliteus	3	S	Line (2)	LineArea (3)	19	18
Psoas Major	5	WS	-	Point	-	-
Quadratus Femoris	4	S	Line(1)	Line (2)	34	33
Rectus Femoris	2	WS	Point	Line (2)	118	114
Sartorius	1	VP	Point	Point	101	98
Semimembranosus	3	S	Line (2)	Line (2)	120	116
Semitendinosus	1	S	Point	Point	111	106
Soleus Lateralis	3	S	Line (2)	Point	150	146
Soleus Medialis	3	S	Line (3)	Point	82	80
Tensor Fasciae latae	2	S	Line (2)	Point	33	34
Tibialis Anterior	3	VP	LineArea (2)	Point	77	75
Tibialis Posterior Lateralis	3	VP	Line (2)	Point	45	43
Tibialis Posterior Medialis	3	VP	Line (2)	Point	45	43
Vastus Intermedius	6	WS	Area	Line (2)	104	101
Vastus Lateralis Inferior	6	WS	Line (2)	Line (3)	84	84
Vastus Lateralis Superior	2	WS	Line (2)	Point	338	330
Vastus Medialis Inferior	2	WS	Line (3)	Line (3)	47	46
Vastus Medialis Mid	2	WS	Line (3)	Line (3)	87	88
Vastus Medialis Superior	4	WS	Line 2	Point	111	112

Table 4.2 - List of ligaments analyzed: number of elements representing the ligament, type of the path line (straight line (S) or passing through via points (VP)), type of the origin and insertion sites (Point or Line (order)).

Ligament	# Elements	Type line	Origin	Insertion
HIP				
Ischiofemoral	2	S	Point	Line (2)
Iliofemoral Medial	3	S	Point	Line (2)
Iliofemoral Lateral	3	S	Point	Line (2)
Pubofemoral	3	S	Line (2)	Line (2)
Ligament of the Head of the Femur	1	S	Point	Point
KNEE				
Tibial Collateral	1	VP	Point	Point
Fibular Collateral	1	VP	Point	Point
Anterior Cruciate	2	S	Point	Point
Posterior Cruciate	2	S	Point	Point
Patellar Ligament	1	S	Point	Point

Segmentation of six body segments (pelvis, femur, patella, tibia and fibula, talus, and foot), 55 muscle volumes, and subcutaneous fat (including skin) volumes were obtained from CT and MRI scans (Figure 4.3A).

Inertial parameters (segment mass, center of mass, principal axes of inertia and principal moments of inertia) of each body segment and coordinates of 22 bony landmarks, with respect to the relative local reference frame, are contained in Table A1 and Table A2.

Table A3 and Table A4 contain the coordinates of origin, insertion and via points of each muscle-tendon element and ligament, with respect to the relative local reference frame.

The geometrical definition of the cylinders representing the wrapping surfaces used to describe the curved lines-of-action of the Gluteus Maximus, Iliopsoas, Quadriceps Femoris and Gastrocnemius muscles is contained in Table A5.

Table A6 contains the estimated joint rotation centers and axes expressed in the relative local reference frames. The average RMSE fitting errors were 0.86 mm, 2.52 mm, 1.83 mm, 2.30 mm and 2.60 mm for the hip, knee, patellofemoral, talocrural and subtalar joint, respectively. Figure 4.3B shows the final musculoskeletal model based on TLEM 2.0, implemented in the AnyBody Modeling System™. The model consists of 12 body segments: head-arms-trunk, pelvis, and right and left femur, patella, tibia, talus and foot. The fibula was considered as one unit in combination with the tibia. The model comprises 11 joints: L5S1 and left and right hip, knee, patellofemoral, talocrural and subtalar. The L5S1 and hip joints are modeled as a ball-and-socket, defined by a rotation center and three orthogonal axes. The knee, patellofemoral, talocrural and subtalar joints are defined as a hinge, with a fixed rotation center and axis. The patellar tendon is defined as a non-deformable element that connects the patella to the tibia, therefore the orientation and position of the patella depends solely on the knee flexion angle, without introducing an extra degree of freedom (DOF). The orientation and position of the center of mass of the pelvis with respect to a 3D global frame, together with the joint rotations of the L5S1, hip, knee, talocrural and subtalar joints, results in a model with 21 DOFs. The model contains 55 muscle actuators, described by 166 Hill-type muscle-tendon elements. Nominal muscle fiber length, tendon slack length, nominal pennation angle, and PCSA of each muscle-tendon element are presented in Table A7.

Figure 4.3 –A: Image-based segmentation using Mimics® 17.0 (Materialise N.V., Leuven, Belgium). From left to right: Bone surfaces and single muscle volumes, muscle volumes per segment, and subcutaneous fat and skin volumes per segment. B: TLEM 2.0 musculoskeletal model implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark). The obtained model consists of 12 body segments (head-arms-trunk, pelvis, and right and left femur, patella, tibia, talus and foot), 11 joints (L5S1 and left and right hip, knee, patellofemoral, talocrural and subtalar) and 21 degrees of freedom. Each leg contains 55 muscle actuators, described by 166 Hill-type muscle-tendon elements.

The complete TLEM 2.0 dataset is freely shared with the scientific community to be used for non-commercial use only. Electronic Appendix (Tables A1-A7) and the segmented bone surfaces are available at <http://www.utwente.nl/ctw/bw/research/projects/TLEMsafe> under acceptance of the TLEMsafe Research License Agreement. CT and MRI scans, and segmented muscle and subcutaneous fat (including skin) volumes are available upon request to be sent to the TLEMsafe project coordinator, prof. dr. ir. Nico Verdonchot (n.verdonchot@utwente.nl), after approval of the TLEMsafe consortium.

4.4 Discussion

In this paper, we presented the Twente Lower Extremity Model 2.0, a new comprehensive musculoskeletal geometry dataset of the lower extremity. Most existing models have been based on one or more cadaver studies to represent the musculoskeletal geometry of an average adult subject (Delp et al., 1990; Klein Horsman et al., 2007; Arnold et al., 2010), but no prior dataset in the literature has been accompanied by detailed medical images and post-processing data. To the best of our knowledge, TLEM 2.0 represents the first consistent and

most complete ‘atlas’ model, which includes a set of CT and MRI scans, segmented bone, muscle and subcutaneous fat (including skin) volumes, inertial parameters, coordinates of bony landmarks, muscle and ligaments attachment sites and lines-of-action, bony wrapping surfaces, and joint centers and axes of rotation.

TLEM 2.0 is freely shared so that the scientific community can utilize the presented dataset for their own research purposes, for instance to develop new personalization techniques, in order to help to accelerate the development and adoption of subject-specific models on large scale. For this reason, data not used yet in the presented musculoskeletal model (such as fat and skin volumes, or ligament attachment sites) were also included in the shared dataset. Further data that was beyond the scope of this study, such as identification of muscle fibers direction, segmentation of articular cartilage and articular capsule, or a more sophisticated and realistic description of the knee joint and the foot model, could be also estimated in the future, in order to extend and improve the TLEM 2.0 dataset. Nevertheless, several limitations affect the presented dataset.

Firstly, medical images were taken with the cadaver in a supine position, resulting in a compression of muscles and other soft tissues in the gluteal region. Although unavoidable, we think that this phenomenon had low effect on the calculation of the total volume of muscle and fat tissue, and subsequently on the calculation of the inertial parameters of the pelvis segment. Furthermore, muscle-tendon lines-of-action and wrapping surfaces were measured during the cadaver dissection, and were not affected by tissue compression. However, we presume that future studies attempting to estimate muscle fibers direction and moment arms in the gluteal region, in particular for Gluteus Maximus, from the TLEM 2.0 datasets could yield inaccurate results.

Secondly, similarly to the original TLEM (Klein Horsman et al., 2007) and others lower extremity musculoskeletal geometry dataset in literature (Delp et al., 1990), TLEM 2.0 is based on a single Caucasian white male cadaver. The wide inter-individual anatomical variability in size and shape of muscle attachment sites (White et al., 1989; Duda et al., 1996) and the gender and ethnical variation (Kepple et al., 1998) reported in literature suggest that linear scaling of a model based on a single specimen may not be representative for individual applications. In these cases, image-based subject-specific models that take into account non-linear differences are more advisable and could be used to create additional ‘atlas’ models in order to represent different age, gender or ethnical variations.

Another limitation of this dataset is that parameters of the muscle-tendon architecture were not measured on the cadaver specimen. This would have required a much longer timespan to perform the measurements, and was beyond the scope of this study. We were aware of the fact that inaccuracies in muscle-tendon parameters (in particular tendon slack length) can largely affect musculoskeletal model prediction (Scovil et al., 2006; Redl et al., 2007). For this reason, the new cadaver study was planned so that the resulting dataset was compatible with the original TLEM model, which represents the most complete and consistent muscle-tendon architecture dataset of the lower extremity to date. Moreover, muscle-tendon

parameters were not simply scaled linearly with bone length, but they were individually adapted from the original TLEM to the new TLEM 2.0, taking into account the non-linear differences in bone size and muscle-tendon lengths, and preserving the originally measured relative sarcomere lengths, in order to guarantee consistency in muscle function between the two models.

It is important to note that TLEM 2.0 was not created to be used as a generic musculoskeletal model, but was purposely built as a template to obtain subject-specific models. The advantage of TLEM 2.0 is that it can be easily combined with medical imaging scaling methods, allowing to create personalized musculoskeletal geometry, including better estimation of muscle-tendon total length, line-of-action and moment arms, that in turn can allow to obtain better estimation of muscle-tendon parameters. For instance, several scaling techniques were developed parallel to TLEM 2.0 within the *TLEMsafe* project. Pellikaan et al. (2014) used a morphing based method to estimate the muscle attachment sites of the lower extremity, based on TLEM 2.0 and a second cadaver dissection dataset, showing that for 69% of the muscle attachment sites the estimation error was smaller than 15 mm, and that the largest errors affected only the least sensitive attachment sites. Then, Carbone et al. (2013b) combined TLEM 2.0 with morphing of bone surfaces, non-rigid registration of muscle volumes and functional optimization of muscle-tendon architecture in a streamlined modeling workflow, showing that subject-specific models result in more reliable outcome, while conventional anthropometric scaling laws were inadequate and caused unrealistic muscle activity predictions. Furthermore, the combination of patient-specific joint and muscle forces models with geometrically consistent bone geometry into finite element analyses is expected to be essential in the near future for predicting the individual functional outcome of patient treatments, allowing for example to obtain a better prediction of bone density remodeling and healing (Vahdati et al., 2014), or individualized predictions of fracture risk or peri-prosthetic micromotions (van der Ploeg et al., 2012). Moreover, the techniques applied to obtain personalized musculoskeletal models could also be applied to develop a population of subject-specific models to be used in statistical shape modeling of bone geometry (Baldwin et al., 2010).

However, obtaining personalized models that accurately reproduce the musculoskeletal system and the force-generating characteristics of a subject represents only one of several aspects to consider when aiming at reliable model predictions. For example, inverse dynamics simulations are sensitive to inaccuracies in the measured kinematic and kinetic data (Pàmies-Vilà et al., 2012), and the resulting dynamic inconsistency can lead to unrealistic model predictions (Kuo, 1998). Deriving the force plates data from three-dimensional full-body motion (Robert et al., 2013; Fluit et al., 2014a) represents a promising technique to both improve the dynamic consistency as well as remove the dependency of the model on measured external forces. Moreover, for individual applications such as prediction of functional outcome after a complex orthopedic surgery, kinematic data of the patient are missing and using pre-recorded measurements from different subjects would lead to obvious

inconsistency. Many forward dynamics methods have been developed in recent years to predict gait movements (Fluit et al., 2012; Wang et al., 2012), but their complexity and large computational cost prevented their application in a clinical setting. To deal with this restriction, recently principal component analysis (PCA) has been proposed to interpret and evaluate gait data (Daffertshofer et al., 2004) and predict new gait movements (Safonova et al., 2004; Fluit et al., 2014b), by eliminating dependency on measured kinematic input data. We expect such techniques to evolve in the near future, increasing our confidence in the individual predictions of musculoskeletal models, and we believe that a consistent and comprehensive dataset like TLEM 2.0 represents the ideal foundation for such complex applications.

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Chapter 5

Effect of image-based automatic scaling of musculoskeletal geometry of the lower extremity on model predictions

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Abstract

Musculoskeletal models of the lower extremity have been used in the past to explore complex biomechanical problems, such as to investigate neuromuscular pathologies or to predict the functional effect of orthopedic procedures. For these applications, an accurate description of the musculoskeletal geometry is essential to obtain reliable model predictions. However, creating detailed subject-specific models in a fast and preferably automatic way represents a significant challenge. In this study, the recently developed Twente Lower Extremity Model 2.0 was combined with novel image-based scaling techniques to calculate bone surfaces, joint geometry, and muscle-tendon attachment sites and lines-of-action, allowing to build ten subject-specific musculoskeletal models with limited manual intervention. Subsequently, the effects of the personalized musculoskeletal geometry on the model predictions was quantified. Subject-specific models presented substantial differences in the estimated body segment size (>10 mm), joint center position (>15 mm), joint axis direction ($>10^\circ$), muscle-tendon attachment sites and total length (>10 mm) and muscle-tendon moment arms (>5 mm) when compared to generic models. These discrepancies in musculoskeletal geometry resulted in different joint kinematics predicted during gait, in particular for subtalar inversion/eversion (11.8°) and hip internal/external rotation (6.6°), with some subjects presenting differences larger than 20° . Moreover, large differences in the peaks of net joint moments were found for subtalar eversion (0.12 Nm/kg) and hip extension (0.12 Nm/kg), followed by ankle plantarflexion (0.09 Nm/kg), hip flexion (0.07 Nm/kg) and hip abduction (0.06 Nm/kg), with some subjects presenting differences larger than 0.15 Nm/kg. These results shows that generic models and linear scaling techniques cannot account for inter-individual anatomical variability, and that subject-specific models are indeed necessary to reduce error in model predictions.

5.1 Introduction

Musculoskeletal models of the lower extremity have been used in the past to study the functional effect of orthopedic procedures (Piazza et al., 2001; Reinbolt et al., 2009), to investigate neuromuscular pathologies (Paul et al., 2005; Higginson et al., 2006; van der Krogt et al., 2013), or to optimize sport performances (Pandy et al., 1990; Rasmussen et al., 2012). For these complex applications, an accurate description of the musculoskeletal geometry is essential to obtain reliable model predictions.

It is well known that inaccuracies in muscle-tendon (MT) moment arms (Hoy et al., 1990; Out et al., 1996; Maganaris, 2004), MT attachment sites and lines-of-action (Pal et al., 2007; Carbone et al., 2012; Valente et al., 2014; Bosmans et al., 2015), and joint geometry (Martelli et al., 2015; Valente et al., 2015) affect model outcomes. Unfortunately, application of linear scaling laws to generic models (Delp et al., 1990; Klein Horsman et al., 2007; Arnold et al., 2010) cannot account for the inter-individual anatomical variability due to differences in age, height, weight and gender (White et al., 1989; Duda et al., 1996; Kepple et al., 1998). For these reasons, subject-specific models are necessary when exploring complex problems, such as surgical planning and clinical decision making (Cohen et al., 2003; Taddei et al., 2012).

Combining medical imaging techniques with musculoskeletal modeling to obtain subject-specific accuracy in a fast and preferably automated way represents a significant challenge (Blemker et al., 2007). Arnold et al. (2000) demonstrated the potential to build MRI-based models, but their approach was time consuming and cost-ineffective, since it required extensive manual intervention to segment bone and MT contours. A semi-automatic atlas-based method was introduced by Scheys et al. (2009), however this method, although allowing a considerable reduction of the processing time, was still relying on the user experience for visual inspection and manual correction.

In our study we used a streamlined modeling workflow, combining the recently developed Twente Lower Extremity Model 2.0 (Carbone et al., 2015) with image-based scaling methods, to obtain ten subject-specific musculoskeletal models with limited manual intervention. Subsequently, we aimed to assess the effects of the personalized musculoskeletal geometry on the model predictions by comparing generic and subject-specific models.

5.2 Methods

5.2.1 TLEMsafe healthy subjects dataset

A dataset of ten healthy subjects (five males, age 40.1 ± 15.7 years, height 174.9 ± 11.1 cm, weight 74.8 ± 11.9 kg, BMI 24.4 ± 2.3 kg/m², fat percentage $27.8 \pm 5.8\%$) was obtained at the Radboud University Medical Center in Nijmegen, the Netherlands. For each subject, an MRI scan of the lower extremity was obtained (3T, T1-weighted axial spin echo (SE), voxel size of $1.0 \times 1.0 \times 3.0$ mm for pelvis, knee and ankle region, and $1.0 \times 1.0 \times 8.0$ mm for the remaining upper and lower leg) using a Siemens 3T MAGNETOM[®] Skyra (Siemens AG,

Munich, Germany) (Figure 5.1A). Then, a six-camera digital optical motion capture system (Vicon Motion System Ltd., Oxford, UK) with synchronized custom built force plates (AMTI, Watertown, MA, U.S.A.) were used during walking trials at a level walkway (Figure 5.1B). 35 optical markers were placed according to the standard Vicon Plug-in-Gait marker set, and 10 additional markers were placed on the right and left thigh, shank, medial femoral epicondyle, medial malleolus and fifth metatarsal head of the foot. For each subject, 9 gait trials were selected: 3 trials at comfortable walking speed (CWS), 3 trials at slow walking speed (SWS) equal to 70% of CWS, and 3 trials at fast walking speed (FWS) equal to 130% of CWS. In total, $10 \times 9 = 90$ gait trails were analyzed.

Figure 5.1 - TLEMsafe healthy subjects dataset. A: MRI scan of the lower extremities. B: Healthy subject wearing reflective markers during a recording session of 3D motion analysis and force plates data. The TLEMsafe healthy subjects dataset is available for the scientific community for non-commercial use only, upon request to be sent to the TLEMsafe project coordinator, prof. dr. ir. Nico Verdonchot (n.verdonchot@utwente.nl), and after approval of the TLEMsafe consortium.

5.2.2 Musculoskeletal modeling

Modeling was performed using the Twente Lower Extremity Model 2.0 (Carbone et al., 2015) implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006) (Figure 5.2). TLEM 2.0 represents a comprehensive MS geometry dataset including medical images (CT and MRI) and segmented bone and muscle volumes. The model consisted of 12 body segments, 11 joints and 21 degrees of freedom. To accurately describe the functionality of the MS system, each leg contained in total 55 MT parts whose mechanical effect was described by 166 three-elements Hill-type MT elements (Zajac, 1989).

For each subject, two MS models were created:

5.2.2.1 Generic model

The TLEM 2.0 model was linearly scaled by fitting the anthropometry of the subject to the relative position of the measured optical markers, using a parameter optimization algorithm (Andersen et al., 2010).

Figure 5.2 - TLEM 2.0 dataset. A: CT and MRI scans. B: Bone surfaces, muscle volumes, and subcutaneous fat and skin volumes segmented from MRI and CT scans. C: TLEM 2.0 musculoskeletal model implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark), anterior and posterior view. TLEM 2.0 model consisted of 12 body segments (head-arms-trunk, pelvis, and right and left femur, patella, tibia, talus and foot), 11 joints (L5S1 and left and right hip, knee, patellofemoral, talocrural and subtalar) and 21 degrees of freedom. Each leg contained 55 muscle actuators, described by 166 Hill-type muscle-tendon elements.

5.2.2.2 Subject-specific model

Pelvis, femur, tibia, fibula, talus and calcaneus of the left leg were semi-automatically segmented from MRI scan, requiring manual adjustments, and re-meshed using Mimics® 17.0 (Materialise N.V., Leuven, Belgium) (Figure 5.A1), and bony landmarks necessary to define local reference frames were manually identified. More information about local reference frames are included in Appendix A2.

Joint geometry was estimated from the segmented bone surfaces using 3-matic® 10.0 (Materialise N.V., Leuven, Belgium). The hip joint was assumed to be a ball-and-socket joint, calculated from the spheres that best fitted the acetabulum and the head of the femur. The knee joint was defined as a hinge, with a fixed rotation center and axis, calculated from the cylinder that best fitted the posterior part of the femoral condyles. L5S1, patellofemoral, talocrural and subtalar joints were linearly scaled based on the size of the segmented bone surfaces and on the position of the bony landmarks (Figure 5.A2). Length of head-arms-trunk and foot segments were optimized based on the relative position of the measured optical markers (Andersen et al., 2010).

To estimate MT attachment sites, an automatic morphing from TLEM 2.0 bones to segmented bones was applied using Mimics® 17.0 (Materialise N.V., Leuven, Belgium), under the assumption that MT attachment sites followed the morphed bone surfaces (Pellikaan et al., 2014) (Figure 5.A3). 3D coordinates of the origin points of the Psoas, located on the trunk, via points not located on the bone surfaces (for example via points of the Sartorius), and via points and insertion points located on the foot were linearly scaled.

Inertial parameters, such as segment mass, center of mass, principal axes of inertia and principal moments of inertia were linearly scaled, based on the anthropometry of the subject.

Both generic and subject-specific models were built having identical left and right sides, under the assumption that the ten healthy subjects analyzed were symmetric. Personalized scaling of MT parameters (such as tendon slack length, nominal muscle fiber length and maximal isometric muscle force) was considered to be outside the scope of this study.

5.2.2.3 Simulations

Inverse kinematics was used for each subject and for each model to predict joint kinematics. Subsequently, inverse dynamics analysis was performed to calculate the net joint moments necessary to reproduce the measured gait trials. In total, 10 healthy subjects x 2 models x 9 gait trials = 180 simulations were performed and analyzed in this study.

5.2.3 Analysis

In order to assess the effects of the automatic personalization, differences in musculoskeletal geometry parameters and model predictions between generic and subject-specific models were calculated.

5.2.3.1 Musculoskeletal geometry

Several musculoskeletal geometry parameters were analyzed. Regarding the body segment sizes, differences in pelvis width (distance between hip joints), pelvis depth (distance between the midpoint of the two anterior superior iliac spines and the midpoint of the two posterior superior iliac spines), femur length (distance between the hip joint and the midpoint of the medial and lateral epicondyles of the femur) and tibia length (distance between the midpoint of the tips of the medial and lateral malleoli and the midpoint of the most medial point of the medial condyle of the tibia and the most lateral point of the lateral condyle of the tibia) were calculated. Regarding the joint geometry, differences in hip joint position (in the pelvis and femur local reference frames), knee joint position (in the femur and tibia local reference frames), knee joint axis direction (YZ-plane and XZ-plane in the femur and tibia local reference frames), knee varus/valgus (angle between Y-axes of the femur and tibia segments) and tibial rotation (angle between knee and talocrural joint axes in XZ-plane of the tibia local reference frame) were calculated. Moreover, for each MT part, differences in attachment site position, total length at the anatomical position, and moment arms at representative joint ranges of motion (Table 5.4) were calculated.

One-tailed Wilcoxon rank sum tests ($\alpha=0.05$) were performed to assess whether differences in musculoskeletal geometry parameters between generic and subject-specific models were significantly greater in male or female subjects.

5.2.3.2 Model predictions

In order to assess the effects of personalized musculoskeletal geometry parameters, joint kinematics and net joint moments predicted by generic and subject-specific models were compared. Regarding the joint kinematics, mean absolute differences during gait cycle were calculated for hip flexion/extension, hip abduction/adduction, hip internal/external rotation, knee flexion/extension, ankle dorsi/plantarflexion and subtalar inversion/eversion.

Regarding the net joint moments, mean absolute differences at specific representative peaks (Table 5.5) during the simulated gait cycle were calculated.

One-tailed Wilcoxon signed-rank tests ($\alpha=0.05$) were performed to assess significant differences in the outcomes predicted by generic and subject-specific models.

Model predictions which were dependent on MT parameters, such as muscle force or muscle activity, were not analyzed since personalization of MT architecture was outside the scope of this study.

5.3 Results

Subject-specific musculoskeletal geometry parameters were automatically loaded into the AnyBody Modeling System™, and ten subject-specific musculoskeletal models of the lower extremity were obtained (Figure 5.3).

