

**SUBJECT-SPECIFIC MUSCULOSKELETAL MODELING OF THE
LOWER EXTREMITIES IN PERSONS WITH UNILATERAL
CEREBRAL PALSY**

by

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May 2011
Technical reports from
Royal Institute of Technology
KTH Mechanics
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ABSTRACT

The computational musculoskeletal models that are used to study muscle moment-generating capacities of persons with movement disorders and planning treatment options must be accurate, and take into account the inter-individual variability of musculoskeletal geometry.

In Paper I the methods of creating the subject-specific musculoskeletal model of the lower extremities from magnetic resonance images (MRIs) were developed. The subject-specific model was used to analyze hip, knee and ankle muscle moment arms (MALs) and muscle-tendon lengths (MTLs) during gait in a subject with unilateral cerebral palsy (CP), and to evaluate the accuracy of widespread and commonly-used scaled generic model.

It was found that the scaled generic model delivered accurate values for changes in MTLs in most muscles. However, the scaled generic and the subject-specific lower extremity musculoskeletal models showed substantial differences in MALs calculated during gait.

In Paper II subject-specific musculoskeletal models of nine subjects with unilateral CP were created to study muscles volumes, MTLs and MALs; and to examine the accuracy of MALs calculated by the scaled generic models.

It was shown that the scaled generic model significantly underestimated hip MALs discrepancies between the affected and the non-affected sides of the lower extremities. However, it significantly overestimated hip adduction/abduction of gluteus maximus, gluteus medius, gluteus minimus, tensor fascia latae and biceps femoris long head; and hip flexion of adductor longus and rectus femoris in the affected and the non-affected sides.

It was also found that muscle volumes and hip abduction MALs in gluteus medius and gluteus minimus, hip flexion MALs in iliacus and hip rotation in gluteus maximus were smaller in the affected side of lower extremities. MTLs in the affected and the non-affected sides throughout the range of hip motion were similar.

This thesis suggests the need for the subject-specific musculoskeletal models that can account for variability of muscle attachments and musculoskeletal geometry of persons with movement disorders. Based on inaccuracies of the scaled generic model reported here, the generic models that are used to guide treatment decisions must be tested, and interpreted with care.

Descriptions: cerebral palsy, moment arm, muscle length, hemiplegic, MRI, subject-specific, musculoskeletal modeling, lower extremities, muscle volume.

PREFACE

This thesis is based upon studies conducted during April 2009 to May 2011 at the Department of Mechanical Engineering, Royal Institute of Technology, Stockholm, Sweden; and is built on the following papers, which will be referred to in the text by their Roman numerals.

I. **Klets O**, Riad J, Broström EW, Gutierrez-Farewik EM. Comparison between a subject-specific and a scaled generic musculoskeletal model of the lower extremities in a subject with unilateral cerebral palsy. *Clinical Biomechanics*, April 2011, submitted.

II. **Klets O**, Riad J, Broström EW, Gutierrez-Farewik EM. Moment-generating biomechanical factors of hip muscles in persons with unilateral CP with subject-specific models. *Gait&Posture*, May 2011, submitted

Division of work between authors

The research was initiated by Dr. Elena Gutierrez-Farewik (EGF), who was the main supervisor and co-author in Paper I and Paper II.

Dr. Eva Weidenhielm Broström (EWB) provided the gait analysis. Dr. Jacques Riad (JR) provided medical imaging data of studied subjects. EWB and JR were clinical advisors.

The methods of building the subject-specific musculoskeletal models were developed by Olesya Klets (OK). The calculations were done by OK with supervision from EGF. Articles were written by OK with input from EGF, JR and EWB.

LIST OF ABBREVIATIONS

3D	Three-dimensional
CP	Cerebral palsy
CT	Computer tomography
EMG	Electromyography
MTL	Muscle-tendon length
MAL	Muscle moment arm length
MRI	Magnetic resonance imaging

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1. INTRODUCTION

For an airplane, mechanics enables us to design its structure and predict its performance. For an organism, biomechanics helps us to understand its normal function, predict changes due to alterations, and propose methods of artificial intervention.