Large differences were found between musculoskeletal geometry parameters of generic and subject-specific models (Table 5.1). Taking into account all the ten subjects analyzed, mean absolute differences when estimating body segment size varied from 7.9 mm for femur length to 12.5 mm for pelvis depth, with some subjects presenting differences larger than 40 mm. Also, we found mean absolute differences of 24.9 mm and 7.6 mm when estimating hip joint position in the pelvis and femur reference frame, respectively, and mean absolute differences of 13.5 mm and 19.0 mm when estimating knee joint position in the femur and tibia reference frame, respectively. Differences in knee joint axis direction were relatively larger in the XZ-plane (10.3° and 16.4° in the femur and tibia reference frame, respectively, with some subjects presenting differences larger than 30.0°) and less severe in the XY-plane (1.4° and 2.0° in the femur and tibia reference frame, respectively). Also, mean absolute differences in knee varus/valgus and tibial rotation angle were 2.4° and 10.0° , respectively. Pelvis depth was the only segment size that showed larger difference measured in females (mean 18.8 mm) than in males (mean 6.2 mm) ($p=0.11$).

When estimating MT attachment site position (Table 5.2), the mean absolute difference for the complete lower extremity was 11.0 mm, varying from 9.7 mm for tibia to 12.7 mm for femur, with some subjects presenting differences larger than 25 mm. Pelvis was the only segment that showed significant larger differences measured in females (mean 14.0 mm) than in males (mean 10.1 mm) ($p<0.05$). In particular, differences were larger than 20 mm for several MT parts acting on hip joint, such as Gluteal muscles, Biceps Femoris and Piriformis. Overall, differences in segment size, joint geometry, and MT attachment site position affected the MT element length (Table 5.3) and moment arms (Table 5.4). Mean absolute difference of the MT element length for the complete lower extremity was equal to 9.7 mm, varying from 5.4 mm for muscle acting on the ankle joint to 12.6 mm for muscles acting on the hip joint, with some subjects presenting differences larger than 30 mm. Muscles acting on the hip joint showed significant larger differences in females (mean 13.5 mm) than in males (mean 11.6 mm) ($p<0.05$). In percentage, mean absolute difference of the MT element

Figure 5.3 - Ten subject-specific musculoskeletal models of the lower extremity, obtained using an MRI-based streamlined modeling workflow, implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark).

Table 5.1 - Mean absolute differences in body segment size, joint center position and joint axis direction, when comparing generic and subject-specific models. The results are averaged over ten healthy subjects. More information about local reference frames are included in Appendix A2.

Differences in body segment size (mm)					
			mean	std	max
Pelvis	Width		11.0	7.3	27.5
Pelvis	Depth	M	6.2	4.0	11.8
		F	18.8	15.7	44.7
		M + F	12.5	13.1	44.7
Femur	Length		7.9	4.4	15.1
Tibia	Length		8.3	7.0	19.9
Differences in joint center position (mm)					
			mean	std	max
Hip	Pelvis	X-direction	15.5	9.0	32.5
		Y-direction	15.5	8.8	32.5
		Z-direction	5.5	3.7	13.8
		Total	24.9	7.9	34.6
	Femur	X-direction	0.0	0.0	0.0
		Y-direction	7.6	4.0	15.3
		Z-direction	0.0	0.0	0.0
		Total	7.6	4.0	15.3
Knee	Femur	X-direction	4.4	1.6	7.0
		Y-direction	12.6	1.5	15.0
		Z-direction	0.7	0.5	1.9
		Total	13.5	1.7	15.7
	Tibia	X-direction	8.6	4.8	14.0
		Y-direction	15.0	7.0	24.8
		Z-direction	3.7	1.7	6.9
		Total	19.0	5.1	27.6
Differences in joint axis direction (°)					
			mean	std	max
Knee	Femur	YZ-plane	1.4	0.8	2.4
		XZ-plane	10.3	1.6	12.9
	Tibia	YZ-plane	2.0	1.3	4.3
		XZ-plane	16.4	8.1	33.4
Knee varus/valgus		YZ-plane	2.4	1.4	5.1
Tibial rotation		XZ-plane	10.0	5.8	17.9

Table 5.2 - (Top) Mean absolute differences in MT attachment site position, when comparing generic and subject-specific models. (Bottom) MT attachment sites of the lower extremity presenting the largest differences between generic and subject-specific models. The results are averaged over ten healthy subjects.

Differences in MT attachment site position (mm)				
		mean	std	max
Pelvis	<i>M</i>	10.1	5.1	25.0
	<i>F</i>	14.0	8.2	39.7
	M + F	12.0	7.1	39.7
Femur		12.2	6.9	36.6
Tibia		9.7	5.6	43.0
		11.0	6.5	43.0

MT attachment sites with the largest differences (mm)				
MT part	Segment	mean	std	max
Gluteus Medius Anterior	Femur	23.1	8.4	36.6
Biceps Femoris Caput Breve	Tibia	23.0	11.3	43.0
Gluteus Minimus	Femur	22.9	6.6	33.7
Piriformis	Femur	21.2	8.5	35.9
Gluteus Medius Posterior	Femur	21.0	7.7	34.3
Vastus Lateralis Superior	Femur	20.0	6.2	31.1
Gluteus Maximus Inferior	Pelvis	19.9	10.7	39.7
Quadratus Femoris	Femur	17.9	6.0	27.3
Obturator Internus	Femur	17.8	7.0	29.7
Soleus Lateralis	Tibia	17.6	8.6	32.3

Table 5.3 - (Top) Mean absolute differences in MT element length, when comparing generic and subject-specific models. (Bottom) MT element lengths of the lower extremity presenting the largest differences between generic and subject-specific models. The results are averaged over ten healthy subjects.

Differences in MT element length (mm)				
		mean	std	max
Hip	<i>M</i>	11.6	7.1	34.3
	<i>F</i>	13.5	8.0	44.4
	M + F	12.6	7.6	44.4
Knee		8.3	6.9	35.0
Ankle		5.4	4.4	29.3
		9.7	7.3	44.4

Differences in MT element length (%)				
		mean	std	max
Hip	<i>M</i>	5.1%	5.7%	42.6%
	<i>F</i>	7.0%	10.2%	78.3%
	M + F	6.0%	8.3%	78.3%
Knee		2.6%	2.1%	10.1%
Ankle		1.5%	1.1%	6.6%
		6.5%	8.8%	78.3%

MT element lengths with the largest differences (mm)				
MT part	Joint	mean	std	max
Psoas Major	Hip	20.4	8.9	34.3
Obturator Internus	Hip	20.3	10.8	44.4
Adductor Brevis Proximal	Hip	19.8	5.7	28.7
Adductor Magnus Proximal	Hip	19.5	4.9	28.2
Adductor Longus	Hip	17.0	6.6	30.6
Semitendinosus	Hip/Knee	16.4	11.6	35.0
Adductor Brevis Mid	Hip	16.4	5.6	25.5
Obturator Externus Superior	Hip	16.3	3.9	21.4
Quadratus Femoris	Hip	14.9	6.0	26.4
Gracilis	Hip/Knee	14.5	7.4	27.2

MT element lengths with the largest differences (%)				
MT part	Joint	mean	std	max
Quadratus Femoris	Hip	34.5%	18.8%	78.3%
Gemellus Inferior	Hip	31.1%	19.7%	69.3%
Gemellus Superior	Hip	18.8%	13.6%	47.8%
Obturator Externus Inferior	Hip	18.2%	7.7%	31.7%
Obturator Externus Superior	Hip	17.8%	4.5%	24.3%
Adductor Magnus Proximal	Hip	17.6%	4.5%	24.0%
Obturator Internus	Hip	17.6%	10.4%	40.4%
Adductor Brevis Proximal	Hip	15.7%	4.9%	25.6%
Adductor Brevis Mid	Hip	11.8%	4.1%	17.8%
Pectineus	Hip	9.7%	3.9%	15.1%

Please note that biarticular muscles are taken into account only once when calculating the mean absolute difference for the complete lower extremity, but they are taken into account twice when calculating the mean absolute difference at joint level. For this reason, mean absolute difference for the complete lower extremity (6.5%) is larger than the mean absolute difference for each joint (6.0%, 2.6% and 1.5% for hip, knee and ankle joint, respectively).

length for the complete lower extremity was 6.5%, varying from 1.5% for muscles acting on the ankle joint to 6.0% for muscles acting on the hip joint, with some subjects presenting differences larger than 40%. On average, muscles acting on the hip joint presented the biggest difference between generic and subject-specific models, larger than 15 mm or 10%.

Mean absolute difference of the MT moment arms for the complete lower extremity was equal to 4.9 mm, varying from 2.7 mm for muscles acting on hip internal/external rotation to 8.1 mm for muscles acting on knee flexion/extension, with some subjects presenting differences larger than 20 mm. Muscles acting on the hip joint showed significant larger differences measured in females (mean 5.9 mm, 7.2 mm and 2.9 mm for hip flexion/extension, hip abduction/adduction and hip internal/external rotation, respectively) than in males (mean 4.4 mm, 5.7 mm and 2.5 mm for hip flexion/extension, hip abduction/adduction and hip internal/external rotation, respectively) ($p < 0.05$). In percentage, mean absolute difference of the MT moment arms for the complete lower extremity was 34.8%, varying from 22.5% for muscles acting on ankle dorsi/plantarflexion to 53.0% for muscles acting on hip internal/external rotation, with some subjects presenting differences larger than 100%. On average, muscles acting on the hip and knee joint presented the biggest differences between generic and subject-specific models, larger than 10 mm or 100%.

Table 5.4 - (Top) Mean absolute differences in MT moment arms when comparing generic and subject-specific models. **(Bottom)** MT moment arms of the lower extremity presenting the largest differences between generic and subject-specific models. The results are averaged over ten healthy subjects.

Differences in MT moment arms (mm)					Differences in MT moment arms (%)				
		mean	std	max		mean	std	max	
Hip flex./ext.	M	4.4	3.8	25.7	Hip flex./ext.	M	26.3%	27.3%	156.8%
	F	5.9	4.3	23.5		F	35.8%	32.0%	189.7%
	M + F	5.2	4.1	25.7		M + F	31.0%	30.1%	189.7%
Hip abd./add.	M	5.7	5.0	22.7	Hip abd./add.	M	21.6%	24.3%	113.5%
	F	7.2	6.1	29.9		F	34.2%	35.6%	206.5%
	M + F	6.4	5.6	29.9		M + F	27.9%	31.1%	206.5%
Hip int./ext. rot.	M	2.5	1.8	11.1	Hip int./ext. rot.	M	47.0%	44.4%	206.1%
	F	2.9	1.9	10.1		F	58.9%	50.6%	217.1%
	M + F	2.7	1.9	11.1		M + F	53.0%	48.0%	217.1%
Knee flex./ext.		8.1	3.7	25.5	Knee flex./ext.		36.7%	38.0%	268.1%
Ankle dorsi/plantarflex.		3.1	2.6	13.3	Ankle dorsi/plantarflex.		22.5%	23.1%	98.9%
Subtalar inver./ever.		3.8	3.5	15.6	Subtalar inver./ever.		27.2%	39.0%	196.5%
		4.9	4.3	29.9			34.8%	37.9%	268.1%

MT moment arms with the largest differences (mm)					MT moment arms with the largest differences (%)				
MT part	DOF	mean	std	max	MT part	DOF	mean	std	max
Adductor Brevis Distal	Hip abd./add.	21.3	4.9	29.9	Extensor Digitorum Longus	Subtalar inver./ever.	146.9%	21.0%	196.5%
Adductor Brevis Mid	Hip abd./add.	16.9	4.3	26.7	Semitendinosus	Hip int./ext. rot.	145.0%	53.3%	217.1%
Popliteus	Knee flex./ext.	16.5	4.3	25.5	Popliteus	Knee flex./ext.	134.6%	56.0%	268.1%
Gluteus Maximus Superior	Hip flex./ext.	16.3	5.0	25.7	Semimembranosus	Hip int./ext. rot.	131.0%	39.6%	206.1%
Adductor Brevis Proximal	Hip abd./add.	14.3	3.6	21.9	Piriformis	Knee flex./ext.	130.8%	34.6%	189.7%
Adductor Longus	Hip abd./add.	13.2	3.3	21.6	Pectineus	Hip int./ext. rot.	114.0%	46.1%	163.8%
Adductor Magnus Distal	Hip abd./add.	12.7	3.4	21.3	Adductor Brevis Proximal	Hip int./ext. rot.	108.5%	38.5%	159.2%
Gastrocnemius Lateralis	Knee flex./ext.	12.2	1.8	15.5	Gluteus Maximus Superior	Hip abd./add.	107.9%	42.6%	206.5%
Adductor Magnus Mid	Hip abd./add.	11.0	2.5	17.3	Adductor Brevis Mid	Hip int./ext. rot.	97.4%	33.2%	132.7%
Adductor Longus	Hip flex./ext.	10.9	5.3	23.5	Iliopsoas	Hip int./ext. rot.	96.3%	50.1%	153.8%

To analyze moment arms, the following joint ranges of motion were analyzed starting from anatomical position: hip flexion/extension (from 90° flexion to 30° extension), hip abduction/adduction (from 45° abduction to 30° adduction), hip internal/external rotation (from 30° external rotation to 30° internal rotation), knee flexion/extension (from 120° flexion to 0° extension), ankle dorsi/plantarflexion (from 15° dorsiflexion to 30° plantarflexion) and subtalar inversion/eversion (from 15° inversion to 15° eversion).

Differences in body segment size and joint geometry affected model outcomes too. Inverse kinematics simulations, based on the same 3D motion analysis data, predicted different joint kinematics for generic and subject-specific models (Figure 5.4). The largest mean absolute differences for gait trials at CWS (Table 5.5) were found for subtalar inversion/eversion (11.8°) followed by hip internal/external rotation (6.6°), with some subjects presenting differences larger than 20°. On average, differences in joint kinematics increased with the walking speed for hip abduction/adduction, hip internal/external rotation, ankle dorsi/plantarflexion and subtalar inversion/eversion, while decreased for hip flexion/extension and knee flexion/extension.

Figure 5.4 - Joint kinematics predicted by inverse kinematics simulations using generic (red) and subject-specific model (blue) to reproduce the same gait trial. In this example, we show simulated gait at comfortable walking speed for a representative subject.

Table 5.5 - Mean absolute differences in joint kinematics predicted during gait by generic and subject-specific models. The results are averaged over ten healthy subjects.

	Differences in joint kinematics (°)								
	SWS			CWS			FWS		
	mean	std	max	mean	std	max	mean	std	max
Hip flex./ext.	1.7	1.2	4.2	1.6	1.1	4.1	1.4	0.9	3.4
Hip abd./add.	1.9	1.0	3.8	2.1	1.0	4.4	2.2	1.0	4.2
Hip int./ext. rot.	6.3	2.3	9.8	6.6	2.5	10.9	6.7	2.6	10.9
Knee flex./ext.	1.7	1.1	3.8	1.7	1.0	3.9	1.6	0.9	3.6
Ankle dorsi/plantarflex.	2.5	1.1	5.0	2.6	1.1	5.0	2.7	1.1	5.1
Subtalar inver./ever.	11.6	6.1	21.8	11.8	6.2	23.0	11.9	6.4	23.2

Finally, inverse dynamics simulations, based on the same 3D motion analysis and force plates data, predicted different net joint moments for generic and subject-specific models (Figure 5.5). The largest mean absolute differences for peaks of net joint moments during gait trials at CWS (Table 5.6) were found for subtalar eversion (0.12 Nm/kg) and hip extension (0.12 Nm/kg), followed by ankle plantarflexion (0.09 Nm/kg), hip flexion (0.07 Nm/kg) and hip abduction (0.06 Nm/kg), with some subjects presenting differences larger than 0.15 Nm/kg. In percentage, mean absolute differences for peaks of net joint moments were larger for subtalar eversion (39.85%) and hip extension (30.76%), followed by hip internal rotation (16.06%), hip flexion (12.49%), and knee flexion and extension (12.23% and 10.66% respectively). Overall, average values, mean absolute differences and max absolute differences of peaks of net joint moments increased with the walking speed, while in percentage mean absolute differences had a tendency to decrease with the walking speed. Moreover, peaks in net joint moments of hip flexion, hip extension during swing, knee extension, knee flexion during swing and ankle plantarflexion were significantly lower in subject-specific models ($p < 0.05$), while peaks in hip extension during stance, hip internal rotation, knee flexion during stance and subtalar eversion were significantly higher in subject-specific models ($p < 0.05$).

Figure 5.5 - Net joint moments predicted by inverse dynamics simulations using generic (red) and subject-specific model (blue) to reproduce the same gait trial. In this example, we show simulated gait at comfortable walking speed for a representative subject.

Table 5.6 – Mean absolute differences in net joint moments at specific representative peaks during gait predicted by generic and subject-specific models. The results are averaged over ten healthy subjects.

Differences in net joint moments														
SWS					CWS					FWS				
	average value	mean absolute difference	max abs. diff.	# subjects showing reduction	average value	mean absolute difference	max abs. diff.	# subjects showing reduction	average value	mean absolute difference	max abs. diff.	# subjects showing reduction		
	Nm/kg	Nm/kg	Nm/kg		Nm/kg	Nm/kg	Nm/kg		Nm/kg	Nm/kg	Nm/kg			
Gait phase														
Net joint moment peaks														
Hip Extension #1	0%-5%	0.41	0.02	4.88%	0.09	5	0.72	0.01	2.16%	1.05	0.02	2.37%	0.06	2
Hip Extension #2	10%-15%	0.48	0.10	19.60%	0.18	0	0.63	0.12	18.11%	0	0.21	0	0.23	0
Hip Flexion #1	45%-55%	-0.36	0.07	19.95%	0.15	8	-0.61	0.07	12.49%	-1.01	0.05	5.93%	0.15	9
Hip Extension #3	90%-100%	0.16	0.05	41.99%	0.09	10	0.29	0.08	30.76%	0.13	0.09	22.90%	0.15	10
Hip Abduction #1	10%-15%	0.79	0.05	6.88%	0.11	6	0.79	0.05	6.51%	0.11	0.11	0.12	0.12	6
Hip Abduction #2	40%-50%	0.81	0.05	6.41%	0.12	6	0.84	0.06	6.85%	0.16	0.16	0.15	0.15	6
Hip Internal Rotation #1	10%-20%	-0.14	0.02	17.87%	0.04	0	-0.22	0.01	6.66%	0.04	0.04	0.03	0.03	3
Hip Internal Rotation #2	50%-60%	-0.06	0.01	20.23%	0.03	0	-0.09	0.01	16.06%	0.04	0	-0.09	0.05	0
Knee Extension #1	10%-20%	0.35	0.04	39.44%	0.09	8	0.59	0.04	10.66%	0.10	0.10	0.06	0.14	9
Knee Flexion #1	40%-50%	-0.22	0.03	16.87%	0.09	3	-0.29	0.03	12.23%	0.09	2	-0.34	0.09	2
Knee Extension #2	50%-60%	0.14	0.01	9.93%	0.03	6	0.23	0.02	8.38%	0.04	6	0.33	0.02	7
Knee Flexion #2	90%-100%	-0.16	0.01	3.97%	0.01	9	-0.26	0.01	4.84%	0.02	10	-0.33	0.02	10
Ankle Plantarflexion	45%-55%	1.30	0.08	6.00%	0.15	8	1.44	0.09	6.47%	0.18	8	1.52	0.11	7.51%
Subtalar Eversion	50%-60%	-0.19	0.10	44.43%	0.19	1	-0.26	0.12	39.85%	0.24	1	-0.47	0.14	32.12%
													0.30	2

5.4 Discussion

In this study, we used a streamlined modeling workflow to obtain personalized musculoskeletal geometry of the lower extremity from MRI in a mostly automatic way, in order to build ten subject-specific musculoskeletal models. Compared to generic models, subject-specific models presented substantial differences in musculoskeletal geometry parameters. Body segment sizes in generic models, optimized based on the relative position of the measured optical markers, were likely affected by soft-tissue artifacts, that is the errors associated with non-rigid movement between the optical markers applied on the skin and the underlying bone (Cappozzo et al., 1996). Differences in joint location and direction (in particular knee direction in XZ-plane and tibial rotation) was ascribable to subject-specific details that were incorporated in the image-based bone segmentation but that could not be taken into account by rescaled generic models. Also, large differences in MT attachment site position indicated that generic models cannot represent inter-individual anatomical variability (White et al., 1989; Duda et al., 1996), while morphing methods guaranteed that attachment sites were on the subject-specific bone surfaces. Consequently, large differences were found in the calculated MT element lengths and MT moment arms, similarly to what found by Scheys et al. (2008), affecting the capacity of muscles to generate moment around the joint.

In general, we found larger differences in musculoskeletal geometry parameters related to pelvis and muscles acting on the hip joint when analyzing female subjects, accordingly to the gender differences found by Kepple et al. (1998), since the TLEM 2.0 dataset is based on a male specimen. The differences found are likely to increase even further when modeling patients affected by musculoskeletal pathologies. These results highlight how image-based subject-specific models are needed for applications that require detailed knowledge of the musculoskeletal system, such as surgical planning and clinical decision.

Subsequently, we assessed the effect of personalized musculoskeletal geometry on outcomes of inverse kinematics and inverse dynamics simulations. Differences in the predicted joint kinematics were a direct consequence of the differences found in the musculoskeletal geometry parameters, as indicated by Scheys et al. (2011a). In particular, joint kinematic differences were more pronounced for subtalar inversion and hip rotation, allegedly caused by the large differences measured in the knee joint direction on the XZ-plane and the tibial rotation. It is known that estimation of joint kinematics for generic models using conventional motion capture technologies is affected by soft-tissue artifacts (Reinschmidt et al., 1997; Leardini et al., 2005), however it is important to note that these limitations are likely to affect subject-specific models too, although to a smaller extent.

Differences in the predicted joint kinematics directly affected the outcome of inverse dynamics simulations, showing a redistribution of net joint moments. For example, at the beginning of the single stance phase, subject-specific models predicted a simultaneous reduction of knee extension moment and increase of hip extension and hip internal rotation

moment. Similarly, at the end of the single stance phase, subject-specific models predicted a simultaneous reduction of the hip flexion moment and increase of hip internal rotation and knee flexion moment, and a shift of net joint moment from ankle plantarflexion to subtalar eversion. Finally, a consistent reduction of hip extension and knee flexion moment was predicted during swing phase. These results highlighted once more how subject-specific models are essential to accurately study muscle joint function (Jonkers et al., 2008; Lenaerts et al., 2009; Scheys et al., 2011b), while generic models can be sufficient for other purposes, for example in ergonomic studies to analyze and prevent injuries (Manal et al., 2005; Wu et al., 2009).

It is important to note that obtaining a detailed description of the musculoskeletal geometry represents only one of several aspects to consider when aiming at reliable model predictions. For example, optimization of MT parameters (Garner et al., 2003; Carbone et al., 2013a; van Campen et al., 2014), greater accuracy of the measured kinematic and kinetic data (Pàmies-Vilà et al., 2012) and reduction of the resulting dynamic inconsistency have an important role into the improvement of model predictions.

As simplification in our subject-specific models, 3D coordinates of attachments sites located on the trunk and foot segments, and via points not located on the bone surfaces were linearly scaled. However, this simplification had hardly an effect on the model outcomes, since these points have shown really low sensitivity (Carbone et al., 2012). Similarly, low sensitivity of segment inertial parameters (Bosmans et al., 2015) ensure negligible effects of the linear scaling on the model predictions.

The main limitation of the subject-specific models used in this study lies in the resolution and overall quality of the available medical images. For example, it was not possible to obtain a fitting-based calculation of the talocrural and subtalar joint geometry, and a morphing-based estimation of MT via points and attachment sites on the foot segment, since the voxel size in that region was relatively too large to guarantee an accurate segmentation of the underlying bones. An improvement of the accuracy of the model in the ankle and foot area would have required an increase of the acquisition time, affecting the potential application in clinical scenario. However, a very important aspect of the used workflow is its modularity, making it easier to include more details depending on the purpose of the model. To prove this point, the modeling workflow was adapted to include a detailed 11 degrees of freedom force-dependent-kinematic knee complex joint model (Marra et al., 2015), and allowed to win the “5th Grand Challenge Competition to Predict In Vivo Knee Loads” (Fregly et al., 2012) at the 7th World Congress of Biomechanics (July 6–11, 2014, Boston, MA, U.S.A.). Moreover, the same workflow has been used to build asymmetric personalized models for patients affected by hip dysplasia (Fluit et al., 2013) or osteosarcoma and soft-tissue sarcoma (Fluit, 2015).

In conclusion, the large differences found between generic and subject-specific models highlight the importance to use efficient methods to obtain detailed musculoskeletal geometry from medical images. Application of subject-specific models on a large scale

would permit to reduce errors in muscle force predictions, achieving the validity and reliability necessary in critical applications such as clinical decision making.

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Appendix A1 - Subject-specific musculoskeletal geometry

Figure 5.A1 - Subject-specific bone surfaces (bottom) segmented from MRI scans (top) using Mimics® 17.0 (Materialise NV, Leuven, Belgium).

HS01: M, 27 yrs, 180.0 cm, 91.7 kg
HS02: M, 23 yrs, 182.0 cm, 83.1 kg
HS03: M, 25 yrs, 195.0 cm, 90.4 kg
HS04: F, 27 yrs, 166.1 cm, 58.0 kg
HS05: F, 23 yrs, 187.5 cm, 77.6 kg
HS06: F, 59 yrs, 160.0 cm, 64.5 kg
HS07: M, 57 yrs, 162.5 cm, 55.5 kg
HS08: F, 60 yrs, 164.0 cm, 70.7 kg
HS09: M, 56 yrs, 178.3 cm, 75.9 kg
HS10: M, 44 yrs, 173.5 cm, 81.0 kg

Figure 5.A2 - Subject-specific joint geometry was estimated from the segmented bone surfaces using 3-matic® 10.0 (Materialise NV, Leuven, Belgium). The hip joint was assumed to be a ball-and-socket joint, calculated from the spheres that best fitted the acetabulum and the head of the femur. The knee joint was defined as a hinge, with a fixed rotation center and axis, calculated from the cylinder that best fitted the posterior part of the femoral condyles.

Figure 5.A3 - Frontal and dorsal view of the subject-specific bony landmarks (red), MT attachment sites and via points (grey) for pelvis (top), femur (center) and tibia-fibula (bottom). Subject-specific points were calculated applying an automatic morphing from TLEM 2.0 bones to segmented bones using Mimics® 17.0 (Materialise NV, Leuven, Belgium), under the assumption that MT attachment sites followed the morphed bone surface.

Appendix A2 - Local reference frames

For each body segment, the following local reference frames were defined (see Figure 5.A4):

- Pelvis
 - O: The origin coincident with the right (or left) hip joint.
 - Z: The line parallel to the line connecting the right and left anterior superior iliac spine, and pointing to the right.
 - X: The line parallel to a line lying in the plane defined by the two anterior superior iliac spines and the midpoint of the two posterior superior iliac spines, perpendicular to the Z-axis and pointing anteriorly.
 - Y: The line perpendicular to both X- and Z-axis, pointing cranially.
- Femur
 - O: The origin coincident with the midpoint between the medial and lateral epicondyles of the femur.
 - Y: The line connecting the origin and the hip joint, pointing cranially.
 - Z: The line lying in the plane defined by the medial and lateral epicondyles of the femur and the hip joint, perpendicular to the Y-axis, pointing to the right.
 - X: The line perpendicular to both Y- and Z-axis, pointing anteriorly.
- Patella
 - O: The origin coincident with the center of mass of the patella.
 - X, Y, Z: Coordinate system parallel to the coordinate system of the femur when the knee joint angle is equal to 0° , with position and orientation of the patella being estimated during cadaver dissection and using MRI.
- Tibia
 - O: The origin coincident with the midpoint between the tips of the medial and lateral malleoli.
 - Y: The line connecting the midpoint between the tips of the medial and lateral malleoli, and the midpoint between the most medial point of the medial condyle of the tibia and the most lateral point of the lateral condyle of the tibia, pointing cranially.
 - Z: The line lying in the plane defined by the most medial point of the medial condyle of the tibia, the most lateral point of the lateral condyle of the tibia and the midpoint between the tips of the medial and lateral malleoli, perpendicular to the Y-axis, pointing to the right.
 - X: The line perpendicular to both Y- and Z-axis, pointing anteriorly.
- Talus
 - O: The origin coincident with the center of mass of the talus.
 - X, Y, Z: Coordinate system parallel to the coordinate system of the tibia when talocrural joint angle is equal to 0° , with position and orientation of the talus being estimated during cadaver dissection and using MRI.

- Foot

O: The origin coincident with the center of the subtalar joint.

Y: The line perpendicular to the plane defined by the contact points of heel, first metatarsal and fifth metatarsal, pointing cranially.

X: The line perpendicular to the Y-axis, pointing toward the contact point of the second metatarsal.

Z: The line perpendicular to both Y- and X-axis, pointing to the right.

Figure 5.A4 - Local coordinate frames of the body segments: A: Pelvis (ASIS: anterior superior iliac spine, PSIS: posterior superior iliac spine). B: Femur and patella (ME: medial epicondyle of the femur, LE: lateral epicondyle of the femur). C: Tibia and talus (MC: most medial point of the medial condyle of the tibia, LC: most lateral point of the lateral condyle of the tibia, MM: medial malleolus, LM: lateral malleolus). D: Foot (HC: heel contact point, 1C: first metatarsal contact point, 2C: second metatarsal contact point, 5C: fifth metatarsal contact point).

Chapter 6

Effect of global optimization of muscle-tendon parameters of the lower extremity on model predictions

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Abstract

Use of subject-specific musculoskeletal models to explore complex biomechanical problems is rapidly increasing. However, in vivo measurement of muscle-tendon parameters such as tendon slack length L_T^s , nominal muscle fiber length $\overline{L_f}$, muscle volume Vol_M , and maximal isometric muscle force $\overline{F^M}$ are still laborious and cannot be applied to all muscles. In this study, a global optimization method was used for estimating muscle-tendon parameters from MRI and dynamometry data, in combination with previously obtained image-based musculoskeletal geometry, in order to build ten subject-specific musculoskeletal models with limited manual intervention. Then, the effect of subject-specific parameters on model predictions was quantified. Each step of the personalization had an increasing effect on the estimated model parameters. Subject-specific models presented on average differences larger than 15% for L_T^s and $\overline{L_f}$, and larger than 35% for $\overline{F^M}$ and Vol_M , when compared to generic models. These differences had a large effect on model outcomes. Average error in the predicted maximum joint torques was reduced from 64.1 Nm to 23.2 Nm. Mean absolute difference of 120.3 N was measured in the muscle-tendon force peaks during gait when comparing generic and subject-specific models. Moreover, muscle activity drastically decreased to more realistic values (<1) for prime mover muscles during gait, such as Soleus and Gastrocnemius. However, when comparing the predicted muscle activity with the measured EMG signal, it was not possible to prove any significant improvement, likely due to the limitations of EMG as a reliable validation tool. These results highlight the importance of obtaining accurate estimates of musculoskeletal geometry and muscle-tendon parameters in order to achieve more realistic model predictions.

6.1 Introduction

Use of subject-specific musculoskeletal (MS) models to explore complex biomechanical problems, such as representing pathologies of the MS anatomy (Lenaerts et al., 2009; Scheys et al., 2011b; van der Krogt et al., 2013; Marra et al., 2015) and predicting the outcome of orthopedic surgery (Cohen et al., 2003; Taddei et al., 2012; Fluit et al., 2013) is rapidly increasing. In MS models, the muscle-tendon (MT) force-generating characteristics are often described by the phenomenological Hill-type model proposed by Zajac (1989), which has been shown to be very sensitive to tendon slack length, followed by nominal muscle fiber length and maximal isometric muscle force (Scovil et al., 2006; Redl et al., 2007; De Groote et al., 2010; Ackland et al., 2012; Carbone et al., 2016c). These parameters are known to vary with age, gender and activity (Brand et al., 1981; Friederich et al., 1990) and are very difficult to measure directly (Blemker et al., 2007). Previous studies have presented methods to measure MT parameters using non-invasive modality such as ultrasound (Maganaris et al., 1998; Maganaris et al., 2006; Albracht et al., 2008) or medical images (Galbán et al., 2004; Heemskerk et al., 2005; Yuen et al., 2006; Hainisch et al., 2012), but these methods are still laborious and cannot be used for all muscles of the lower extremity, hence they are not feasible for a clinical application on a large scale.

To represent various subjects, linear scaling laws are usually applied to generic models, which are based on one or more cadaver specimens (Delp et al., 1990; Klein Horsman et al., 2007; Arnold et al., 2010). However, it is likely that data from cadaveric specimens do not accurately reflect absolute or relative size of muscles in young and healthy subjects (Tate et al., 2006). Moreover, linear scaling is inaccurate, since MT parameters do not correlate with bone dimensions (Ward et al., 2005; Ward et al., 2007), and muscle operative range has been shown to vary between muscles (Cutts, 1988, 1989; Arnold et al., 2011) and between subjects (Herzog et al., 1991; Abe et al., 2000; Blazevich et al., 2003).

Winby et al. (2008) suggested that a first step to estimate subject-specific MT parameters is to apply an anthropometric scaling, based on body segment size and MT element lengths, to preserve the operating range of the muscles, in order to guarantee a consistency in muscle function. Subsequently, a functional scaling should be applied to take into account subject-specific muscle strength and moment-angle relationship based on dynamometry data (Hatze, 1981; Koo et al., 2002; Garner et al., 2003; van Campen et al., 2014).

In this study, we used a global optimization method to estimate MT parameters of 55 MT parts (represented by 166 MT elements) from MRI and dynamometry data, in order to build ten subject-specific musculoskeletal models with increasing details. This study builds on a previously presented streamlined modeling workflow, used to obtain subject-specific musculoskeletal geometry from MRI (Carbone et al., 2016a). Subsequently, we aimed to assess the effects of personalized MT parameters on the model predictions by comparing generic and subject-specific models.

6.2 Methods

6.2.1 TLEMsafe healthy subjects dataset

A dataset of ten healthy subjects (five males, age 40.1 ± 15.7 years, height 174.9 ± 11.1 cm, weight 74.8 ± 11.9 kg, BMI 24.4 ± 2.3 kg/m², fat percentage $27.8 \pm 5.8\%$) was obtained at the Radboud University Medical Center in Nijmegen, the Netherlands. For each subject, an MRI scan of the lower extremity was obtained (3T, T1-weighted axial spin echo (SE), voxel size of $1.0 \times 1.0 \times 3.0$ mm for pelvis, knee and ankle region, and $1.0 \times 1.0 \times 8.0$ mm for the remaining upper and lower leg) (Figure 6.1A) using a Siemens 3T MAGNETOM® Skyra (Siemens AG, Munich, Germany). Then, a six-camera digital optical motion capture system (Vicon Motion System Ltd., Oxford, UK) with synchronized custom built force plates (AMTI, Watertown, MA, U.S.A.) were used during walking trials at a level walkway (Figure 6.1B). 35 optical markers were placed according to the standard Vicon Plug-in-Gait marker set, and 10 additional markers were placed on the right and left thigh, shank, medial femoral epicondyle, medial malleolus and fifth metatarsal head of the foot. During each trial, EMG signals were obtained for Tibialis Anterior, Gastrocnemius Medialis, Gastrocnemius Lateralis, Soleus Medialis, Peroneus Longus, Vastus Lateralis, Vastus Medialis, Rectus Femoris, Biceps Femoris Caput Longum, Semitendinosus, Gluteus Maximus Superior and Gluteus Medius Posterior of the dominant leg using wireless ZeroWire EMG system (Aurion s.r.l., Milano, Italy). EMG signals were demeaned, rectified, low-pass filtered at 6 Hz using a second order zero-phase Butterworth filter, and normalized to maximum voluntary contractions in order to obtain EMG envelopes. For each subject, 9 gait trials were selected: 3 trials at comfortable walking speed (CWS), 3 trials at slow walking speed (SWS) equal to 70% of CWS, and 3 trials at fast walking speed (FWS) equal to 130% of CWS. In total,

Figure 6.1 - TLEMsafe healthy subjects dataset. A: MRI scan of the lower extremities. B: Healthy subject wearing reflective markers and wireless EMG sensors during a recording session of 3D motion analysis and force plates data. C: Measurement of isometric and isokinetic torques during maximum voluntary contractions. The TLEMsafe healthy subjects dataset is available for the scientific community for non-commercial use only, upon request to be sent to the TLEMsafe project coordinator, prof. dr. ir. Nico Verdonchot (n.verdonchot@utwente.nl), and after approval of the TLEMsafe consortium.

10 x 9 = 90 gait trials were analyzed. Finally, for each subject, isometric and isokinetic torques during maximum voluntary contractions were measured using a Biodex Dynamometer (Biodex Medical Systems, Inc., Shirley, NY, U.S.A.) (Figure 6.1C): ankle plantarflexion and dorsiflexion at ankle plantarflexion angles of 0°, 15° and 30° and at constant velocities of 30°/s and 90°/s; knee flexion and extension at knee flexion angles of 30°, 60° and 90° and at constant velocities of 60°/s and 120°/s; hip flexion and extension at hip flexion angles of 0°, 30° and 60° and at constant velocities of 60°/s and 120°/s; hip abduction and adduction at hip abduction angles of 0°, 15° and 30° and at constant velocities of 30°/s and 60°/s. During each dynamometry trial, all adjacent joints were fixed and their joint angle was measured.

6.2.2 Musculoskeletal modeling

Modeling was performed using the Twente Lower Extremity Model 2.0 (Carbone et al., 2015) (Figure 6.2) implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006). TLEM 2.0 represents a comprehensive MS geometry datasets including medical images (CT and MRI) and segmented bone and muscle volumes. The model consisted of 12 body segments, 11 joints and 21 degrees of freedom. To accurately describe the functionality of the MS system, each leg contained 55 MT parts whose mechanical effect was described by 166 MT elements.

Force-generating characteristics of each MT element were described by the phenomenological Hill-type model proposed by Zajac (1989) (Figure 6.3A). MT forces were constrained to the dynamic equilibrium equations, taking into account the physiological bounds imposed by force-length and force-velocity characteristics of the contractile element CE, and the elasticity of the passive element PE and the tendon T (Figure 6.3B).

Figure 6.2 - TLEM 2.0 dataset. A: CT and MRI scans. B: Bone surfaces, muscle volumes, and subcutaneous fat and skin volumes segmented from MRI and CT scans. C: TLEM 2.0 musculoskeletal model implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark), anterior and posterior view. TLEM 2.0 model consisted of 12 body segments (head-arms-trunk, pelvis, and right and left femur, patella, tibia, talus and foot), 11 joints (L5S1 and left and right hip, knee, patellofemoral, talocrural and subtalar) and 21 degrees of freedom. Each leg contained 55 muscle actuators, described by 166 Hill-type muscle-tendon elements.

Figure 6.3 - Schematic representation of the three-elements Hill-type muscle-tendon model proposed by Zajac (1989). A: The MT element consists of an active muscle, represented by a contractile element CE in parallel with a passive element PE, in series with an elastic tendon T, modeled as a nonlinear spring. L_f is the muscle fiber length, L_T is the tendon length, γ is the pennation angle between the muscle fiber and the tendon. L_{MT} is the total length of the MT element, which is equal to the sum of tendon length L_T and muscle fiber length L_f adjusted by pennation angle γ : $L_{MT} = L_T + L_f \cos \gamma$. Force in the contractile element is expressed as $F^M = F^{CE} + F^{PE} = \bar{F}^M * F_l(L_f) * F_v(\dot{L}_f) * a + F_p(L_f)$, where $\bar{F}^M$ denotes the maximal isometric muscle force, F_l , F_p and F_v denote the active and passive force-length and the force-velocity relationships, and a denotes the muscle activity. Force in the tendon F^{MT} is equal to the summed force in the muscle fibers F^M adjusted by pennation angle γ : $F^{MT} = F^M \cos \gamma$. B: Active force-length relationship F_l , passive force-length relationship F_p and force-velocity F_v relationships. Effective operating range of muscle begins at roughly $0.5 \bar{L}_f$ and ends at $1.5 \bar{L}_f$. In addition, when the muscle is stretched to lengths greater than $\bar{L}_f$ it starts producing passive force.

For each MT element, the most important parameters were: nominal muscle fiber length $\bar{L}_f$ at which the muscle can produce the maximal isometric force $\bar{F}^M$, and tendon slack length L_T^S at which the tendon starts transmitting force. $\bar{F}^M$ was assumed to be proportional to physiological cross-sectional area (PCSA), which can be approximated from muscle volume Vol_M and $\bar{L}_f$ (Lieber et al., 2000), with maximum muscle stress σ_0 equal to 50 N/cm²:

$$\bar{F}^M = PCSA * \sigma_0 = \frac{Vol_M}{\bar{L}_f} * \sigma_0 \quad (1)$$

For each subject, four MS models with increasing subject-specific details were created:

6.2.2.1 Model 1 – Generic model

The TLEM 2.0 model was linearly scaled by fitting the anthropometry of the subject to the relative position of the measured optical markers, using a parameter optimization algorithm (Andersen et al., 2010). $\bar{L}_f$ and L_T^S were linearly scaled based on the body segment sizes, Vol_M was linearly scaled based on the weight of the subject and $\bar{F}^M$ was calculated accordingly to equation (1).

6.2.2.2 Model 2 – Subject-specific musculoskeletal geometry

Subject-specific MS geometry was obtained from MRI scan, using the TLEM 2.0 dataset as a starting template (Carbone et al., 2016a) (Figure 6.A1). Then, an anthropometric scaling

was applied to $\bar{L}_f$ and L_T^s of each MT element, taking into account the subject-specific body segment sizes and MT lengths, in order to maintain consistency in muscle function along operating range (Winby et al., 2008). Vol_M was linearly scaled, based on the weight of the subject, and $\bar{F}^M$ was calculated accordingly to equation (1).

6.2.2.3 Model 3 – Subject-specific muscle volumes

An atlas-based non-rigid MRI image registration implemented in Mimics® 17.0 (Materialise N.V., Leuven, Belgium) was used to automatically segment muscle volume contours (Kolk et al., 2015) (Figure 6.A2). Then $\bar{F}^M$ was updated accordingly to equation (1) taking into account the subject-specific Vol_M .

6.2.2.4 Model 4 – Functional scaling of muscle-tendon parameters

Starting from Model 3, functional scaling was applied to $\bar{L}_f$, L_T^s and $\bar{F}^M$ of each MT element in the model, in order to find the best possible match between the strength profiles measured during the dynamometry trials and the maximum torques predicted by the model. All the collected isometric and isokinetic trials were fit within one optimization. A global optimization problem was solved, using the simulated annealing solver in Matlab 2013a (The MathWorks, Inc., Natick, MA, U.S.A.) in order to avoid local minima. The optimization problem was stated as:

$$\min J(\bar{L}_f, L_T^s, \bar{F}^M(\bar{L}_f)) = \sum_j \|\tau_{meas.}^j - \tau_{pred.}^j\| \quad (2)$$

where j denotes the j -th dynamometry trial, $\tau_{meas.}^j$ is the maximum joint torque measured in the j -th trial for the subject, and $\tau_{pred.}^j$ is the corresponding maximum joint torque predicted by the model, with all the remaining joint angles fixed as measured on the subject. Similarly to van Campen et al. (2014), $\tau_{pred.}^j$ was calculated assuming maximum muscle activity equal to 0.8, since it has been reported that no true maximum activation is reached during dynamometry trials (Babault et al., 2002). In order to avoid combinations of MT parameters that were not physiologically correct, for each MT element $\bar{L}_f$ was constrained between 80% and 120% of initial values (based on anthropometric scaling), while L_T^s was constrained to maintain the muscle fiber operative range between 0.5 and 1.5 during the trial.

6.2.2.5 Simulations

For each subject and each model, all j dynamometry trials were reproduced and maximum isometric and isokinetic torques $\tau_{pred.}^j$ were predicted. Then, inverse dynamics analysis and static optimization problems were solved to calculate the MT forces and muscle activity necessary to reproduce the measured gait trials. The muscle recruitment problem was solved minimizing the sum of the cubes of muscle activity at each time step (Crowninshield et al., 1981), using a normalization factor based on the muscle volume according to Happee et al. (1995). In total, 10 healthy subjects x 4 models x 9 gait trials = 360 simulations were performed and analyzed in this study.

6.2.3 Analysis

In order to assess the effects of the personalization techniques in the various models, differences in the estimated values of nominal muscle fiber length $\overline{L_f}$, tendon slack length L_T^s , maximal isometric muscle force $\overline{F^M}$ and muscle volume Vol_M were calculated.

In order to assess the effects of the personalized MT parameters on the model outcomes, differences between measured maximum joint torques τ_{meas}^j and predicted maximum joint torques τ_{pred}^j were calculated for each model. Then, for each MT part, mean absolute difference of the peaks of the MT force and muscle activity predicted during gait were calculated. Finally, Pearson product-moment correlation coefficients r between measured EMG envelopes and predicted muscle activity were calculated. To account for the time lag in EMG onset and force production, an electromechanical delay (EMD) of 54 ms, based on Cavanagh et al. (1979) was imposed on the EMG envelopes.

6.3 Results

Large differences were found between MT parameters when comparing generic and subject-specific models, and each step of the personalization had an increasing effect on the estimated model parameters (Table 6.1). Taking into account all the ten healthy subjects analyzed, L_T^s showed larger mean absolute differences (1.2 cm in Model 2-3 and 1.6 in Model 4) than $\overline{L_f}$ (0.6 cm in Model 2-3 and 1.1 cm in Model 4). The mean difference between linearly scaled and segmented Vol_M was equal to 37.2 cm³, with some subjects presenting muscles with differences larger than 500 cm³. Differences in Vol_M and $\overline{L_f}$ resulted in mean differences in $\overline{F^M}$ up to 302.5 N in Model 4. In percentage, $\overline{F^M}$ and Vol_M were the MT parameters presenting the largest differences (38.2% and 34.7%, respectively, in Model 4), while L_T^s showed larger difference compared to $\overline{L_f}$ (16.5% and 15.3%, respectively, in Model 4).

Table 6.1 - Mean absolute differences in the estimated values of nominal muscle fiber length $\overline{L_f}$, tendon slack length L_T^s , maximal isometric muscle force $\overline{F^M}$ and muscle volume Vol_M , when comparing generic and subject-specific models. The results are averaged over ten healthy subjects.

	$\overline{L_f}$ (cm)			L_T^s (cm)			$\overline{F^M}$ (N)			Vol_M (cm ³)		
	mean	std	max	mean	std	max	mean	std	max	mean	std	max
Model 1 → Model 2	0.6	0.6	3.2	1.2	1.1	6.1	94.9	238.8	2497.9	-	-	-
Model 1 → Model 3							279.5	370.6	2750.3	37.2	55.1	540.3
Model 1 → Model 4	1.1	1.2	10.0	1.6	1.2	8.1	302.5	409.4	3279.3			

	$\overline{L_f}$ (%)			L_T^s (%)			$\overline{F^M}$ (%)			Vol_M (%)		
	mean	std	max	mean	std	max	mean	std	max	mean	std	max
Model 1 → Model 2							9.7%	10.7%	70.4%	-	-	-
Model 1 → Model 3	9.2%	11.6%	112.1%	10.2%	10.9%	74.7%	35.1%	35.2%	255.3%	34.7%	33.2%	266.3%
Model 1 → Model 4	15.3%	14.0%	152.4%	16.5%	22.0%	165.7%	38.2%	38.7%	304.4%			

Model 1 indicates generic linearly scaled models. Model 2 includes subject-specific MS geometry and anthropometric scaling of MT parameters. Model 3 includes subject-specific muscle volumes. Model 4 includes functional scaling of MT parameters.

Table 6.2 - MT parts presenting the largest absolute differences in the estimated values of nominal muscle fiber length $\bar{L}_f$, tendon slack length L_T^s , maximal isometric muscle force $\bar{F}^M$ and muscle volume Vol_M , when comparing generic and subject-specific models. The results are averaged over ten healthy subjects.

MT part	$\bar{L}_f$		L_T^s		$\bar{F}^M$		Vol_M	
	cm	%	cm	%	N	%	cm ³	%
Adductor Brevis Distal	*	%	*	%%		%%		%%
Adductor Brevis Mid	**	%%	*	%%		%%		%%
Adductor Brevis Proximal	*	%		%%		%%		%%
Adductor Longus	*	%	*	%	***	%%	*****	%%
Adductor Magnus Distal	*	%	*		**	%	***	%
Adductor Magnus Mid	*		*	%		%	**	%
Adductor Magnus Proximal	**	%	*	%%		%%		%
Biceps Femoris Caput Breve	*	%	*	%	*	%%	**	%%
Biceps Femoris Caput Longum	*	%	*		**	%%	***	%%
Extensor Digitorum Longus			**		*	%%	*	%%
Extensor Hallucis Longus		%	*		*	%%	*	%%
Flexor Digitorum Longus		%	**		*	%%	*	%%
Flexor Hallucis Longus		%	**		*****	%%	**	%%
Gastrocnemius Lateralis		%	*		****	%%	*****	%%
Gastrocnemius Medialis	*	%			*****	%%	*****	%%
Gemellus Inferior		%%		%%		%%		%%
Gemellus Superior		%		%		%%		%%
Gluteus Maximus Inferior	**	%	**	%%	**	%%	*****	%%
Gluteus Maximus Superior	**	%	*	%	**	%%	*****	%%
Gluteus Medius Anterior					*****	%%	*****	%%
Gluteus Medius Posterior		%	*	%	*****	%%	*****	%%
Gluteus Minimus Anterior		%			*	%%	*	%%
Gluteus Minimus Mid		%			*	%%	*	%%
Gluteus Minimus Posterior				%	*	%%	*	%%
Gracilis	*		*			%%	*	%
Iliacus Lateralis	*	%	*	%	*	%%	**	%%
Iliacus Medialis	*	%	*	%	*	%%	**	%%
Iliacus Mid		%	*	%	**	%%	**	%%
Obturator Externus Inferior	*	%		%%		%%	*	%%
Obturator Externus Superior		%	*	%	****	%%	**	%%
Obturator Internus		%	**	%	**	%%	*	%%
Pectineus	*	%	*	%%	*	%%	*	%%
Peroneus Brevis			*		*****	%%	***	%%
Peroneus Longus		%	*		**	%%	*	%
Piriformis		%	*	%	*	%%	*	%%
Plantaris		%				%%		%%
Popliteus		%			*	%%	*	%%
Psoas Major	*	%	***	%	*	%%	**	%
Quadratus Femoris		%%		%%	**	%%	**	%%
Rectus Femoris	*	%			*****	%%	*****	%%
Sartorius	*****	%	**	%%		%%	**	%
Semimembranosus	*	%	*		**	%%	*****	%%
Semitendinosus	*	%	*		*	%%	****	%%
Soleus Lateralis	*	%%			*****	%%	*****	%%
Soleus Medialis	*	%%	*		*****	%%	*****	%%
Tensor Fasciae Latae	*	%	*			%%	*	%%
Tibialis Anterior		%	*		****	%%	**	%
Tibialis Posterior Lateralis		%	*		***	%%	*	%%
Tibialis Posterior Medialis					**	%%	*	%%
Vastus Intermedius	*	%	***	%%	*****	%%	*****	%%
Vastus Lateralis Inferior		%	***	%%	**	%%	*	%
Vastus Lateralis Superior		%	***	%	****	%	*****	%
Vastus Medialis Inferior	*	%	**	%%	*	%%	**	%%
Vastus Medialis Mid			**	%%	*	%%	**	%%
Vastus Medialis Superior	*		***	%	**	%%	****	%%

Differences between Model 1 (generic linearly scaled model) and Model 4 (including subject-specific MS geometry and muscle volumes, based on MRI, and functional scaling of MT parameters, based on dynamometry data), shown for each MT part.

For $\bar{L}_f$ and L_T^s : * indicates differences larger than 1 cm; ** indicates differences larger than 2 cm; *** indicates differences larger than 3 cm; **** indicates differences larger than 4 cm; ***** indicates differences larger than 5 cm.

For $\bar{F}^M$: * indicates differences larger than 100 N; ** indicates differences larger than 200 N; *** indicates differences larger than 300 N; **** indicates differences larger than 400 N; ***** indicates differences larger than 500 N.

For Vol_M : * indicates differences larger than 10 cm³; ** indicates differences larger than 20 cm³; *** indicates differences larger than 30 cm³; **** indicates differences larger than 40 cm³; ***** indicates differences larger than 50 cm³.

For all MT parameters: % indicates relative differences larger than 10%; %% indicates relative differences larger than 20%; %%% indicates relative differences larger than 30%; %%%% indicates relative differences larger than 40%; %%%%% indicates relative differences larger than 50%.

In particular, the largest differences in $\bar{L}_f$ were found for the MT parts with the longest muscle fibers, such as Sartorius, Gracilis, Gluteal muscles, Adductor, Hamstrings and Pectineus, while in percentage the most affected MT part was the Soleus, followed by short muscles acting on the hip joint such as Quadratus, Gemelli, Piriformis, Adductors and Obturators. The largest differences in L_f^s were found for Vasti and Psoas Major, followed by Sartorius, Gluteus Maximus Inferior, Flexor and Extensor Digitorum Longus. Then, the largest differences in $\bar{F}^M$ were found for Flexor Hallucis Longus, Gastrocnemius, Soleus, Gluteus Medius, Peroneus Brevis, Rectus Femoris, Vastus Intermedius and Lateralis, and were more a consequence of the large differences in Vol_M than in $\bar{L}_f$ (Table 6.2).

Personalization of MT parameters had a large effect on the predicted maximum joint torques (Figure 6.4). Comparing $\tau_{meas.}^j$ and $\tau_{pred.}^j$, the mean error of 64.1 Nm when using Model 1 was reduced to 47.5 Nm for Model 2, 44.7 Nm for Model 3 and 23.2 Nm for Model 4 (Table 6.3). On average, the largest errors, even after functional scaling, were found for hip extension and hip adduction ($\tau_{pred.}^j > \tau_{meas.}^j$) and ankle plantarflexion ($\tau_{pred.}^j < \tau_{meas.}^j$).

Figure 6.4 - Comparison of the measured maximum joint torques $\tau_{meas.}^j$ (black line) with the predicted maximum joint torques $\tau_{pred.}^j$ for slow isokinetic trials using: Model 1 - generic linearly scaled model (red line); Model 2 - subject-specific MS geometry and anthropometric scaling of MT parameters (blue line); Model 3 - subject-specific muscle volumes (cyan line); Model 4 - functional scaling of MT parameters (green line). The results are averaged over ten healthy subjects.

Table 6.3 - Differences between measured and predicted maximum joint torques, calculated as root mean square error (Nm) and relative error (%), when comparing generic and subject-specific models. The results are averaged over ten healthy subjects.

Maximum Joint Torque - RMSE (Nm)					Maximum Joint Torque - Relative error (%)				
	Model 1	Model 2	Model 3	Model 4		Model 1	Model 2	Model 3	Model 4
Ankle Plantarflexion	39.6	37.6	29.7	27.7	Ankle Plantarflexion	42.2%	39.3%	22.5%	20.6%
Ankle Dorsiflexion	9.5	7.4	8.4	8.3	Ankle Dorsiflexion	45.5%	25.1%	33.3%	29.4%
Knee Flexion	45.3	31.8	22.4	16.2	Knee Flexion	24.1%	36.8%	20.0%	12.8%
Knee Extension	73.8	43.8	33.2	22.0	Knee Extension	40.4%	23.0%	20.1%	9.1%
Hip Flexion	35.0	28.5	23.2	19.2	Hip Flexion	33.4%	28.1%	20.9%	12.8%
Hip Extension	134.9	116.9	127.0	46.6	Hip Extension	157.7%	139.8%	141.7%	52.8%
Hip Abduction	66.6	49.2	38.6	20.8	Hip Abduction	54.8%	41.4%	33.1%	13.3%
Hip Adduction	108.5	64.8	75.3	24.9	Hip Adduction	113.3%	72.1%	65.4%	18.5%
	64.1	47.5	44.7	23.2		63.9%	50.7%	44.6%	21.2%

Model 1 indicates generic linearly scaled model. Models 2 includes subject-specific MS geometry and anthropometric scaling of MT parameters. Model 3 includes subject-specific muscle volumes. Model 4 includes functional scaling of MT parameters. Cells shading is directly proportional to the error values.

Inverse dynamics simulations, based on the same 3D motion analysis and force plates data, predicted different MT forces and muscle activity for generic and subject-specific models (Table 6.4). When compared with Model 1, mean absolute differences in predicted MT force peaks during gait at CWS increased from 82.5 N for Model 2 up to 120.3 N for Model 4, with some subjects presenting MT force peaks with differences larger than 1000 N. Similarly, mean absolute difference in predicted muscle activity peaks increased from 0.11 for Model 2 up to 0.21 for Model 4, with some subjects presenting muscle activity peaks with differences larger than 1. Overall, differences in MT force and muscle activity were higher for gait trials at FWS and lower for gait trials at SWS.

Table 6.4 - Mean absolute differences in the predicted MT force peaks and muscle activity peaks during gait, when comparing generic and subject-specific models. The results are averaged over ten healthy subjects.

Differences in MT force peaks (N)									
	SWS			CWS			FWS		
	mean	std	max	mean	std	max	mean	std	max
Model 1 → Model 2	58.3	100.0	1142.3	82.5	128.8	1228.1	118.3	178.6	1471.5
Model 1 → Model 3	73.7	142.3	1639.9	101.0	171.9	1760.5	151.6	236.9	1965.6
Model 1 → Model 4	88.4	126.4	921.1	120.3	161.0	1032.4	173.6	232.8	1447.2

Differences in muscle activity peaks									
	SWS			CWS			FWS		
	mean	std	max	mean	std	max	mean	std	max
Model 1 → Model 2	0.07	0.07	0.79	0.11	0.11	0.87	0.16	0.17	1.63
Model 1 → Model 3	0.10	0.11	0.84	0.15	0.19	1.67	0.23	0.27	2.70
Model 1 → Model 4	0.14	0.15	1.16	0.21	0.23	1.77	0.30	0.33	3.10

Model 1 indicates generic linearly scaled model. Models 2 includes subject-specific MS geometry and anthropometric scaling of MT parameters. Model 3 includes subject-specific muscle volumes. Model 4 includes functional scaling of MT parameters.

Table 6.5 - MT parts presenting the largest differences in predicted MT force peaks and muscle activity peaks during gait, when comparing generic and subject-specific models. The results are averaged over ten healthy subjects.

MT part	SWS			CWS			FWS		
	MT force		Muscle activity	MT force		Muscle activity	MT force		Muscle activity
	N	+ / -	+ / -	N	+ / -	+ / -	N	+ / -	+ / -
Adductor Brevis Distal		+	+		-	-		-	*
Adductor Brevis Mid		-	-		-	*		-	**
Adductor Brevis Proximal		-	-		-	*		-	*
Adductor Longus		+	-		+	*	*	+	**
Adductor Magnus Distal		-	+		-	+		+	*
Adductor Magnus Mid		+	*		+	*		+	*
Adductor Magnus Proximal		-	-		-	-		-	-
Biceps Femoris Caput Breve		+	*		+	**		+	**
Biceps Femoris Caput Longum		-	-		-	*		-	*
Extensor Digitorum Longus		+	*	*	+	**	*	+	**
Extensor Hallucis Longus		+	*		+	*		+	*
Flexor Digitorum Longus		-	+		-	*	*	-	*
Flexor Hallucis Longus	**	+	**	**	+	**	***	-	***
Gastrocnemius Lateralis	**	+	***	**	+	*****	***	+	*****
Gastrocnemius Medialis	**	-	*****	**	-	*****	***	-	*****
Gemellus Inferior		+	+		+	+		-	*
Gemellus Superior		+	**		+	**		+	***
Gluteus Maximus Inferior		-	+		-	+		-	+
Gluteus Maximus Superior		+	*		+	*	*	+	*
Gluteus Medius Anterior	**	+	**	**	+	**	***	+	**
Gluteus Medius Posterior	*	+	*	*	+	*	**	-	*
Gluteus Minimus Anterior		-	**	*	-	***	*	-	*****
Gluteus Minimus Mid		+	**	*	+	**	*	+	***
Gluteus Minimus Posterior		+	**		+	**	*	+	**
Gracilis		-	-		-	-		-	*
Iliacus Lateralis		+	*		+	**	*	+	**
Iliacus Medialis		+	*	*	+	*	**	+	*
Iliacus Mid	*	+	*	**	+	***	*****	+	*****
Obturator Externus Inferior		+	+		-	+		-	+
Obturator Externus Superior		-	*		-	**		+	**
Obturator Internus	*	+	*	*	+	*	**	+	**
Pectineus		-	*		-	*		-	*
Peroneus Brevis	*	+	*	*	+	*	*	+	*
Peroneus Longus	*	+	*	**	+	*	**	-	*
Piriformis		+	*	*	+	*	*	+	**
Plantaris		+	**		+	**		+	**
Popliteus		+	**	*	+	***	*	+	***
Psoas Major	*	+	*	**	+	**	***	+	***
Quadratus Femoris		+	+		+	*		-	*
Rectus Femoris		-	*	*	+	**	*	-	***
Sartorius		-	**		-	***	*	-	*****
Semimembranosus		-	+		+	+		+	+
Semitendinosus		+	-		+	-		-	*
Soleus Lateralis	****	-	***	****	-	*****	****	-	*****
Soleus Medialis	**	-	*	**	-	**	**	+	***
Tensor Fasciae Latae		+	*	*	+	**	*	+	***
Tibialis Anterior	*	+	-	*	+	*	*	+	*
Tibialis Posterior Lateralis	*	-	*	***	-	*	*****	-	*
Tibialis Posterior Medialis	*	-	*	***	-	**	*****	-	*
Vastus Intermedius	*	+	+	*	+	*	***	+	*
Vastus Lateralis Inferior		-	+		+	+		+	*
Vastus Lateralis Superior	**	-	*	***	-	*	*****	-	*
Vastus Medialis Inferior		+	*		+	*	*	+	**
Vastus Medialis Mid		-	*		-	*		+	*
Vastus Medialis Superior		-	-		+	+	*	+	*

Differences between Model 1 (generic linearly scaled model) and Model 4 (including subject-specific MS geometry and muscle volumes, based on MRI, and functional scaling, based on dynamometry data), shown for each MT part.

For MT force peaks: * indicates differences larger than 100 N; ** indicates differences larger than 200 N; *** indicates differences larger than 300 N; **** indicates differences larger than 400 N; ***** indicates differences larger than 500 N.

For muscle activity peaks: * indicates differences larger than 0.1; ** indicates differences larger than 0.2; *** indicates differences larger than 0.3; **** indicates differences larger than 0.4; ***** indicates differences larger than 0.5.

For both MT force and muscle activity, + and - indicate an average increase or decrease predicted by the subject-specific model.

Underline indicates muscle activity that decreased below 1 after functional scaling. Double underline indicates muscle activity that remained above 1 after functional scaling.

The largest differences in MT forces were found for MT parts in the lower leg, with a decrease for Soleus, Tibialis Posterior and Gastrocnemius Medialis and an increase for Gastrocnemius Lateralis and Flexor Hallucis Longus, together with a decrease for Vastus Lateralis Superior and an increase for Gluteal muscles and Iliopsoas, indicating a redistribution of predicted MT forces after introduction of subject-specific parameters (Table 6.5). Similarly, a redistribution of muscle activity was found, with Gastrocnemius, Soleus, Popliteus, Gluteal muscles, Sartorius, Iliopsoas, and Rectus Femoris being the most affected MT parts. On average, muscle activity predicted during gait trials at SWS was below 1 for all MT parts for both generic and subject-specific models. When simulating gait trials at CWS and FWS, muscle activity predicted by generic models was above 1 for Gastrocnemius, Soleus and Sartorius, while it decreased below 1 after functional scaling. However, muscle activity predicted during gait trials at FWS for Gluteus Minimus, Iliacus and Tensor Fasciae Latae remained above 1 even after functional scaling.

Finally, we did not find any clear improvement in the correlation between measured EMG envelopes and predicted muscle activity (Figure 6.5). On average, very good correlation ($0.81 < r < 1.00$) was found for Gastrocnemius and Soleus, good correlation ($0.61 < r < 0.80$) was found for Vasti, Gluteus Maximus and Peroneus Longus, moderate correlation ($0.41 < r < 0.60$) for Tibialis Anterior, while fair to poor correlation ($r < 0.40$) was found for Rectus Femoris and Hamstrings (Table 6.6). For some MT parts, like Peroneus Longus and Gluteus Medius, correlation increased with walking speed, while for Tibialis Anterior correlation decreased with walking speed.

Figure 6.5 - Comparison of the measured EMG envelopes (black line) with the muscle activity predicted during gait at comfortable walking speed using: Model 1 - generic linearly scaled model (red line); Model 2 - subject-specific MS geometry and anthropometric scaling of MT parameters (blue line); Model 3 - subject-specific muscle volumes (cyan line) and Model 4 - functional scaling of MT parameters (green line). In this example, we show simulated gait at comfortable walking speed for a representative subject.

Table 6.6 - Pearson product-moment correlation coefficients r between measured EMG envelopes and predicted muscle activity for generic and subject-specific models.

	SWS				CWS				FWS			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Tibialis Anterior	0.54	0.55	0.57	0.56	0.43	0.46	0.46	0.44	0.39	0.39	0.37	0.37
Gastrocnemius Medialis	0.84	0.90	0.91	0.89	0.79	0.89	0.90	0.85	0.77	0.86	0.87	0.83
Gastrocnemius Lateralis	0.84	0.85	0.86	0.85	0.83	0.85	0.85	0.82	0.82	0.84	0.85	0.79
Soleus Medialis	0.87	0.87	0.83	0.87	0.83	0.84	0.80	0.84	0.80	0.79	0.71	0.80
Peroneus Longus	0.42	0.44	0.43	0.44	0.60	0.62	0.59	0.62	0.66	0.66	0.59	0.67
Vastus Lateralis	0.82	0.74	0.66	0.74	0.76	0.75	0.72	0.74	0.79	0.76	0.73	0.74
Vastus Medialis	0.75	0.72	0.67	0.73	0.75	0.74	0.71	0.76	0.67	0.66	0.62	0.66
Rectus Femoris	0.32	0.45	0.42	0.39	-0.16	0.07	0.04	0.10	-0.01	0.20	0.16	0.23
Biceps Femoris Caput Longum	0.18	-0.10	-0.10	0.20	0.33	0.13	0.06	0.38	0.27	0.04	0.08	0.27
Semitendinosus	0.14	-0.03	0.00	0.03	0.20	0.12	0.15	0.24	0.11	-0.02	0.08	0.12
Gluteus Maximus Superior	0.77	0.78	0.75	0.77	0.62	0.63	0.62	0.62	0.51	0.57	0.56	0.56
Gluteus Medius Posterior	0.00	-0.07	-0.12	0.00	0.50	0.41	0.33	0.46	0.67	0.60	0.54	0.62

Model 1 indicates generic linearly scaled model. Models 2 includes subject-specific MS geometry and anthropometric scaling of MT parameters. Model 3 includes subject-specific muscle volumes. Model 4 includes functional scaling of MT parameters. The results are averaged over ten healthy subjects.

6.4 Discussion

In this study, we expanded a streamlined modeling workflow, previously used to obtain subject-specific musculoskeletal geometry (Carbone et al., 2016a), with additional methods for estimating MT parameters of 55 MT parts (represented by 166 MT elements) from MRI and dynamometry data, in order to build ten personalized musculoskeletal models with increasing detail, and we assessed the effects of personalized MT parameters on the model predictions. Differences in $\overline{L_f}$, L_T^s and $\overline{F^M}$ between Model 1 and Model 2 depended mainly on the inter-individual anatomical variability in body segment sizes and MT element lengths taken into account by personalized MS geometry (Carbone et al., 2016a). These differences resulted in a reduced error in $\tau_{pred.}^j$, although no information about subject-specific torque-generating characteristics was used, and had a large effect on the predicted MT force and muscle activity during gait, indicating how anthropometric scaling is a very important first step when estimating MT parameters, as suggested by Winby et al. (2008).

Subject-specific Vol_M introduced in Model 3 had a larger effect on the estimated $\overline{F^M}$, allowing a further reduction of errors in $\tau_{pred.}^j$ and further differences in the predicted MT force and muscle activity during gait. This redistribution of Vol_M indicated how the original TLEM 2.0 dataset, which is based on a cadaver specimen similarly to other models in literature (Delp et al., 1990; Klein Horsman et al., 2007; Arnold et al., 2010), is unlikely to be representative of healthy subjects, as shown by Tate et al. (2006).

Finally, the functional scaling introduced in Model 4, whose objective was to reduce the error between $\tau_{meas.}^j$ and $\tau_{pred.}^j$, resulted in the largest differences in the optimized $\overline{L_f}$, L_T^s and $\overline{F^M}$ when compared to Model 1. As expected, these differences resulted also in the largest reduction of the error in $\tau_{pred.}^j$. Moreover, the large differences in MT parameters affected the capacity of MT elements to generate moments around the joints, and resulted in large

differences in the predicted MT force and muscle activity peaks during gait, allowing to further reduce the muscle activity below 1 for prime mover muscles such as Soleus and Gastrocnemius. Although it is not part of this study, we expect that use of subject-specific models would allow to improve the prediction of joint reaction forces too, as shown by Marra et al. (2015).

Unfortunately, quantitative comparison between predicted muscle activity and measured EMG envelopes did not show a clear improvement in the outcome of subject-specific models, since personalized parameters affected mostly the magnitude of the muscle activity but not the timing. Moreover, EMG signal is known to be sensitive to the placement of the electrodes on the surfaces of the skin above muscles (De Luca, 1993). Also, electromechanical delay has been reported to be dependent on several factors, such as MT stiffness (Grosset et al., 2008), the type of muscular contraction (Cavanagh et al., 1979; Zhou et al., 1995), joint angle (Grabiner, 1986), age (Grosset et al., 2005) and gender (Winter et al., 1991) of the subject. All these factors are likely to affect the reliability of EMG measurements for quantitative validation, as suggested by Lund et al. (2012).

The method used in this study to obtain functional scaling of MT parameters is similar in principle to the one presented by Garner et al. (2003). However, the authors of that study combined dynamometry data averaged across three subjects with medical imaging data from a different source, in order to create a generic dataset of MT parameters in the human upper extremity, but the effect of the optimized parameter during simulated movements was not assessed. In our study, we used consistent datasets of medical imaging and dynamometry to obtain ten subject-specific models, and isokinetic trials were added to obtain more information about force-generating characteristics of the subjects.

The estimated subject-specific parameters and model predictions are likely affected by the potential measurement errors in the medical images and dynamometry data. However, an improvement of the resolution of the medical images or the accuracy of the dynamometry data would obviously require an increase in the acquisition and processing time, affecting the application in real scenario. Assessment of the sensitivity of the personalization process to modeling assumptions and to potential errors in the MS geometry, muscle volumes and measured strength profile, as well as of the efficiency of the methods used (similarly to what shown by van Campen et al. (2014)) were not part of this study and should be addressed in future work.

Moreover, availability of strength profiles at multiple configurations of the primary joint and of the neighboring joints is likely to improve the reliability of the results of the functional scaling, but this would affect the total burden for the subject being analyzed and subsequently the quality of the measurement data. Similarly to what has been proposed by van Campen et al. (2013) for the knee joint, designing an optimal dynamometer set up for all the joints and degrees of freedom of the lower extremity, in order to extract maximum information from a minimum set of experiments, would greatly improve the accuracy and reliability of strength

profile measurements and subsequently of the functional scaling outcome, while minimizing the burden for the subject.

In conclusion, the large differences found between generic and subject-specific models, and their effect on the model predictions, highlight the importance to obtain an accurate estimate of musculoskeletal geometry and MT parameters. It should be noted that the level of subject-specific details of the model should depend on the scope of the model and the study, on the required accuracy of the application and on the resources available.

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Appendix - Subject-specific musculoskeletal models

Figure 6.A1 - Subject-specific musculoskeletal geometry of ten healthy subjects, obtained using an MRI-based streamlined modeling workflow (Carbone et al., 2016a), implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark).

Figure 6.A2 - Subject-specific muscle volume contours of ten healthy subjects, segmented using an atlas-based non-rigid MRI image registration implemented in Mimics® 17.0 (Materialise N.V., Leuven, Belgium) (Kolk et al., 2015).

Chapter 7

Quantitative validation of subject-specific musculoskeletal models of the lower extremity using FDG-PET

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Abstract

Validation of musculoskeletal models represents a crucial challenge to gain the necessary confidence for critical applications, such as surgical planning and decision making in orthopedics. Electromyography (EMG) and, recently, near infrared spectroscopy (NIRS) have been used as convenient and non-invasive techniques for indirect validation of model predictions. However, they can be applied only to a small number of superficial muscles. Positron emission tomography (PET) combined with the radioactive tracer [18F]-Fluoro-deoxy-glucose (FDG) is a novel approach that allows measuring the muscular activity of all the muscles of the lower extremity, including the deep muscles, in a single session. In this study, we used for the first time FDG-PET for validation of subject-specific musculoskeletal models, comparing the measured %FDG glucose uptake with the predicted % E_m metabolic energy consumption of each muscle of the lower extremity for ten healthy subjects. When analyzing each individual subject, good to very good correlations were found between %FDG and % E_m (Spearman's $\rho=0.87\pm0.04$, Pearson's $r=0.77\pm0.10$). Higher correlations were found when analyzing results averaged over ten healthy subjects (Spearman's $\rho=0.96$, Pearson's $r=0.91$). Correlations were slightly higher for subject-specific models compared to generic models, but it was not possible to prove the significance of this improvement ($p=0.17$). These results provide great confidence on the validity of the model outcomes when analyzing muscle function during gait. We conclude that FDG-PET should be considered as a complimentary validation tool to EMG.

7.1 Introduction

Recent improvements in medical imaging techniques and increase of computational power allow to estimate subject-specific parameters of musculoskeletal (MS) geometry (Scheys et al., 2009; Hausselle et al., 2014; Carbone et al., 2016a) and muscle-tendon (MT) architecture (Hainisch et al., 2012; van Campen et al., 2014; Carbone et al., 2016b) in a semi-automatic way. Since the use of MS models in critical applications, such as surgical planning and decision making in orthopedics (Cohen et al., 2003; Reinbolt et al., 2009; Taddei et al., 2012) is rapidly increasing, extensive validation of model predictions is crucial (Prilutsky et al., 2002; Lund et al., 2012).

In-vivo measurement of muscle and joint reaction forces requires special tools, such as use of optic-fiber technique (Finni et al., 2000), in situ buckle-type force transducers (Gregor et al., 1991), or instrumented joint replacements (Bergmann et al., 2001; Fregly et al., 2012). For these reasons, direct validation of MS models is inherently difficult, costly and ethically problematic to perform.

Comparison of electromyography (EMG) measurements with predicted muscle activity represents a common example of indirect validation of MS models (Asadi Nikooyan et al., 2011; Giroux et al., 2013). Next to EMG, measurement of local oxygen consumption of muscle tissue, reflecting the energy consumption process, through near infrared spectroscopy (NIRS) has been proposed as a validation tool for MS models (Praagman et al., 2003; Praagman et al., 2006). Although both EMG and NIRS represent convenient and non-invasive techniques for indirect validation of MS models, they share important limitations such as the limited number of muscles that can be measured at the same time, the lack of information on deep muscles, and the fact that adipose tissue and crosstalk from other muscles are important confounding factors.

Positron emission tomography (PET) combined with the radioactive tracer [^{18}F]-Fluoro-deoxy-glucose (FDG) is a novel technique that can be used to measure the intensity of carbohydrate metabolism in muscle tissue (Kemppainen et al., 2002). Unlike EMG and NIRS, FDG-PET can be used to estimate activity in all the muscles of the lower extremity, including deep muscles, in a single session (Kolk et al., 2015). Recently, FDG-PET has been successfully used to measure the intensity of muscular activity of the lower extremity during aerobic exercises such as walking (Oi et al., 2003; Shimada et al., 2007), running (Fujimoto et al., 1996; Tashiro et al., 1999; Fujimoto et al., 2000), and cycling (Gondoh et al., 2009). It has been shown that FDG-PET is able to distinguish the relative contributions of individual muscles to joint moments (Pappas et al., 2001; Masood et al., 2014), and to show differences between subjects with different age or physical conditions (Fujimoto et al., 2003; Shimada et al., 2009; Rudroff et al., 2013; Kolk et al., 2015). Hence, it can be used to indirectly measure the functional differences in the muscle recruitment process. Oi et al. (2003) compared FDG uptake results with EMG and kinematic and kinetic studies and demonstrated the validity of

measuring the muscular activity of the lower extremity with FDG-PET. Therefore, FDG-PET seems to be a promising tool for validation of MS models.

In this study, we used FDG-PET for validation of comprehensive musculoskeletal models. We compared the activity of all the muscles of the lower extremity during walking, previously measured on ten healthy subjects using FDG-PET (Kolk et al., 2015), with the metabolic energy consumption predicted by the corresponding ten subject-specific models, based on MRI and dynamometry data (Carbone et al., 2016a, b). Moreover, we aimed to determine whether subject-specific models provided better predictions than generic models when compared to FDG-PET measurements.

7.2 Methods

7.2.1 TLEMsafe healthy subjects dataset

A dataset of ten healthy subjects (five males, age 40.1 ± 15.7 years, height 174.9 ± 11.1 cm, weight 74.8 ± 11.9 kg, BMI 24.4 ± 2.3 kg/m², fat percentage $27.8 \pm 5.8\%$) was obtained at the Radboud University Medical Center in Nijmegen, the Netherlands. For each subject, an MRI scan of the lower extremity was obtained (3T, T1-weighted axial spin echo (SE), voxel size of $1.0 \times 1.0 \times 3.0$ mm for pelvis, knee and ankle region, and $1.0 \times 1.0 \times 8.0$ mm for the remaining upper and lower leg) (Figure 7.1A) using a Siemens 3T MAGNETOM® Skyra (Siemens AG, Munich, Germany). Then, a six-camera digital optical motion capture system (Vicon Motion System Ltd., Oxford, UK) with synchronized custom built force plates (AMTI, Watertown, MA, U.S.A.) were used during walking trials at a level walkway (Figure 7.1B). 35 optical markers were placed according to the standard Vicon Plug-in-Gait marker set, and 10 additional markers were placed on the right and left thigh, shank, medial femoral

Figure 7.1 - TLEMsafe healthy subjects dataset. A: MRI scan of the lower extremities. B: Healthy subject wearing reflective markers during a recording session of 3D motion analysis and force plates data. C: Measurement of isometric and isokinetic joint torques during maximum voluntary contractions. The TLEMsafe healthy subjects dataset is available for the scientific community for non-commercial use only, upon request to be sent to the TLEMsafe project coordinator, prof. dr. ir. Nico Verdonchot (n.verdonchot@utwente.nl), and after approval of the TLEMsafe consortium.

epicondyle, medial malleolus and fifth metatarsal head of the foot. For each subject, 3 gait trials at comfortable walking speed (CWS) were selected. In total, $10 \times 3 = 30$ gait trials were analyzed. Subsequently, for each subject, an extensive set of isometric and isokinetic torques during maximum voluntary contractions were measured using a Biodex Dynamometer (Biodex Medical Systems, Inc., Shirley, NY, U.S.A.) for ankle plantar/dorsiflexion, knee flexion/extension, hip flexion/extension and hip abduction/adduction (Figure 7.1C).

7.2.2 FDG-PET volumetric analysis

Each subject walked on a treadmill for 90 minutes at the same CWS measured in the gait lab, 60 minutes before and 30 minutes after injection with FDG. Then, 30 minutes after finishing the last walking phase, a PET/CT scan was obtained using a Biograph 40 mCT (Siemens AG, Munich, Germany) in 3D mode, using an extended axial field of view of 216 mm and slice thickness of 2.0 mm, with the legs of the subject positioned on the table to reproduce as closely as possible their position as during the MRI scan.

Muscle volumes of the left lower extremity were semi automatically segmented from MRI scan and subsequently registered onto the corresponding PET/CT scan, in order to obtain FDG uptake values for each individual muscle (Figure 7.2). Finally, %FDG uptake values were calculated to reflect the amount of FDG accumulated in each muscle relative to the total amount of FDG in all the muscles of the lower extremity. More details about the FDG-PET

Figure 7.2 - FDG-PET volumetric analysis. A: MRI scan with segmented muscle volumes. B: Segmented muscle volumes registered onto the PET scan. C: Frontal view of a PET scan with registered muscle volumes. D: MRI and PET scan slices of the pelvis, upper leg and lower leg regions, with the registered muscle volumes. Reprinted from Kolk et al. (2015) with permission from Wolters Kluwer.

protocol and medical imaging analysis, and complete results of the study are presented in Kolk et al. (2015). Study procedures were approved by the ethical committee of the region Arnhem-Nijmegen, the Netherlands, and written informed consent was obtained from each subject.

7.2.3 Musculoskeletal modeling

Modeling was performed using the Twente Lower Extremity Model 2.0 (Carbone et al., 2015) implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al., 2006) (Figure 7.3). TLEM 2.0 represents a comprehensive MS geometry dataset including medical images (CT and MRI) and segmented bone, muscle and subcutaneous fat volumes. The musculoskeletal model consisted of 12 body segments, 11 joints and 21 degrees of freedom. To accurately describe the functionality of the MS system, each leg contained in total 55 MT parts whose mechanical effect was described by 166 three-elements Hill-type MT elements (Zajac, 1989).

Figure 7.3 - TLEM 2.0 dataset. A: CT and MRI scans. B: Bone surfaces, muscle volumes, and subcutaneous fat and skin volumes segmented from MRI and CT scans. C: TLEM 2.0 musculoskeletal model implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark), anterior and posterior view. TLEM 2.0 model consisted of 12 body segments (head-arms-trunk, pelvis, and right and left femur, patella, tibia, talus and foot), 11 joints (L5S1 and left and right hip, knee, patellofemoral, talocrural and subtalar) and 21 degrees of freedom. Each leg contained 55 muscle actuators, described by 166 Hill-type muscle-tendon elements. D: Schematic representation of the three-elements Hill-type muscle-tendon model proposed by Zajac (1989). The MT element consists of an active muscle, represented by a contractile element CE in parallel with a passive element PE, in series with an elastic tendon T, modelled as a nonlinear spring. L_{MT} is the total length of the MT element, which is equal to the sum of tendon length L_T and muscle-fiber length L_f adjusted by pennation angle γ : $L_{MT} = L_T + L_f \cos \gamma$. Force in the tendon F^{MT} is equal to the summed force in the muscle fiber F^M adjusted by pennation angle γ : $F^{MT} = F^M \cos \gamma$.

For each subject, two MS models were created:

7.2.3.1 Generic model

The TLEM 2.0 model was linearly scaled by fitting the anthropometry of the subject to the relative position of the measured optical markers, using a parameter optimization algorithm (Andersen et al., 2010).

7.2.3.2 Subject-specific model

Subject-specific MS geometry was obtained from MRI scan, using the TLEM 2.0 dataset as a starting template (Carbone et al., 2016a). Then, an atlas-based non-rigid MRI image registration implemented in Mimics® 17.0 (Materialise N.V., Leuven, Belgium) was used to automatically segment muscle volumes contours (Kolk et al., 2015), and functional scaling was applied to MT parameters, in order to find the best possible match between the strength profiles measured during dynamometry trials and the maximum joint torques predicted by the model (Carbone et al., 2016b) (Figure 7.4).

Figure 7.4 - Subject-specific musculoskeletal models of ten healthy subjects, based on MRI and dynamometry measurements (Carbone et al., 2016a, b), implemented in the AnyBody Modeling System™ ver. 6.0.3 (AnyBody Technology A/S, Aalborg, Denmark).

7.2.3.3 Simulations

For each subject and each model, inverse dynamics analysis and static optimization problems were solved to calculate the MT forces necessary to reproduce the measured gait trials. The muscle recruitment problem was solved minimizing the sum of the cubes of muscle activity at each time step (Crowninshield et al., 1981), using a normalization factor based on the muscle volume according to Happee et al. (1995). In total, 10 healthy subjects x 2 models x 3 gait trials = 60 simulations were performed and analyzed in this study.

For each MT element of the left lower extremity, the mechanical power was calculated as:

$$P_{mech} = F^{MT} v_{MT} = F^{MT} \dot{L}_{MT}$$

where F^{MT} represents the predicted MT force, and v_{MT} represents the lengthening velocity of the MT element, calculated as the first derivative of the total length of the MT element L_{MT} (Figure 7.3D). Then, the metabolic power of each MT element was calculated based on the efficiency on the contractile element as:

$$P_m = \frac{P_{mech}}{\mu}, \begin{cases} \mu = 0.25 & \text{for shortening } \dot{L}_{MT} < 0 \\ \mu = -1.20 & \text{for lengthening } \dot{L}_{MT} > 0 \end{cases}$$

assuming an efficiency $\mu=25\%$ for concentric muscle work (De Haan et al., 1989) and $\mu=-120\%$ for eccentric work (Asmussen, 1953), as previously used by Voigt et al. (1995), in order to reflect the thermodynamic fact that muscle work is irreversible, and that even

negative muscle work requires positive combustion. Metabolic power was then integrated over a complete gait cycle in order to calculate metabolic energy consumption. Metabolic energy consumption E_m of each muscle actuator was then calculated as the sum of each corresponding MT element. For each subject and each muscle, the average metabolic energy consumption over 3 gait trials at CWS was calculated. $\%E_m$ values were calculated to reflect the amount of E_m in each muscle relative to the total amount of E_m in all the muscles of the left lower extremity. One-tailed Wilcoxon rank sum tests ($\alpha=0.05$) were performed to assess whether subject-specific models predicted a significantly lower energy consumption compared to generic models.

7.2.4 Analysis

For each muscle, $\%FDG$ uptake values measured through the PET/CT scans were compared with the $\%E_m$ metabolic energy consumption predicted by generic and subject-specific models, with respect to the complete lower extremity and for the pelvis, upper leg and lower leg regions separately. Correlations between $\%FDG$ and $\%E_m$ were assessed using two metrics: the Spearman's rank correlation coefficient ρ , to assess how well their relationship could be described using a monotonic function, and the Pearson product-moment correlation coefficient r , as a measure of their linear correlation. Spearman's ρ and Pearson's r were calculated for each individual subject and for the average $\%FDG$ and $\%E_m$ per muscle calculated over all ten healthy subjects, with respect to the complete lower extremity, and for the pelvis, upper leg and lower leg regions separately. One-tailed Wilcoxon rank sum tests ($\alpha=0.05$) were performed to assess whether subject-specific models showed a significantly higher correlation with $\%FDG$ compared to generic models.

7.3 Results

The average metabolic power P_m during gait was equal to 3.82 ± 0.44 W/kg for generic models and 3.73 ± 0.48 W/kg for subject-specific models, however the slight reduction of metabolic power consumption in personalized models was not significant ($p=0.13$).

Qualitatively, the measured $\%FDG$ uptakes and the predicted $\%E_m$ metabolic energy consumption corresponded well (Figure 7.5). Quantitatively, the muscles in the lower leg consumed most of the metabolic energy ($\%E_m$ equal to $48.1 \pm 3.4\%$ and $46.2 \pm 4.4\%$ for generic and subject-specific models, respectively), which was similar to the FDG-PET data ($\%FDG$ equal to $45.2 \pm 11.1\%$) (Table 7.1). The subject-specific models showed higher metabolic energy consumption in the pelvis region than in the upper leg ($\%E_m$ equal to $30.8 \pm 4.9\%$ and $23.1 \pm 3.8\%$, respectively), whereas this was the other way around in the FDG-PET data ($\%FDG$ equal to $22.6 \pm 7.7\%$ and $32.3 \pm 5.9\%$ in the pelvis and upper leg region, respectively) and in the generic models ($\%E_m$ equal to $24.5 \pm 3.4\%$ and $27.4 \pm 3.4\%$ in the pelvis and upper leg region, respectively).

Figure 7.5 - Qualitative comparison of distribution of $\%FDG$ and $\%E_m$ between the muscles of the lower extremity. A: $\%FDG$ uptake, based on PET volumetric analysis. B: $\%E_m$ metabolic energy consumption, predicted using subject-specific musculoskeletal models (anterior, posterior and lateral view). Color of muscles is proportional to the $\%FDG$ and $\%E_m$ values. Results are averaged over ten healthy subjects.

Table 7.1 - Distribution of $\%FDG$ uptake and $\%E_m$ metabolic energy consumption between the pelvis, upper leg and lower leg regions. Results are averaged over ten healthy subjects.

	$\%FDG$				$\%E_m$ - Generic models				$\%E_m$ - Subject-specific models			
	mean	std	min	max	mean	std	min	max	mean	std	min	max
Pelvis	22.6%	7.7%	12.4%	41.3%	24.5%	3.4%	16.1%	27.6%	30.8%	4.9%	20.7%	37.2%
Upper leg	32.3%	5.9%	22.0%	40.9%	27.4%	3.4%	24.3%	34.4%	23.1%	3.8%	15.6%	29.3%
Lower leg	45.2%	11.1%	29.2%	65.6%	48.1%	3.4%	40.8%	55.1%	46.2%	4.4%	38.3%	54.6%

$\%FDG$ uptake based on PET volumetric analysis, $\%E_m$ metabolic energy consumption predicted using generic and subject-specific musculoskeletal models. Cell shading is proportional to the $\%FDG$ and $\%E_m$ values.

Many similarities were found between the muscles with the highest $\%FDG$ uptake and the muscles with the highest $\%E_m$ metabolic energy consumption (Table 7.2). The Soleus was consistently the most consuming muscle ($\%FDG$ equal to 20.6%, $\%E_m$ equal to 20.1% and 21.7% for generic and subject-specific models, respectively), followed by the Gastrocnemius Medialis, the Gluteal muscles and the Adductor Magnus. The $\%E_m$ of the Gastrocnemius Medialis was consistently overestimated by the models (17.0% and 10.0% for generic and subject-specific models, respectively) compared to $\%FDG$ (6.6%). Between the Gluteal muscles, the Gluteus Maximus and the Gluteus Minimus showed consistent results, while the Gluteus Medius had a relatively large $\%E_m$ (7.5% and 9.1% for generic and subject-specific models, respectively) compared to $\%FDG$ (5.7%). The Tibialis Anterior and the Vasti muscles exhibited a much smaller $\%E_m$ compared to $\%FDG$, while the Iliopsoas and the Rectus Femoris showed a larger $\%E_m$ compared to $\%FDG$. The detailed results of $\%FDG$ uptake and $\%E_m$ metabolic energy consumption of all muscles for all the ten healthy subjects are available in the Appendix.

Table 7.2 - Comparison between %FDG uptake and %E_m metabolic energy consumption of the ten muscles showing the highest %FDG uptake values. Results are averaged over ten healthy subjects.

	%FDG				%E _m - Generic models				%E _m - Subject-specific models			
	mean	std	min	max	mean	std	min	max	mean	std	min	max
Soleus	20.6%	11.0%	8.8%	40.5%	20.1%	3.1%	14.5%	25.0%	21.7%	5.3%	11.0%	27.9%
Gluteus Maximus	7.5%	2.5%	4.1%	11.6%	4.1%	1.5%	1.3%	5.6%	6.9%	2.5%	3.3%	10.9%
Gastrocnemius Medialis	6.6%	3.4%	1.9%	13.7%	17.0%	1.3%	15.2%	19.9%	10.0%	5.9%	2.4%	19.1%
Gluteus Medius	5.7%	5.0%	2.5%	19.5%	7.5%	1.6%	5.1%	9.3%	9.1%	1.6%	5.8%	10.8%
Vastus Lateralis	5.6%	1.5%	3.6%	7.6%	5.4%	2.5%	1.2%	9.8%	1.4%	1.5%	0.3%	4.2%
Adductor Magnus	4.9%	1.1%	3.6%	6.9%	2.4%	0.8%	1.1%	3.6%	3.7%	1.9%	0.9%	7.8%
Tibialis Anterior	4.9%	1.6%	2.8%	7.1%	2.3%	1.0%	1.3%	4.9%	2.1%	1.0%	1.1%	4.2%
Vastus Intermedius	4.2%	1.3%	2.5%	6.0%	0.4%	0.2%	0.1%	0.7%	1.5%	1.9%	0.0%	4.9%
Vastus Medialis	3.9%	1.1%	2.3%	5.4%	1.7%	0.7%	0.5%	3.0%	2.0%	1.6%	0.3%	5.7%
Gluteus Minimus	2.6%	1.9%	0.6%	6.2%	3.7%	0.5%	2.8%	4.4%	3.6%	1.5%	1.3%	6.0%

%FDG uptake based on PET volumetric analysis, %E_m metabolic energy consumption predicted using generic and subject-specific musculoskeletal models. Cell shading is proportional to the %FDG and %E_m values.

Good correlation was found between %FDG uptake and %E_m metabolic energy consumption (Table 7.3). When analyzing each individual healthy subject, good to very good correlations were found for generic models (mean $\rho=0.88\pm0.04$, mean $r=0.74\pm0.09$) and for subject-specific models (mean $\rho=0.87\pm0.04$, mean $r=0.77\pm0.10$) and for the complete lower extremity, but the difference was not significant ($p=0.17$). Very good correlations were found for the pelvis region (mean $\rho=0.85\pm0.10$ and mean $r=0.71\pm0.15$ for generic models, mean $\rho=0.84\pm0.05$ and mean $r=0.78\pm0.13$ for subject-specific models) and lower leg (mean $\rho=0.71\pm0.12$ and mean $r=0.85\pm0.07$ for generic models, mean $\rho=0.71\pm0.12$ and mean $r=0.88\pm0.08$ for subject-specific models), while poor correlation was found for the upper leg (mean $\rho=0.24\pm0.22$ and mean $r=0.24\pm0.26$ for generic models, mean $\rho=0.20\pm0.31$ and mean $r=0.18\pm0.27$ for subject-specific models). Correlation values were higher when analyzing %FDG and %E_m results averaged over the ten healthy subjects analyzed ($\rho=0.91$ and $r=0.84$ for generic models, $\rho=0.96$ and $r=0.91$ for subject-specific models) (Figure 7.6). On the level of body segments, very good correlations were found for the pelvis region ($\rho=0.91$ and $r=0.83$ for generic models, $\rho=0.95$ and $r=0.92$ for subject-specific models) and lower leg ($\rho=0.89$ and $r=0.87$ for generic models, $\rho=0.89$ and $r=0.95$ for subject-specific models), but poor correlation was found for the upper leg ($\rho=0.26$ and $r=0.35$ for generic models, $\rho=0.15$ and $r=0.27$ for subject-specific models).

Table 7.3 - Spearman's rank correlation ρ and Pearson product-moment correlation r between %FDG uptake and %E_m metabolic energy consumption.

	Mean values of the correlations between %FDG and %E _m calculated for each of the ten healthy subjects								Correlations between the %FDG and %E _m values averaged over ten healthy subjects			
	Generic				Subject-specific				Generic		Subject-specific	
	ρ		r		ρ		r		ρ		r	
	mean	std	mean	std	mean	std	mean	std	ρ	r	ρ	r
Pelvis	0.85	0.10	0.71	0.15	0.84	0.05	0.78	0.13	0.91	0.83	0.95	0.92
Upper leg	0.24	0.22	0.24	0.26	0.20	0.31	0.18	0.27	0.26	0.35	0.15	0.27
Lower leg	0.71	0.12	0.85	0.07	0.71	0.12	0.88	0.08	0.89	0.87	0.89	0.95
Lower extremity	0.88	0.04	0.74	0.09	0.87	0.04	0.77	0.10	0.91	0.84	0.96	0.91

%FDG uptake based on PET volumetric analysis, %E_m metabolic energy consumption predicted using generic and subject-specific musculoskeletal models. Cell shading is proportional to the correlation values.

Figure 7.6 - Linear correlation between %FDG uptake, based on PET volumetric analysis, and % E_m metabolic energy consumption, predicted using generic and subject-specific musculoskeletal models. Results are averaged over ten healthy subjects. Linear trend lines are based on Pearson product-moment correlation coefficient r .

7.4 Discussion

In this study, we used FDG-PET to indirectly validate muscle energy consumption predicted by generic and subject-specific MS models. The validity of FDG-PET to measure muscular activity during walking has been previously demonstrated by Oi et al. (2003), however to our knowledge this is the first time that MS model predictions have been compared with FDG-PET data. Very good correlation was found between the measured %FDG glucose uptake and the predicted % E_m metabolic energy consumption, giving more confidence on the validity of the model outcomes when analyzing muscle function during gait.

Almost 50% of the predicted % E_m metabolic energy was consumed by muscles in the lower leg, in particular the Soleus and the Gastrocnemius, in accordance with the %FDG uptake values, confirming the key role of the ankle plantarflexors during walking (Winter, 1983; Liu et al., 2006). Moreover, the fact that a deep and relatively small muscle like the Gluteus Minimus appeared among the most consuming muscles during gait, according to both %FDG and % E_m and as previously indicated by Oi et al. (2003), shows the advantages of FDG-PET compared to EMG, which allows to measure only the superficial muscles.

Very good correlation was found between %FDG uptake and % E_m metabolic energy consumption in the pelvis region and the lower leg, while poor correlation was found in the upper leg. This result may be dependent on the task analyzed, since %FDG uptake values during gait showed small variability between muscles within the upper leg (Kolk et al., 2015). Results are likely to be different for more demanding task such as running or stairs climbing. Unlike the FDG-PET results, the models predicted larger % E_m metabolic energy consumption in the pelvis region, in particular the Gluteal muscles and the Iliopsoas that provide stability to the hip joint during gait, and a smaller consumption in the upper leg, in particular in the Vasti muscles compared to the Rectus Femoris, probably due to the fact that the model includes a 1 degree of freedom knee joint that requires less muscle-induced

stability. A thorough comprehension of these differences remains very important to better understand the functioning of comprehensive musculoskeletal models of the lower extremity, in order to further improve their predictions.

Subject-specific models used in this study predicted more realistic MT forces and muscle activity during gait compared to generic models (Carbone et al., 2016b). These differences resulted in slight improvements in the predicted metabolic power consumption and in the correlation between %FDG uptakes and % E_m metabolic energy consumption. However, it was not possible to statistically prove the significance of these improvements, probably due to the fact that FDG-PET is not accurate enough to detect the improvements of personalized models for healthy subjects and for relatively simple tasks such as walking. Differences between generic and subject-specific models are likely to be magnified for more strenuous activities such as running, climbing stairs or getting up from a chair, and when analyzing patients affected by musculoskeletal pathologies, where larger differences in MS geometry and MT parameters are expected.

On average, predicted metabolic power P_m (3.82 W/kg for generic models and 3.73 W/kg for subject-specific models) was lower than the measured value found in literature (4.67 W/kg) (Inman et al., 1981). However, P_m depended exclusively on the predicted mechanical power of the muscles of the lower extremity, while the measured metabolic power consumption, based on the oxygen uptake, likely included the contribution of the muscles of the upper body and of the resting metabolism of the whole body. Moreover, the precise relation between metabolic energy consumption and predicted muscle forces is unknown. We assumed the same efficiency for all the muscles, whereas uptake of the glucose into a muscle depends on many factors, including the fiber types (Henriksen et al., 1990). Hence, it is possible that the different fiber composition in the muscles of the lower extremity (Johnson et al., 1973) affects the efficiency and energy consumption of muscles. FDG-PET results provides precious information to better understand the functional differences in the muscle energy consumption and recruitment process, and should be used to improve the static optimization criteria used in MS models, for example introducing energy-based cost functions as suggested by Praagman et al. (2006).

The main limitation of the FDG-PET results depends on the quality of the medical images used and on the segmentation accuracy. Errors in muscle segmentation would directly affect the glucose uptake measurement, however Kolk et al. (2015) showed that the method used in this study had a small sensitivity to this kind of errors. Compared to EMG, FDG-PET results have a cumulative nature, therefore the measured glucose uptake represents an accumulation of all the muscle metabolic activity during the task and cannot be used to measure temporal variations of muscle force or energy consumption. Also, validity of this method to measure muscular activity has been proven only for aerobic tasks. Most importantly, FDG-PET requires specialized equipment and involves a low dose of radiation, hence it is difficult to perform repeated measurements on the same subject because of ethical issues.

In conclusion, the good to very good correlation between the measured %*FDG* glucose uptake and the predicted %*E_m* metabolic energy consumption that was found when analyzing each individual subject and when analyzing averaged results gives great confidence on the validity of model outcomes when analyzing muscle function during gait. However, significant improvements in the subject-specific models compared to generic models were not proven. Given its advantages and limitations, FDG-PET should be considered as a complimentary tool to EMG when validating MS models.

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Appendix

Tables 7.A1, 7.A2, 7.A3, 7.A4 and 7.A5 contain detailed results of the measured %FDG uptake, and the predicted % E_m and E_m metabolic energy consumption for ten healthy subjects.

Table 7.A1 –Detailed results of %FDG uptake values measured on ten healthy subjects, based on PET volumetric analysis. Reprinted from Kolk et al. (2015) with permission from Wolters Kluwer.

	%FDG uptake - Ten healthy subjects										mean	std	median	min	max
	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10					
Gemellus Inferior	0.1%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.1%	0.0%	0.1%
Gemellus Superior	0.2%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.2%
Gluteus Maximus	4.1%	4.6%	7.2%	6.7%	7.0%	11.5%	7.9%	11.6%	7.4%	6.7%	7.5%	2.3%	7.1%	4.1%	11.6%
Gluteus Medius	2.5%	2.5%	4.0%	3.0%	5.5%	4.8%	4.3%	19.5%	6.1%	4.5%	5.7%	4.8%	4.4%	2.5%	19.5%
Gluteus Minimus	1.1%	0.6%	1.5%	1.2%	3.9%	3.0%	2.8%	4.8%	6.2%	1.2%	2.6%	1.8%	2.2%	0.6%	6.2%
Iliacus	1.3%	1.5%	2.0%	2.1%	2.3%	3.0%	2.6%	1.2%	2.7%	1.3%	2.0%	0.6%	2.0%	1.2%	3.0%
Obturator Externus	0.5%	0.4%	0.3%	0.3%	0.3%	0.4%	0.4%	0.2%	0.2%	0.3%	0.3%	0.1%	0.3%	0.2%	0.5%
Obturator Internus	2.0%	0.3%	0.9%	1.4%	0.5%	0.7%	0.4%	0.3%	0.5%	0.4%	0.7%	0.5%	0.5%	0.3%	2.0%
Pectineus	0.5%	0.5%	0.8%	0.8%	0.4%	0.5%	0.8%	0.4%	0.7%	0.4%	0.6%	0.2%	0.5%	0.4%	0.8%
Piriformis	2.7%	0.4%	1.1%	0.5%	0.2%	0.3%	0.5%	1.4%	0.6%	0.3%	0.8%	0.7%	0.5%	0.2%	2.7%
Psoas Major	1.1%	1.0%	1.4%	1.3%	1.6%	1.7%	1.7%	0.8%	1.7%	1.5%	1.4%	0.3%	1.4%	0.8%	1.7%
Quadratus Femoris	0.2%	0.2%	0.4%	0.2%	0.3%	0.5%	0.5%	0.2%	0.7%	0.3%	0.3%	0.2%	0.3%	0.2%	0.7%
Tensor Fasciae Latae	0.3%	0.4%	0.4%	0.4%	0.5%	0.6%	0.6%	0.9%	0.5%	0.3%	0.5%	0.2%	0.5%	0.3%	0.9%
PELVIS REGION	16.5%	12.4%	20.1%	18.0%	22.5%	27.3%	22.7%	41.3%	27.3%	17.3%	22.6%	7.7%	21.3%	12.4%	41.3%
Adductor Brevis	2.0%	1.4%	1.2%	1.6%	1.0%	1.3%	1.3%	3.4%	1.9%	1.7%	1.7%	0.6%	1.5%	1.0%	3.4%
Adductor Longus	1.2%	1.2%	1.5%	5.1%	1.2%	2.2%	2.1%	3.9%	3.5%	1.1%	2.3%	1.3%	1.8%	1.1%	5.1%
Adductor Magnus	4.0%	3.6%	5.7%	5.3%	5.4%	6.9%	5.7%	3.7%	5.5%	3.6%	4.9%	1.1%	5.4%	3.6%	6.9%
Biceps Femoris Caput Breve	0.4%	0.7%	0.9%	0.8%	1.2%	1.0%	1.2%	0.5%	1.4%	0.5%	0.9%	0.3%	0.8%	0.4%	1.4%
Biceps Femoris Caput Longum	1.2%	0.9%	1.4%	1.9%	1.4%	1.9%	1.8%	0.8%	2.1%	2.3%	1.6%	0.5%	1.6%	0.8%	2.3%
Gracilis	0.3%	0.6%	0.7%	0.8%	0.6%	0.6%	0.7%	0.6%	0.6%	0.6%	0.6%	0.1%	0.6%	0.3%	0.8%
Rectus Femoris	1.5%	1.3%	2.1%	1.8%	1.9%	2.0%	2.8%	1.0%	2.4%	2.0%	1.9%	0.5%	1.9%	1.0%	2.8%
Sartorius	0.6%	1.0%	1.5%	1.4%	1.1%	1.5%	1.6%	4.4%	1.4%	0.8%	1.5%	1.0%	1.4%	0.6%	4.4%
Semimembranosus	2.6%	1.2%	1.7%	1.7%	1.3%	3.6%	1.8%	1.2%	2.7%	2.8%	2.0%	0.8%	1.7%	1.2%	3.6%
Semitendinosus	1.2%	1.0%	1.2%	1.3%	1.3%	1.1%	0.9%	0.6%	1.6%	1.8%	1.2%	0.3%	1.2%	0.6%	1.8%
Vastus Intermedius	2.5%	3.0%	5.9%	4.6%	4.9%	6.0%	5.4%	2.8%	4.0%	3.2%	4.2%	1.3%	4.3%	2.5%	6.0%
Vastus Lateralis	3.6%	3.8%	6.7%	6.4%	6.4%	7.6%	7.4%	3.8%	4.7%	5.3%	5.6%	1.5%	5.8%	3.6%	7.6%
Vastus Medialis	2.4%	2.3%	5.4%	4.7%	4.2%	5.3%	4.2%	2.7%	4.2%	3.2%	3.9%	1.1%	4.2%	2.3%	5.4%
UPPER LEG	23.5%	22.0%	36.0%	37.2%	31.8%	40.9%	36.8%	29.5%	35.9%	29.0%	32.3%	5.9%	33.8%	22.0%	40.9%
Extensor Digitorum Longus	0.7%	4.6%	1.2%	3.4%	1.1%	0.9%	1.6%	1.7%	1.8%	1.3%	1.8%	1.2%	1.5%	0.7%	4.6%
Extensor Hallucis Longus	1.5%	1.9%	0.8%	1.7%	1.0%	0.8%	0.8%	1.0%	1.3%	1.4%	1.2%	0.4%	1.2%	0.8%	1.9%
Flexor Digitorum Longus	0.2%	0.9%	0.7%	0.4%	1.5%	0.9%	1.5%	0.6%	0.9%	0.4%	0.8%	0.4%	0.8%	0.2%	1.5%
Flexor Hallucis Longus	0.6%	4.6%	0.7%	0.7%	1.2%	1.4%	2.3%	1.2%	0.8%	1.8%	1.5%	1.1%	1.2%	0.6%	4.6%
Gastrocnemius Lateralis	2.3%	1.0%	4.0%	1.3%	1.4%	1.8%	1.7%	4.6%	2.0%	3.1%	2.3%	1.1%	1.9%	1.0%	4.6%
Gastrocnemius Medialis	5.1%	1.9%	8.6%	6.6%	13.7%	4.8%	4.0%	4.9%	6.1%	9.9%	6.6%	3.2%	5.6%	1.9%	13.7%
Peroneus Brevis	0.8%	0.6%	0.8%	1.4%	1.2%	0.5%	0.6%	0.3%	0.5%	4.8%	1.2%	1.3%	0.7%	0.3%	4.8%
Peroneus Longus	0.5%	2.6%	1.2%	4.4%	0.7%	0.8%	1.1%	0.6%	1.0%	3.2%	1.6%	1.3%	1.0%	0.5%	4.4%
Plantaris	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.4%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.4%
Popliteus	0.5%	0.3%	0.4%	0.2%	0.5%	0.4%	0.5%	0.4%	0.7%	0.4%	0.4%	0.1%	0.4%	0.2%	0.7%
Soleus	39.5%	40.5%	17.3%	17.0%	15.2%	13.5%	21.2%	8.8%	11.5%	21.5%	20.6%	10.4%	17.1%	8.8%	40.5%
Tibialis Anterior	7.0%	5.0%	4.6%	6.4%	7.1%	2.9%	2.8%	3.7%	5.2%	4.4%	4.9%	1.5%	4.8%	2.8%	7.1%
Tibialis Posterior	1.1%	1.7%	3.4%	1.2%	1.1%	2.9%	2.0%	1.2%	4.7%	1.3%	2.1%	1.2%	1.5%	1.1%	4.7%
LOWER LEG	59.9%	65.6%	43.8%	44.8%	45.8%	31.8%	40.5%	29.2%	36.7%	53.6%	45.2%	11.1%	44.3%	29.2%	65.6%
LOWER EXTREMITY	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%				

Table 7.A2 - Detailed results of % E_m metabolic energy consumption values predicted for ten healthy subjects using generic musculoskeletal models.

%E _m metabolic energy consumption - Ten healthy subjects - Generic musculoskeletal models															
	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	mean	std	median	min	max
Gemellus Inferior	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
Gemellus Superior	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
Gluteus Maximus	3.3%	5.2%	4.8%	2.6%	1.3%	5.6%	2.7%	5.6%	4.7%	5.0%	4.1%	1.4%	4.7%	1.3%	5.6%
Gluteus Medius	9.3%	7.7%	5.1%	8.8%	5.4%	8.3%	7.8%	5.5%	9.0%	7.9%	7.5%	1.5%	7.8%	5.1%	9.3%
Gluteus Minimus	4.3%	3.4%	3.1%	4.1%	2.8%	3.8%	3.9%	3.4%	3.7%	4.4%	3.7%	0.5%	3.8%	2.8%	4.4%
Iliacus	3.7%	2.5%	2.4%	3.5%	2.1%	3.1%	3.8%	3.1%	2.7%	3.3%	3.0%	0.6%	3.1%	2.1%	3.8%
Obturator Externus	0.4%	0.4%	0.3%	0.6%	0.3%	0.3%	0.4%	0.7%	0.4%	0.5%	0.4%	0.1%	0.4%	0.3%	0.7%
Obturator Internus	0.1%	0.2%	0.3%	0.2%	0.1%	0.3%	0.2%	0.4%	0.2%	0.2%	0.2%	0.1%	0.2%	0.1%	0.4%
Pectineus	0.5%	0.3%	0.3%	0.6%	0.4%	0.5%	0.8%	0.7%	0.4%	0.5%	0.5%	0.2%	0.5%	0.3%	0.8%
Piriformis	0.4%	0.2%	0.4%	0.2%	0.2%	0.5%	0.3%	0.7%	0.5%	0.6%	0.4%	0.2%	0.4%	0.2%	0.7%
Psoas Major	3.0%	2.0%	1.9%	2.9%	1.6%	2.7%	3.2%	3.0%	2.2%	2.9%	2.5%	0.5%	2.8%	1.6%	3.2%
Quadratus Femoris	0.1%	0.1%	0.2%	0.1%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.2%
Tensor Fasciae Latae	2.1%	1.9%	1.7%	2.5%	1.8%	1.8%	2.0%	1.7%	2.0%	2.1%	2.0%	0.2%	1.9%	1.7%	2.5%
PELVIS REGION	27.2%	24.0%	20.6%	26.1%	16.1%	27.0%	25.2%	25.0%	25.9%	27.6%	24.5%	3.4%	25.6%	16.1%	27.6%
Adductor Brevis	0.2%	0.1%	0.1%	0.3%	0.1%	0.1%	0.5%	0.5%	0.1%	0.3%	0.2%	0.2%	0.2%	0.1%	0.5%
Adductor Longus	1.4%	0.7%	0.5%	1.5%	0.6%	1.2%	2.2%	1.7%	0.8%	1.4%	1.2%	0.5%	1.3%	0.5%	2.2%
Adductor Magnus	2.5%	1.8%	1.7%	2.8%	5.6%	0.6%	2.1%	2.8%	2.2%	1.9%	2.4%	1.2%	2.1%	0.6%	5.6%
Biceps Femoris Caput Breve	1.5%	1.2%	0.9%	1.6%	1.0%	1.2%	1.3%	1.3%	1.6%	1.8%	1.3%	0.3%	1.3%	0.9%	1.8%
Biceps Femoris Caput Longum	2.5%	3.1%	2.3%	2.4%	1.1%	2.1%	2.4%	1.5%	3.5%	3.6%	2.4%	0.7%	2.4%	1.1%	3.6%
Gracilis	0.8%	0.5%	0.5%	1.0%	0.5%	0.7%	1.1%	1.3%	0.8%	0.7%	0.8%	0.3%	0.7%	0.5%	1.3%
Rectus Femoris	2.5%	3.8%	2.9%	3.6%	0.4%	2.6%	3.5%	2.9%	3.0%	3.9%	2.9%	1.0%	3.0%	0.4%	3.9%
Sartorius	5.2%	3.4%	3.1%	4.4%	2.0%	4.2%	4.9%	3.9%	3.8%	4.9%	4.0%	0.9%	4.0%	2.0%	5.2%
Semimembranosus	2.3%	2.2%	1.6%	2.4%	4.7%	2.0%	2.1%	2.1%	2.3%	2.3%	2.4%	0.8%	2.2%	1.6%	4.7%
Semitendinosus	2.6%	2.1%	1.3%	2.3%	4.9%	1.3%	2.1%	2.0%	2.0%	2.2%	2.3%	1.0%	2.1%	1.3%	4.9%
Vastus Intermedius	0.2%	0.4%	0.5%	0.6%	0.7%	0.4%	0.3%	0.4%	0.2%	0.1%	0.4%	0.2%	0.4%	0.1%	0.7%
Vastus Lateralis	3.0%	5.4%	6.8%	7.7%	9.8%	6.0%	4.9%	5.4%	3.3%	1.2%	5.4%	2.3%	5.4%	1.2%	9.8%
Vastus Medialis	1.0%	1.7%	2.1%	2.5%	3.0%	1.8%	1.7%	1.7%	1.3%	0.5%	1.7%	0.7%	1.7%	0.5%	3.0%
UPPER LEG	25.8%	26.5%	24.4%	33.1%	34.4%	24.3%	28.9%	27.5%	25.0%	24.7%	27.4%	3.4%	26.1%	24.3%	34.4%
Extensor Digitorum Longus	0.3%	0.2%	0.2%	0.3%	0.3%	0.2%	0.3%	0.4%	0.3%	0.3%	0.3%	0.0%	0.3%	0.2%	0.4%
Extensor Hallucis Longus	0.1%	0.1%	0.1%	0.2%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.1%	0.0%	0.1%	0.1%	0.2%
Flexor Digitorum Longus	0.2%	0.0%	0.1%	0.1%	0.1%	0.1%	0.2%	0.0%	0.1%	0.1%	0.1%	0.0%	0.1%	0.0%	0.2%
Flexor Hallucis Longus	1.0%	0.2%	0.2%	0.6%	0.3%	0.7%	0.9%	0.4%	0.4%	0.5%	0.5%	0.3%	0.5%	0.2%	1.0%
Gastrocnemius Lateralis	5.6%	5.7%	7.2%	5.0%	6.0%	6.4%	5.4%	5.8%	5.8%	5.3%	5.8%	0.6%	5.7%	5.0%	7.2%
Gastrocnemius Medialis	16.8%	17.5%	19.9%	15.2%	16.2%	17.6%	15.6%	16.2%	17.9%	17.2%	17.0%	1.3%	17.0%	15.2%	19.9%
Peroneus Brevis	0.2%	0.0%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.1%	0.0%	0.1%	0.0%	0.2%
Peroneus Longus	0.8%	0.4%	0.3%	0.6%	0.5%	0.8%	0.7%	0.5%	0.6%	0.5%	0.6%	0.2%	0.6%	0.3%	0.8%
Plantaris	0.2%	0.2%	0.2%	0.1%	0.2%	0.2%	0.1%	0.2%	0.2%	0.2%	0.2%	0.0%	0.2%	0.1%	0.2%
Popliteus	0.2%	0.2%	0.2%	0.3%	0.3%	0.2%	0.3%	0.2%	0.3%	0.2%	0.2%	0.0%	0.2%	0.2%	0.3%
Soleus	17.8%	23.2%	25.0%	14.5%	23.8%	19.4%	18.6%	20.2%	19.4%	19.3%	20.1%	3.0%	19.4%	14.5%	25.0%
Tibialis Anterior	2.0%	1.8%	1.3%	3.2%	1.4%	2.0%	1.9%	3.1%	3.5%	3.0%	2.3%	0.8%	2.0%	1.3%	3.5%
Tibialis Posterior	2.0%	0.1%	0.1%	0.7%	0.2%	1.0%	1.7%	0.4%	0.4%	1.0%	0.8%	0.6%	0.6%	0.1%	2.0%
LOWER LEG	47.1%	49.6%	55.1%	40.8%	49.6%	48.8%	45.9%	47.6%	49.1%	47.7%	48.1%	3.4%	48.2%	40.8%	55.1%
LOWER EXTREMITY	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%				

Table 7.A3 - Detailed results of % E_m metabolic energy consumption values predicted for ten healthy subjects using subject-specific musculoskeletal models.

	%E _m metabolic energy consumption - Ten healthy subjects - Subject-specific musculoskeletal models														
	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	mean	std	median	min	max
Gemellus Inferior	0.0%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.1%	0.1%	0.0%	0.0%	0.2%
Gemellus Superior	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	0.1%	0.1%	0.0%	0.1%	0.0%	0.1%
Gluteus Maximus	6.1%	8.8%	4.5%	6.7%	7.8%	3.3%	3.6%	10.9%	9.3%	7.6%	6.9%	2.4%	7.2%	3.3%	10.9%
Gluteus Medius	10.8%	9.5%	5.8%	8.8%	8.3%	10.3%	8.7%	8.0%	10.6%	10.5%	9.1%	1.5%	9.1%	5.8%	10.8%
Gluteus Minimus	4.8%	2.4%	2.4%	5.8%	3.0%	6.0%	3.9%	1.3%	3.3%	3.2%	3.6%	1.4%	3.3%	1.3%	6.0%
Iliacus	5.3%	3.2%	3.9%	5.5%	2.1%	3.8%	5.2%	3.7%	2.8%	3.9%	3.9%	1.0%	3.8%	2.1%	5.5%
Obturator Externus	0.1%	0.2%	0.0%	0.3%	0.1%	0.2%	0.4%	0.5%	0.2%	0.2%	0.2%	0.1%	0.2%	0.0%	0.5%
Obturator Internus	0.7%	1.6%	0.5%	0.2%	0.0%	0.7%	0.0%	0.5%	0.7%	0.2%	0.5%	0.4%	0.5%	0.0%	1.6%
Pectineus	0.5%	0.4%	0.8%	1.1%	0.3%	0.3%	0.1%	0.3%	0.5%	0.4%	0.5%	0.3%	0.4%	0.1%	1.1%
Piriformis	1.2%	0.6%	0.9%	0.3%	0.0%	0.7%	1.0%	1.2%	2.5%	1.2%	1.0%	0.7%	0.9%	0.0%	2.5%
Psoas Major	2.2%	2.2%	0.2%	2.9%	1.5%	2.3%	2.7%	5.0%	1.9%	4.1%	2.5%	1.3%	2.3%	0.2%	5.0%
Quadratus Femoris	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%	0.9%	0.7%	0.3%	0.4%	0.0%	0.0%	1.1%
Tensor Fasciae Latae	1.9%	2.2%	1.6%	0.9%	1.3%	1.6%	2.7%	4.6%	2.8%	1.7%	2.1%	1.0%	1.8%	0.9%	4.6%
PELVIS REGION	33.7%	31.5%	20.7%	32.4%	24.3%	29.2%	28.5%	37.2%	35.7%	34.3%	30.8%	4.9%	32.0%	20.7%	37.2%
Adductor Brevis	0.0%	0.2%	0.1%	0.6%	0.3%	0.1%	0.4%	0.5%	0.2%	0.1%	0.3%	0.2%	0.2%	0.0%	0.6%
Adductor Longus	0.4%	0.6%	0.7%	2.0%	1.1%	0.5%	3.5%	0.5%	1.0%	0.5%	1.1%	0.9%	0.7%	0.4%	3.5%
Adductor Magnus	2.3%	3.0%	7.8%	3.9%	5.6%	3.5%	2.2%	3.3%	4.0%	0.9%	3.7%	1.8%	3.4%	0.9%	7.8%
Biceps Femoris Caput Breve	2.6%	2.6%	0.4%	2.3%	1.5%	2.2%	3.1%	0.3%	2.3%	1.9%	1.9%	0.9%	2.2%	0.3%	3.1%
Biceps Femoris Caput Longum	1.5%	2.0%	2.5%	1.4%	2.2%	4.8%	3.9%	1.8%	1.1%	1.8%	2.3%	1.1%	1.9%	1.1%	4.8%
Gracilis	0.4%	0.4%	0.1%	0.7%	0.2%	0.2%	0.6%	0.3%	0.7%	0.2%	0.4%	0.2%	0.4%	0.1%	0.7%
Rectus Femoris	4.1%	3.2%	2.9%	7.8%	2.2%	4.6%	3.2%	2.2%	4.0%	4.9%	3.9%	1.5%	3.6%	2.2%	7.8%
Sartorius	2.3%	1.0%	0.2%	1.1%	0.3%	0.3%	1.1%	1.6%	1.9%	1.1%	1.1%	0.7%	1.1%	0.2%	2.3%
Semimembranosus	1.7%	2.1%	1.5%	1.7%	0.6%	1.3%	0.3%	4.7%	0.3%	1.8%	1.6%	1.2%	1.6%	0.3%	4.7%
Semitendinosus	2.3%	3.4%	1.9%	4.3%	1.8%	0.1%	2.4%	0.1%	1.1%	1.8%	1.9%	1.2%	1.9%	0.1%	4.3%
Vastus Intermedius	0.4%	4.7%	0.4%	0.2%	4.9%	2.1%	0.0%	1.1%	1.1%	0.0%	1.5%	1.8%	0.7%	0.0%	4.9%
Vastus Lateralis	1.3%	0.4%	0.3%	1.4%	1.9%	3.7%	4.2%	0.3%	0.4%	0.3%	1.4%	1.4%	0.9%	0.3%	4.2%
Vastus Medialis	1.4%	0.4%	5.7%	2.1%	2.2%	1.0%	1.9%	3.4%	1.3%	0.3%	2.0%	1.5%	1.6%	0.3%	5.7%
UPPER LEG	20.9%	24.0%	24.7%	29.3%	25.0%	24.7%	26.9%	20.2%	19.3%	15.6%	23.1%	3.8%	24.3%	15.6%	29.3%
Extensor Digitorum Longus	0.3%	1.2%	0.4%	1.0%	0.2%	0.7%	1.5%	1.0%	1.2%	0.4%	0.8%	0.4%	0.8%	0.2%	1.5%
Extensor Hallucis Longus	0.1%	0.3%	0.3%	0.3%	0.2%	0.2%	1.4%	0.5%	0.1%	0.2%	0.3%	0.4%	0.2%	0.1%	1.4%
Flexor Digitorum Longus	0.0%	0.1%	0.4%	0.0%	0.0%	0.1%	0.0%	0.9%	0.1%	0.0%	0.2%	0.3%	0.0%	0.0%	0.9%
Flexor Hallucis Longus	1.3%	3.7%	3.7%	1.2%	2.7%	3.0%	1.3%	2.5%	1.3%	1.9%	2.3%	1.0%	2.2%	1.2%	3.7%
Gastrocnemius Lateralis	11.8%	4.8%	7.1%	6.4%	5.6%	5.2%	0.7%	5.8%	11.6%	6.6%	6.6%	3.1%	6.1%	0.7%	11.8%
Gastrocnemius Medialis	3.2%	4.0%	15.0%	13.3%	14.4%	6.0%	14.3%	8.5%	2.4%	19.1%	10.0%	5.6%	10.9%	2.4%	19.1%
Peroneus Brevis	0.4%	0.0%	0.5%	0.7%	0.2%	0.1%	0.1%	0.3%	0.1%	0.1%	0.2%	0.2%	0.2%	0.0%	0.7%
Peroneus Longus	0.2%	0.4%	0.3%	0.8%	0.1%	0.3%	0.9%	0.7%	0.5%	0.1%	0.4%	0.3%	0.4%	0.1%	0.9%
Plantaris	0.1%	0.0%	0.1%	0.3%	0.3%	0.1%	0.4%	0.2%	0.4%	0.2%	0.2%	0.1%	0.2%	0.0%	0.4%
Popliteus	1.0%	0.1%	0.3%	0.1%	0.1%	0.4%	0.8%	0.2%	0.5%	0.7%	0.4%	0.3%	0.4%	0.1%	1.0%
Soleus	24.4%	27.0%	22.2%	11.0%	25.4%	27.9%	20.9%	19.5%	23.2%	15.1%	21.7%	5.0%	22.7%	11.0%	27.9%
Tibialis Anterior	1.8%	1.8%	1.3%	3.0%	1.3%	1.6%	1.7%	1.1%	3.3%	4.2%	2.1%	1.0%	1.7%	1.1%	4.2%
Tibialis Posterior	0.8%	1.0%	3.1%	0.3%	0.3%	0.4%	0.5%	1.3%	0.4%	1.5%	1.0%	0.8%	0.7%	0.3%	3.1%
LOWER LEG	45.4%	44.5%	54.6%	38.3%	50.7%	46.1%	44.6%	42.5%	45.1%	50.1%	46.2%	4.4%	45.2%	38.3%	54.6%
LOWER EXTREMITY	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%				

Table 7.A4 - Detailed results of E_m metabolic energy consumption values predicted for ten healthy subjects using generic musculoskeletal models.

E_m metabolic energy consumption (J/kg) - Ten healthy subjects - Generic musculoskeletal models															
	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	mean	std	median	min	max
Gemellus Inferior	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gemellus Superior	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gluteus Maximus	0.15	0.20	0.21	0.09	0.05	0.24	0.12	0.23	0.17	0.18	0.16	0.06	0.17	0.05	0.24
Gluteus Medius	0.44	0.29	0.22	0.32	0.23	0.35	0.34	0.23	0.32	0.28	0.30	0.06	0.30	0.22	0.44
Gluteus Minimus	0.20	0.13	0.14	0.15	0.12	0.16	0.17	0.14	0.13	0.16	0.15	0.02	0.15	0.12	0.20
Iliacus	0.18	0.09	0.10	0.13	0.09	0.13	0.17	0.13	0.09	0.12	0.12	0.03	0.12	0.09	0.18
Obturator Externus	0.02	0.01	0.01	0.02	0.01	0.01	0.02	0.03	0.01	0.02	0.02	0.00	0.02	0.01	0.03
Obturator Internus	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.00	0.01	0.00	0.02
Pectineus	0.03	0.01	0.01	0.02	0.02	0.02	0.04	0.03	0.01	0.02	0.02	0.01	0.02	0.01	0.04
Piriformis	0.02	0.01	0.02	0.01	0.01	0.02	0.01	0.03	0.02	0.02	0.02	0.01	0.02	0.01	0.03
Psoas Major	0.14	0.08	0.08	0.11	0.07	0.11	0.14	0.13	0.08	0.11	0.10	0.02	0.11	0.07	0.14
Quadratus Femoris	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.01
Tensor Fasciae Latae	0.10	0.07	0.07	0.09	0.08	0.08	0.08	0.07	0.07	0.08	0.08	0.01	0.08	0.07	0.10
PELVIS REGION	1.28	0.90	0.90	0.95	0.68	1.15	1.09	1.04	0.92	0.99	0.99	0.16	0.97	0.68	1.28
Adductor Brevis	0.01	0.00	0.00	0.01	0.01	0.01	0.02	0.02	0.00	0.01	0.01	0.01	0.01	0.00	0.02
Adductor Longus	0.07	0.03	0.02	0.06	0.03	0.05	0.10	0.07	0.03	0.05	0.05	0.02	0.05	0.02	0.10
Adductor Magnus	0.12	0.07	0.08	0.10	0.23	0.03	0.09	0.12	0.08	0.07	0.10	0.05	0.08	0.03	0.23
Biceps Femoris Caput Breve	0.07	0.05	0.04	0.06	0.04	0.05	0.06	0.06	0.06	0.06	0.05	0.01	0.06	0.04	0.07
Biceps Femoris Caput Longum	0.12	0.12	0.10	0.09	0.05	0.09	0.10	0.06	0.12	0.13	0.10	0.03	0.10	0.05	0.13
Gracilis	0.04	0.02	0.02	0.04	0.02	0.03	0.05	0.05	0.03	0.03	0.03	0.01	0.03	0.02	0.05
Rectus Femoris	0.12	0.14	0.13	0.13	0.02	0.11	0.15	0.12	0.11	0.14	0.12	0.04	0.12	0.02	0.15
Sartorius	0.25	0.13	0.13	0.16	0.08	0.18	0.21	0.16	0.14	0.18	0.16	0.04	0.16	0.08	0.25
Semimembranosus	0.11	0.08	0.07	0.09	0.20	0.08	0.09	0.09	0.08	0.08	0.10	0.03	0.09	0.07	0.20
Semitendinosus	0.12	0.08	0.06	0.08	0.21	0.06	0.09	0.08	0.07	0.08	0.09	0.04	0.08	0.06	0.21
Vastus Intermedius	0.01	0.01	0.02	0.02	0.03	0.02	0.01	0.02	0.01	0.00	0.02	0.01	0.02	0.00	0.03
Vastus Lateralis	0.14	0.20	0.30	0.28	0.41	0.25	0.21	0.22	0.12	0.04	0.22	0.10	0.22	0.04	0.41
Vastus Medialis	0.05	0.06	0.09	0.09	0.13	0.08	0.07	0.07	0.05	0.02	0.07	0.03	0.07	0.02	0.13
UPPER LEG	1.22	0.99	1.07	1.21	1.45	1.03	1.25	1.15	0.89	0.89	1.11	0.17	1.11	0.89	1.45
Extensor Digitorum Longus	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.01
Extensor Hallucis Longus	0.01	0.00	0.00	0.01	0.01	0.00	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.00	0.01
Flexor Digitorum Longus	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01
Flexor Hallucis Longus	0.05	0.01	0.01	0.02	0.01	0.03	0.04	0.02	0.01	0.02	0.02	0.01	0.02	0.01	0.05
Gastrocnemius Lateralis	0.26	0.21	0.31	0.18	0.25	0.27	0.23	0.24	0.21	0.19	0.24	0.04	0.24	0.18	0.31
Gastrocnemius Medialis	0.79	0.66	0.87	0.56	0.68	0.75	0.68	0.68	0.64	0.62	0.69	0.09	0.68	0.56	0.87
Peroneus Brevis	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01
Peroneus Longus	0.04	0.01	0.01	0.02	0.02	0.03	0.03	0.02	0.02	0.02	0.02	0.01	0.02	0.01	0.04
Plantaris	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.01
Popliteus	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.01
Soleus	0.84	0.87	1.10	0.53	1.00	0.82	0.80	0.84	0.69	0.69	0.82	0.15	0.83	0.53	1.10
Tibialis Anterior	0.09	0.07	0.06	0.12	0.06	0.09	0.08	0.13	0.12	0.11	0.09	0.02	0.09	0.06	0.13
Tibialis Posterior	0.09	0.00	0.01	0.03	0.01	0.04	0.07	0.02	0.01	0.04	0.03	0.03	0.02	0.00	0.09
LOWER LEG	2.22	1.86	2.41	1.49	2.09	2.08	1.98	1.98	1.74	1.72	1.96	0.25	1.98	1.49	2.41
LOWER EXTREMITY	4.72	3.76	4.38	3.65	4.21	4.26	4.33	4.17	3.55	3.60	4.06	0.38	4.19	3.55	4.72

Table 7.A5 - Detailed results of E_m metabolic energy consumption values predicted for ten healthy subjects using subject-specific musculoskeletal models.

E_m metabolic energy consumption (J/kg) - Ten healthy subjects - Subject-specific musculoskeletal models															
	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	mean	std	median	min	max
Gemellus Inferior	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.01
Gemellus Superior	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.01
Gluteus Maximus	0.29	0.28	0.20	0.24	0.32	0.13	0.15	0.47	0.31	0.28	0.27	0.09	0.28	0.13	0.47
Gluteus Medius	0.51	0.30	0.25	0.32	0.34	0.43	0.36	0.34	0.35	0.39	0.36	0.07	0.35	0.25	0.51
Gluteus Minimus	0.23	0.08	0.10	0.21	0.12	0.25	0.16	0.06	0.11	0.12	0.14	0.06	0.12	0.06	0.25
Iliacus	0.25	0.10	0.17	0.20	0.09	0.16	0.21	0.16	0.09	0.15	0.16	0.05	0.16	0.09	0.25
Obturator Externus	0.00	0.01	0.00	0.01	0.00	0.01	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.00	0.02
Obturator Internus	0.04	0.05	0.02	0.01	0.00	0.03	0.00	0.02	0.02	0.01	0.02	0.02	0.02	0.00	0.05
Pectineus	0.03	0.01	0.04	0.04	0.01	0.01	0.00	0.01	0.02	0.02	0.02	0.01	0.01	0.00	0.04
Piriformis	0.06	0.02	0.04	0.01	0.00	0.03	0.04	0.05	0.08	0.05	0.04	0.02	0.04	0.00	0.08
Psoas Major	0.10	0.07	0.01	0.11	0.06	0.10	0.11	0.22	0.06	0.15	0.10	0.05	0.10	0.01	0.22
Quadratus Femoris	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.03	0.03	0.01	0.02	0.00	0.00	0.05
Tensor Fasciae Latae	0.09	0.07	0.07	0.03	0.05	0.07	0.11	0.20	0.09	0.06	0.09	0.04	0.07	0.03	0.20
PELVIS REGION	1.61	1.00	0.91	1.17	1.00	1.21	1.17	1.60	1.19	1.28	1.21	0.22	1.18	0.91	1.61
Adductor Brevis	0.00	0.00	0.00	0.02	0.01	0.00	0.02	0.02	0.01	0.00	0.01	0.01	0.01	0.00	0.02
Adductor Longus	0.02	0.02	0.03	0.07	0.05	0.02	0.15	0.02	0.03	0.02	0.04	0.04	0.03	0.02	0.15
Adductor Magnus	0.11	0.10	0.34	0.14	0.23	0.15	0.09	0.14	0.13	0.03	0.15	0.08	0.14	0.03	0.34
Biceps Femoris Caput Breve	0.13	0.08	0.02	0.08	0.06	0.09	0.13	0.01	0.08	0.07	0.08	0.04	0.08	0.01	0.13
Biceps Femoris Caput Longum	0.07	0.06	0.11	0.05	0.09	0.20	0.16	0.08	0.04	0.07	0.09	0.05	0.07	0.04	0.20
Gracilis	0.02	0.01	0.00	0.02	0.01	0.01	0.03	0.01	0.02	0.01	0.02	0.01	0.01	0.00	0.03
Rectus Femoris	0.20	0.10	0.13	0.28	0.09	0.19	0.13	0.10	0.13	0.18	0.15	0.06	0.13	0.09	0.28
Sartorius	0.11	0.03	0.01	0.04	0.01	0.01	0.04	0.07	0.06	0.04	0.04	0.03	0.04	0.01	0.11
Semimembranosus	0.08	0.07	0.07	0.06	0.03	0.06	0.01	0.20	0.01	0.07	0.07	0.05	0.06	0.01	0.20
Semitendinosus	0.11	0.11	0.08	0.15	0.07	0.01	0.10	0.01	0.04	0.07	0.07	0.05	0.08	0.01	0.15
Vastus Intermedius	0.02	0.15	0.02	0.01	0.20	0.09	0.00	0.05	0.04	0.00	0.06	0.07	0.03	0.00	0.20
Vastus Lateralis	0.06	0.01	0.01	0.05	0.08	0.15	0.17	0.01	0.01	0.01	0.06	0.06	0.03	0.01	0.17
Vastus Medialis	0.07	0.01	0.25	0.08	0.09	0.04	0.08	0.15	0.04	0.01	0.08	0.07	0.07	0.01	0.25
UPPER LEG	1.00	0.76	1.09	1.06	1.03	1.02	1.11	0.87	0.64	0.59	0.92	0.18	1.01	0.59	1.11
Extensor Digitorum Longus	0.01	0.04	0.02	0.04	0.01	0.03	0.06	0.04	0.04	0.02	0.03	0.02	0.03	0.01	0.06
Extensor Hallucis Longus	0.01	0.01	0.01	0.01	0.01	0.01	0.06	0.02	0.00	0.01	0.01	0.01	0.01	0.00	0.06
Flexor Digitorum Longus	0.00	0.00	0.02	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.01	0.01	0.00	0.00	0.04
Flexor Hallucis Longus	0.06	0.12	0.16	0.04	0.11	0.13	0.05	0.11	0.04	0.07	0.09	0.04	0.09	0.04	0.16
Gastrocnemius Lateralis	0.56	0.15	0.31	0.23	0.23	0.21	0.03	0.25	0.39	0.25	0.26	0.13	0.24	0.03	0.56
Gastrocnemius Medialis	0.15	0.13	0.66	0.48	0.59	0.25	0.59	0.37	0.08	0.72	0.40	0.23	0.42	0.08	0.72
Peroneus Brevis	0.02	0.00	0.02	0.02	0.01	0.01	0.00	0.01	0.00	0.00	0.01	0.01	0.01	0.00	0.02
Peroneus Longus	0.01	0.01	0.02	0.03	0.00	0.01	0.04	0.03	0.02	0.00	0.02	0.01	0.01	0.00	0.04
Plantaris	0.00	0.00	0.00	0.01	0.01	0.00	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.02
Popliteus	0.05	0.00	0.01	0.00	0.00	0.02	0.03	0.01	0.02	0.03	0.02	0.01	0.01	0.00	0.05
Soleus	1.16	0.86	0.98	0.40	1.04	1.15	0.86	0.84	0.77	0.57	0.86	0.23	0.86	0.40	1.16
Tibialis Anterior	0.08	0.06	0.06	0.11	0.05	0.07	0.07	0.05	0.11	0.16	0.08	0.03	0.07	0.05	0.16
Tibialis Posterior	0.04	0.03	0.13	0.01	0.01	0.02	0.02	0.06	0.01	0.05	0.04	0.04	0.03	0.01	0.13
LOWER LEG	2.16	1.42	2.41	1.38	2.08	1.90	1.84	1.83	1.50	1.88	1.84	0.31	1.86	1.38	2.41
LOWER EXTREMITY	4.77	3.18	4.40	3.62	4.10	4.12	4.12	4.31	3.33	3.74	3.97	0.47	4.11	3.18	4.77

Chapter 8

General discussion and recommendations

8.1 Summary of key results

In Chapter 1, the main goal of this thesis was defined as follows: to develop accurate and effective methods to create subject-specific musculoskeletal models of the lower extremity, and to assess whether personalization of model parameters results in improvements in the model predictions, in order to allow for their application in critical scenarios such as clinical decision making.

Extensive sensitivity analyses (Chapter 2 and Chapter 3) showed that small errors in model parameters can have a significant impact on the model force predictions, and that most of the accuracy of the model depends on the estimation of two points (origin, or pseudo-origin, and insertion, or pseudo-insertion, attachment sites) and three parameters (tendon slack length, nominal muscle fiber length and maximal isometric muscle force) for each muscle-tendon element. This sensitivity analyses provided quantitative information to draw up a priority list of the muscles and the parameters that need to be estimated most accurately to create a reliable subject-specific musculoskeletal model that satisfies the required accuracy of the specific application.

Since the original Twente Lower Extremity Model was not suitable to be combined with image-based personalization techniques, as it was not accompanied by detailed medical images and post-processing data, a new comprehensive dataset of the musculoskeletal geometry of the lower extremity was created, based on new medical images and dissection measurements of a single cadaver specimen (Chapter 4). TLEM 2.0 was purposely built to be easily combined with image-based scaling techniques, and represented the starting point of a streamlined modeling workflow that allowed to obtain subject-specific musculoskeletal geometry (Chapter 5) and muscle-tendon parameters (Chapter 6), based on MRI and functional measurements, in a semi-automatic way with limited manual intervention. This workflow was successfully applied to build ten subject-specific musculoskeletal models, in order to assess the differences between generic and personalized models and their effect on the model predictions during gait.

On average, subject-specific models presented large differences in musculoskeletal geometry parameters, such as body segment size, joint geometry, muscle-tendon attachment site position, muscle-tendon element length and muscle-tendon moment arms, when compared to generic models. These discrepancies resulted in different joint kinematics and net joint moments predicted by generic and subject-specific models when reproducing the same gait trials (Chapter 5). Moreover, personalized models presented large differences in the estimated values of tendon slack length, nominal muscle fiber length and maximal isometric muscle force. All these differences had a significant effect on the calculated muscle forces. Subject-specific models predicted more accurate maximum joint torques, and more realistic muscle activity during gait, indicating an improvement in the model outcomes compared to generic models. However, it was not possible to prove such improvements when comparing the predicted muscle activity with the measured EMG signals (Chapter 6).

To overcome this obstacle, the novel technique of positron emission tomography (PET) combined with the radioactive tracer [18F]-Fluoro-deoxy-glucose was used as an indirect validation tool for the model predictions (Chapter 7). When analyzing each individual subject, good to very good correlation was found between muscle metabolism measured using FDG-PET and metabolic energy consumption predicted by the musculoskeletal models. Moreover, higher correlation values were found when analyzing results averaged over ten healthy subjects, giving great confidence on the validity of the model outcomes when analyzing muscle coordination during gait. Correlation was slightly higher for subject-specific models compared to generic models, but it was not possible to prove the significance of this improvement.

In this final chapter, the added value and limitations of the main results of this thesis will be discussed. Subsequently, recommendations for further research towards clinical application of subject-specific musculoskeletal models are pictured.

8.2 Subject-specific musculoskeletal modeling: is it worth it?

8.2.1 Sensitivity analysis

The extensive sensitivity studies presented in this thesis (Chapter 2 and Chapter 3) represent the first comprehensive analyses that has been performed to assess individual sensitivity in all muscles of a detailed state-of-the-art musculoskeletal model such as the Twente Lower Extremity Model (Klein Horsman et al., 2007). The two metrics used in this studies (Local Sensitivity Index and Overall Sensitivity Index) allowed to distinguish muscles which make only little contributions to joint moments from muscles which have an important role during gait, giving an indication on which muscles and which parameters should be estimated most carefully when creating subject-specific models.

The sensitivity of the model was not merely determined by the size and length of the muscle being perturbed, but depended deeply on its specific role during gait (as shown previously by Ackland et al. (2012)) and on the capability of the model to compensate to each specific perturbation. Very high sensitivity values were found for muscles which were not included in previous analysis (Redl et al., 2007; Xiao et al., 2010; Ackland et al., 2012). Moreover, different sensitivity values were found for the same muscle to different musculoskeletal geometry and muscle-tendon parameters. All these results indicate how extensive sensitivity analyses are indeed essential to quantify the effect of personalizing parameters on the model predictions, but could be used also in clinical applications as an indication to how much perturbation can be tolerated by the musculoskeletal system before normal walking is affected, as suggested by van der Krogt et al. (2012).

Further research to quantify the sensitivity of model predictions to personalization of parameters for different activities of daily living, such as climbing stairs, or sitting and getting up from a chair, will indeed help to better understand the functionality of complex musculoskeletal models.

8.2.2 Streamlined modeling workflow

Based on the priority lists provided by the sensitivity analyses, we developed a streamlined modeling workflow that allowed to estimate musculoskeletal geometry and muscle-tendon parameters, in order to build detailed subject-specific models in an efficient way. To limit the number of measurements and the overall measurement time on subjects, in order to make the workflow feasible for clinical applications, a specific MRI scan protocol (measurement time < 45 minutes) was designed to yield optimal distinction between bone contours and muscle boundaries, while an extended set of dynamometry tests (measurement time < 6 hours) was used to optimize muscle-tendon parameters since no other methods allow to measure them for all muscles of the lower extremity. In order to reduce the time and manual intervention required to create subject-specific musculoskeletal models, the new Twente Lower Extremity Model 2.0 dataset (Chapter 4), which represents the first and most comprehensive musculoskeletal ‘template’ model of the lower extremity, was purposely built to be easily combined with image-based scaling techniques.

To assess the impact of each step of the modeling workflow, ten healthy subject-specific models were built, and a profound analysis of the effect of personalized parameters on the model predictions was performed (Chapter 5 and Chapter 6). First step in the workflow was the semi-automatic segmentation of bone contours from MRI (processing time < 2 hours). Then, identification of bony landmarks and joint geometry (manual intervention < 15 minutes) resulted in significant mean differences in the estimated body segment size (9.9 mm), joint center position (16.3 mm) and joint axis direction (12.2°) when compared to generic models. The completely automatic morphing from the TLEM 2.0 template to the subject-specific bones (processing time < 15 minutes) resulted in significant mean differences in the estimated muscle-tendon attachment site position (11.0 mm), which affected the muscle-tendon total length (9.7 mm corresponding to 6.5%) and moment arms (4.9 mm corresponding to 34.8%), with the largest differences affecting the most sensitive muscles. Personalization of musculoskeletal geometry had also a large effect on the estimated values of nominal muscle fiber length (mean difference 0.6 cm corresponding to 9.2%), tendon slack length (mean difference 1.2 cm corresponding to 10.2%) and maximal isometric muscle force (mean difference 94.9 N corresponding to 9.7%). These large differences indirectly demonstrated the added value of subject-specific models, since generic models cannot take into account inter-individual anatomical variability (White et al., 1989; Duda et al., 1996), hence the necessity of image-based models as previously indicated by Arnold et al. (2000) and Scheys et al. (2008).

Following step in the streamlined modeling workflow was the atlas-based non-rigid registration for the automatic segmentation of muscle volume contours from MRI (processing time < 1 day, manual intervention < 90 minutes), that resulted in significant mean differences in the calculated muscle volumes (37.2 cm³ corresponding to 34.7%) and in further differences in the estimated maximal isometric muscle force (279.5 N corresponding to 35.1%), indicating that generic models based on cadavers are unlikely to be representative of

healthy subjects, as shown by Tate et al. (2006). Finally, muscle-tendon parameters were automatically optimized to find the best possible match between the strength profiles measured during dynamometry trials and the maximum joint torques predicted by the model (processing time < 24 hours). This last step of the personalization workflow resulted in further larger mean differences in the estimated tendon slack length (1.6 cm corresponding to 16.5%), nominal muscle fiber length (1.1 cm corresponding to 15.3%) and maximal isometric muscle force (302.5 N corresponding to 38.2%).

8.2.3 Effect of subject-specific parameters on model predictions

At each step of the personalization, increasing differences in musculoskeletal geometry and muscle-tendon parameters affected the model predictions. Subject-specific musculoskeletal geometry resulted in different joint kinematics during gait, in particular for subtalar inversion/eversion (11.8°) and hip internal/external rotation (6.6°), with some subjects presenting differences larger than 20°, suggesting that generic models fail to accurately reproduce the gait kinematics, as previously shown by Scheys et al. (2011a). Moreover, large mean differences in the peaks of net joint moments during gait were found for subtalar eversion (0.12 Nm/kg corresponding to 39.85%) and hip extension (0.12 Nm/kg corresponding to 18.11%), followed by ankle plantarflexion (0.09 Nm/kg corresponding to 6.47%), hip flexion (0.07 Nm/kg corresponding to 12.49%) and hip abduction (0.06 Nm/kg corresponding to 6.85%). Following the workflow, increasing details in the muscle-tendon parameters affected the capacity of muscles to generate force, having an impact on the distribution of forces based on the muscle recruitment problem, and resulted in increasing mean differences in the predicted muscle-tendon force peaks (from 82.5 N up to 120.3 N) and muscle activity peaks (from 0.11 up to 0.21) during gait compared to the generic models. The impact of these differences on the model predictions, hence the necessity of personalized models, would depend on the specific application of the musculoskeletal model. In general, small differences (< 10%) in the predicted net joint moments or muscle forces will likely not be important when studying the basic principles of movements, for example muscle coordination during gait. On the other hand, such small differences can be crucial when an accurate estimation of muscle and joint functionality is required, for example to help a surgeon to select the optimal surgical plan for a patient. Using the presented modeling workflow, subject-specific models presented large differences (up to 40%) both in the model parameters and in the model predictions, and these differences are likely to increase when modeling patients affected by musculoskeletal pathologies, indicating that personalized models are indeed necessary for clinical applications such as surgical planning and clinical decision-making processes (Jonkers et al., 2008; Lenaerts et al., 2009; Scheys et al., 2011b).

8.2.4 Are subject-specific models more accurate?

Having assessed that personalization of musculoskeletal models results in large differences in the model predictions, it is important to prove that these differences are improvements

indeed. When comparing the measured and the predicted maximum joint torques, each step of the modeling workflow resulted in a significant reduction of the root mean square error (from 47.5 Nm, corresponding to 50.7%, down to 23.2 Nm, corresponding to 21.2%) compared to generic models (64.1 Nm, corresponding to 63.9%), hence showing a clear improvement of subject-specific model predictions. Moreover, personalized models resulted in a reduction of the predicted activity to more realistic values (< 1) for the most important muscles during gait. However, when comparing the predicted muscle activity with the measured EMG signal, it was not possible to prove any significant improvement, since the personalization affected mostly the magnitude of the muscle activity but not the timing, and likely due to the limitations of EMG as a reliable validation tool (Lund et al., 2012).

To further test the subject-specific model predictions, a novel technique of indirect validation was proven by using the positron emission tomography (PET) combined with the radioactive tracer [18F]-Fluoro-deoxy-glucose (Chapter 7), which has been recently used to show functional differences in muscle recruitment (Shimada et al., 2009; Rudroff et al., 2013; Kolk et al., 2015). When analyzing each individual subject, good to very good correlation was found between muscle metabolism measured using FDG-PET and metabolic energy consumption predicted by the musculoskeletal models (Spearman's $\rho=0.87\pm0.04$, Pearson's $r=0.77\pm0.10$). Musculoskeletal models were able to correctly predict very high metabolic energy consumption during walking not only for ankle plantarflexor muscles, as previously indicated in literature (Winter, 1983; Liu et al., 2006), but also for a deep and relatively small muscle like the Gluteus Minimus. These results showed the advantages of FDG-PET as a complimentary validation tool to EMG, which is limited to measure only few superficial muscles. Moreover, higher correlation values were found when analyzing results averaged over ten healthy subjects (Spearman's $\rho=0.96$, Pearson's $r=0.91$), giving great confidence on the validity of the model outcomes when analyzing muscle coordination during gait. Again, correlation was slightly higher for subject-specific models compared to generic models, but it was not possible to prove the significance of this improvement.

8.2.5 Limitations in the validation process

It is important to note that the validation process itself still represents a critical limitation in musculoskeletal mechanics (Lund et al., 2012), and that current non-invasive techniques are likely not accurate enough to detect the improvements of personalized models based on healthy subjects. Future research should focus on improving existing validation techniques and developing new validation tools that are able to reliably verify the distribution of forces between the muscles contained in the model. Moreover, all the results presented in this thesis were obtained with simulations of gait, but it is likely that more strenuous activities, such as getting up from a chair, climbing stairs or running, elicit larger differences between subject-specific and generic musculoskeletal models. Also, results are likely to be different when analyzing patients affected by musculoskeletal pathologies, where larger differences in musculoskeletal geometry and muscle-tendon parameters are expected. Hence, additional

validation is essential to further demonstrate the improvements of subject-specific model predictions, in order to gain credibility amongst surgeons and patients before clinical application.

Efficiency of the presented modeling workflow has been shown in this thesis by building a unique set of ten subject-specific musculoskeletal models, while flexibility and robustness of the workflow has been proven in other studies: osteosarcoma and soft-tissue sarcoma patient-specific models built by Fluit (2015) provided more realistic muscle activity patterns than generic models, while the knee arthroplasty patient-specific model developed by Marra et al. (2015) was successfully validated against in-vivo measured knee joint reaction forces, winning the “5th Grand Challenge Competition to Predict In Vivo Knee Loads” (Fregly et al., 2012) at the 7th World Congress of Biomechanics (July 6–11, 2014, Boston, MA, U.S.A.). Future research should focus on collecting more consistent functional datasets (including medical images, maximum joint torques, kinematics and kinetics data, EMG and FDG-PET measurements, and possibly in-vivo joint reaction forces during different motor tasks), for several healthy subjects and patients. These new datasets could be used to develop a virtual population of personalized models, in order to further validate model predictions.

8.2.6 Limitations in the modeling workflow

Several limitations of the methods presented in this thesis could have affected the model predictions, overshadowing the improvements of subject-specific models, and should be recognized, in order to indicate future research opportunities that might improve the accuracy of personalized model predictions.

The main bottleneck of the subject-specific modeling workflow lies in the accuracy of the available medical images. An improvement of the resolution would obviously require an increase in the acquisition and processing time, affecting the feasibility for clinical applications. In the future, every step of the workflow could be further improved or made more efficient following the progress of medical imaging techniques. New scanners with increased spatial resolution (without increasing the scan time) would obviously improve the quality of the segmented bone surfaces, morphed attachment sites and registered muscle volumes, allowing to estimate subject-specific properties of the ankle and subtalar joints too. Moreover, new imaging techniques could be added to the workflow. For example, kinematic MRI (Shellock, 2003), cine-phase contrast MRI (Sheehan et al., 1999; Asakawa et al., 2003), multi-slice real-time MRI (Gilles et al., 2005) or X-ray fluoroscopy (Tashman et al., 2003) would allow to improve the accuracy of the estimated joint geometry and the predicted muscle deformations. Furthermore, non-invasive methods have been introduced to measure subject-specific muscle-tendon parameters, such as muscle fiber length, pennation angle and PCSA, by using diffusion tensor MRI (Cleveland et al., 1976; Damon et al., 2002; Heemskerk et al., 2005; Lansdown et al., 2007; Longwei, 2012) or ultrasound (Rutherford et al., 1992; Fukunaga et al., 1997; Maganaris et al., 1999; Fry et al., 2004). Unfortunately, the cost and time associated with data acquisition and the substantial manual processing required by these

methods make them still infeasible to be used in clinical scenarios. Future research in the next years should evaluate the advancements in the state-of-the-art imaging processing techniques, and compare the added value of each new technique (improvements in the estimated model parameters and in the model predictions) with its cost (time, money, special equipment and manual intervention required), in order to design an optimal measurement set-up to extract maximum subject-specific information from a minimum set of measurements. The new TLEM 2.0 model is, by definition and for computational reasons, a simplified description of the complex human musculoskeletal system. Hence, every model assumption results in inaccuracies on the model predictions. For example, the simple 1 degree of freedom knee joint used in the model can be good enough for movements with relatively small knee flexion angles, such as walking, while motor tasks with very large joint angles, for example deep squat, would require a more sophisticated joint definition. TLEM 2.0 has been proven to be adaptable to include a detailed 11 degrees of freedom force-dependent-kinematic knee complex joint (Marra et al., 2015). However, the complexity added to the model had a large effect on the computational power required to run the model, increasing the time necessary to perform an inverse dynamics simulation of gait from few minutes to several hours. Similarly, the foot is represented by one single rigid body. Inaccurate description of the deformation of the foot when it hits the ground would affect the position of the ankle joint, resulting in errors in the predicted net joint moments and muscle forces. The development of a sophisticated foot model was outside the scope of this study. Future research could focus on the integration of a detailed foot model, for example the Glasgow-Maastricht AnyBody Foot Model (Tørholm et al., 2013), in the TLEM 2.0 dataset, upon image-based scaling.

Another modeling assumption is the description of muscles with a discrete number of independent straight or curved lines. Future studies could evaluate the possibility to use the segmented muscle volumes of TLEM 2.0 to create a 3D finite element model (Johansson et al., 2000; Blemker et al., 2005). This solution would result in an improved estimation of muscle-tendon moment arms (Webb et al., 2014) and in a better representation of complex deformation and force transmission between muscles (Huijing, 1999; Yucesoy et al., 2002; Bernabei et al., 2015). Moreover, the use of personalized finite element models would allow to obtain a better prediction of bone density remodeling and healing (Vahdati et al., 2014), or individualized predictions of fracture risk or peri-prosthetic micromotions (van der Ploeg et al., 2012). However, the computational cost of these finite element models would make them impractical to simulate complex movements such as walking, hence not feasible for clinical applications. In general, every time complexity is added to the model, improvements in the model predictions should be assessed and compared with the computational power and the extra parameters required to run the model.

8.2.7 Limitations in the inverse dynamics approach

Another source of errors for the model predictions lies in the assumptions of the inverse dynamics approach. All the simulations in this thesis used measured optical markers

trajectories and force plates data as input. However, errors associated with non-rigid movement of the soft-tissue interface between the skin markers and the underlying bone, referred to as soft-tissue artifacts, limit the accuracy with which the motion capture techniques can be used to record 3D joint motion in vivo (Cappozzo et al., 1996; Reinschmidt et al., 1997; Leardini et al., 2005; Akbarshahi et al., 2010). Also, the inaccuracies in the measured kinematic and kinetic data (Pàmies-Vilà et al., 2012) result in dynamic inconsistency that can lead to errors in the predicted net joint moments and muscle forces (Kuo, 1998). Therefore, limitations of these measurement inaccuracies would help to reduce errors in model outcomes.

Another assumption of the inverse dynamics approach is the optimization criterion used to solve the muscle recruitment problem. All the simulations in this thesis were run using a cost function that minimized the cubed muscle activity (Crowninshield et al., 1981). However, there is no proven relation between this cost function and the actual distribution of forces over different muscles, hence this simplification of the neural control of gait may not be accurate and might have a large effect on the model predictions. It is likely that a physiologically more realistic cost function, in combination with subject-specific models, will result in a more accurate estimation of muscle forces and hence joint reaction forces. Praagman et al. (2006) proposed a new cost function, based on muscle energy consumption, which showed better agreement with near infrared spectroscopy (NIRS) measurements. Future research should investigate the effect of an energy based cost function on the subject-specific model predictions. Moreover, since the glucose uptake measured using FDG-PET reflects the different metabolism between muscles and between fibers within a muscle (Kalliokoski et al., 2011), all this data represent valuable information to improve the cost function and to better understand the distribution of forces within larger muscles described by multiple muscle-tendon elements.

8.2.8 Sharing the knowledge

With great confidence about the importance of these findings for the field of subject-specific modeling, most of the data and methods presented in this thesis are freely available for non-commercial use, so that they can be used by the scientific community for their own research purposes, for instance to improve or develop new personalization techniques. TLEM 2.0 and TLEMsafe healthy subjects dataset, including medical images and post-processing data, are available upon request to be sent to the TLEMsafe project coordinator, prof. dr. ir. Nico Verdonshot (n.verdonshot@utwente.nl), after approval of the TLEMsafe consortium. The TLEM 2.0 musculoskeletal model is freely available to be downloaded at the website <http://www.utwente.nl/ctw/bw/research/projects/TLEMsafe> under acceptance of the TLEMsafe Research License Agreement. Up to date, the TLEM 2.0 musculoskeletal model has been requested and downloaded by more than 40 researchers from all around the world. Moreover, the TLEM 2.0 musculoskeletal model has been implemented in the AnyBody Modeling System™ (AnyBody Technology A/S, Aalborg, Denmark) (Damsgaard et al.,

2006) and will be distributed in a future release of the modeling software package to a much larger audience. Moreover, automatic image-based scaling techniques used in this thesis, such as bone morphing and muscle volume registration, were implemented into the commercial software Mimics® Innovation Suite (Materialise N.V., Leuven, Belgium). We strongly believe that this represents a great opportunity to further valorize the scientific contribution of this thesis, and will help to accelerate the development and adoption of subject-specific models on large scale, achieving the validity and reliability necessary in critical applications such as clinical decision making.

8.3 Recommendations for future research towards clinical application

Even though significant improvements have been achieved to build detailed subject-specific musculoskeletal models in an efficient way, several steps are necessary before reaching the ambitious goal of routinely using personalized models in clinical applications.

When using models to predict the functional outcome of a patient after orthopedic surgery, movement data of the patient are not available, and using pre-recorded measurements from different subjects would lead to obvious inconsistency. Future research should focus on eliminating the dependency of inverse dynamics simulations on measured kinematic and kinetic data. Many forward dynamics methods have been developed in recent years to predict gait movements (Fluit et al., 2012; Wang et al., 2012), but their validity has not been proven yet, and their complexity and large computational cost would prevent their application in a clinical setting. To deal with this restriction, principal component analysis (PCA) has been proposed to interpret and evaluate gait data (Daffertshofer et al., 2004) and predict new gait movements (Safonova et al., 2004; Fluit et al., 2014b), eliminating the dependency of the model on measured kinematic input data. Also, deriving the force plates data from three-dimensional full-body motion (Robert et al., 2013; Fluit et al., 2014a) represents a promising technique to both improve the dynamic consistency as well as remove the dependency of the model on measured external forces. Within the TLEMsafe project, Fluit (2015) combined patient-specific models with completely predicted motion and ground reaction forces, with no input from the gait lab, and showed the validity of this method compared to traditional inverse dynamics based simulations.

Today, the functional outcome of a surgical operation is predicted based only on the mechanical properties of the musculoskeletal model, with the neural control of the movement system represented by optimization criteria that minimize muscle activity or muscle energy. However, it is likely that patients will activate their muscles in a way that minimizes pain or fatigue, depending on their age and physical conditions. Moreover, psychology and personality play a significant role in the recovery of patients after surgery. Future research in the neural control and in the adaptive capacity of patients will allow to better predict and even improve the post-operative situation.

Finally, the modeling workflow presented in this thesis was part of the bigger TLEMsafe patient workflow (Chapter 1), where all the different steps were successfully linked and it was proved the possibility to create a personalized musculoskeletal model, perform a virtual surgical operation on it, and exactly reproduce it in the operating room. To reach this goal, special care was taken that the final user of the system, i.e. the surgeon without a technical background, was able to manipulate the musculoskeletal model in a virtual reality environment, visualize and understand the results of a simulation after surgery in order to choose the optimal plan, and follow the instructions of a surgical navigation system. Hence, it is clear that future work should focus to make musculoskeletal models and graphical interfaces simpler and more user-friendly, in order to guarantee that clinical personnel are able to use modeling software in an efficient way, before musculoskeletal models are applied in clinical scenarios on a large scale.

8.4 Concluding remarks

This thesis represents an important step toward efficient subject-specific modeling of the lower extremity. Extensive sensitivity analyses were performed to assess which are the muscles and the parameters that require most accuracy when creating a personalized model. Then, a new complete and consistent musculoskeletal dataset was created from medical images and cadaver measurements. This new model represented the starting point of a streamlined modeling workflow that allowed to build ten subject-specific model in a fast and automatic way with limited manual intervention. Large differences in the musculoskeletal geometry and muscle-tendon parameters between generic and subject-specific models proved that, for clinical applications that require an accurate description of the musculoskeletal system, generic model are insufficient and subject-specific models are required. Moreover, personalization had a large effect on the model force predictions, resulting in more accurate maximum joint torques and more realistic muscle activity. However, it was not possible to prove significant improvements in the subject-specific model predictions, likely due to the limitations of the current validation techniques.

The findings in this thesis show that recent advancements in musculoskeletal mechanics, medical imaging and computer science allow today to build a subject-specific model of the lower extremity in an efficient way, and the improvements in the model predictions make the personalization process worth the effort. However, to avoid that these results are fruitless, future research is necessary to make the necessary steps towards clinical application, amongst others, on reducing the dependency of the model on measured kinematic and kinetic data, improving the cost function of muscle recruitment problem, and developing new validation techniques. We expect personalization techniques to evolve in the near future, increasing our confidence in the individual predictions of musculoskeletal models, and we hope that this thesis represents a solid foundation to reach the ambitious goal of application of subject-specific musculoskeletal models in clinical scenarios on a large scale.

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Acknowledgements

It all started many years ago, when I read about a PhD position on “Prediction of the functional effects due to surgery on the musculoskeletal system of patients using the Twente Lower Extremity Model”. Musculoskeletal models? Predicting surgical effects? Never heard of that before. Twente? Enschede? Where is that place? And how do you pronounce it? But it was so interesting and challenging, so I decided to apply for that position... and here we are now: MIJN PROEFSRIPT IS KLAAR!!!

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bureaucracy or with a flat tire... *Wat een atypische Nederlander!* And Vera, we experienced together the good and bad of being PhD students. At the beginning, great trips around the world to attend conferences, drinking beers at Belgian pubs or caipirinha on the ocean shore, and being late at morning sessions. In the end, being repeatedly asked ‘Have you finished your thesis?’ and ‘Do you have a date?’. Now that my thesis is finally completed, I look forward to attend your defence very soon. By the way... *Do you have a date?*

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Vincenzo Carbone

About the author

Vincenzo Carbone was born in Andria, Italy, on 23rd February 1984, and grew up with his family in Barletta, Italy. In 2002 and 2003, he took part in the national finals of the high school contest “Olimpiadi della Matematica”. This experience greatly aroused his interest in applied mathematics.

In 2003 he started studying Mathematical Modeling in Engineering at the Politecnico di Torino, Italy. During his master, he developed a strong passion for the application of mathematics and technology to medicine and healthcare. In 2009 he received a double M.Sc. degree from the Politecnico di Torino, Italy, and the Politecnico di Milano, Italy. The subject of his master thesis was “Multiphase modeling of tumor growth in Islets of Langerhans”, supervised by prof. dr. Luigi Preziosi. He also received his Diploma from the Alta Scuola Politecnica, where he was a member of the multidisciplinary research project “InfMed - Quantitative methods in cancer treatment: engineering supports the clinical analysis”, in collaboration with the Institute for Cancer Research and Treatment in Candiolo, Italy. The subject of his final report was “Mathematical modeling, collaboration and knowledge sharing for cancer research improvement”.

In 2010 he was employed as PhD researcher at the Laboratory of Biomechanical Engineering at the Faculty of Engineering Technology of the University of Twente, Enschede, the Netherlands. His research, conducted under supervision of prof. dr. ir. Nico Verdonshot and prof. dr. ir. Bart Koopman, focused on the creation and validation of subject-specific musculoskeletal models of the lower extremity, based on medical imaging and functional measurements. His research was carried out within the TLEMsafe project, coordinated by prof. dr. ir. Nico Verdonshot and funded by the European Union under the Seventh Framework Programme (FP7). Goal of TLEMsafe was to create a patient-specific surgical navigation system, to help surgeons to reach optimal functional results for the patient after complex orthopedic operations. In addition to his doctoral studies, from 2013 to 2015 he worked as manager for the TLEMsafe project.

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