(Fung Y, 1993)

Biomechanics is a modern science with ancient roots. One of the earliest books covering the concepts of biomechanics was *On the Parts of Animal* by Aristotle (384-322 B.C.), where the anatomy and function of internal organs is described. Decartes, a great mathematician, suggested a physiological theory upon mechanical grounds. Giovanni Alfonso Borelli, the Italian mathematician and astronomer, successfully explained muscular movement and body dynamics In *On Motion of Animals (De Motu Animalium)* (1680).

Newton's laws of motion are often the basis for biomechanics, since it is difficult to find anything living that does not involve some mechanical problems. Muscles transmit forces through tendons, which connect to bones and span joints that have complicated kinematics [118]. Biomechanical engineers are interested how the geometric relationships among the muscles and bones transform muscle forces into moments about the joints during a variety of activities and under many conditions [36].

Quantifying the muscle moment-generating capacities, forces and muscle lengths in various situations or during different activities may be of value from a medical viewpoint. In sports medicine, biomechanics can be applied to improve performance with minimal risks to muscles and joint structures. In orthopedics, which deals with musculoskeletal problems, biomechanics is used to investigate mechanically the function of diseased muscles or the effects of musculoskeletal deformities on movement patterns, to explore the relationships between muscle excitation and movement, to evaluate joint loading during different movements, to plan a treatment and to adjust post-surgical rehabilitation and physical therapy with minimal risks to damaged or weak structures [9].

1.1. Biomechanics of skeletal muscle

Skeletal muscles provide strength and protection to the skeleton by distributing loads and absorbing shock. The skeletal muscles perform both dynamic and static work. Dynamic work permits locomotion and the positioning of the body segments in space. Static work maintains body posture or position [82]. Such abilities usually represent the action of muscle groups, not of individual muscles.

The tendons and the connective tissues in and around the muscle belly are viscoelastic structures that help to determine the mechanics characteristics of whole muscle during contraction [66].

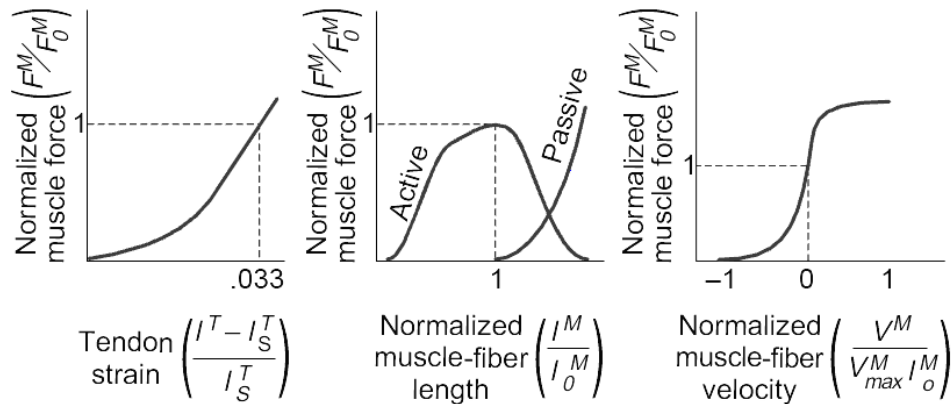


Figure 1.1. Dimensionless model of muscle and tendon. Adapted from Delp et al.[37]

Muscle force is the sum of active muscle force excited by the nervous system and passive force when stretched [83;84] (middle plot) (Fig 1.1). This force is dependent on muscle fiber length (middle plot) and velocity (right plot). Muscle is in series with tendon, which is represented by a nonlinear elastic element (left plot). The pennation angle, α , is the angle between the muscle fibers and the tendon. The forces in muscle and tendon are normalized by peak isometric muscle force (F_0^M). Muscle-fiber length (l^M) and tendon length (l^T) are normalized by optimal muscle fiber length (l_0^M). Tendon slack length (l_S^T) is the length at which tendons begin to transmit force when stretched. Velocities are normalized by the maximum contraction velocity of muscle (v_{max}^M). For a given muscle-tendon length (l^{MT}), velocity, and activation level, the model computes muscle force (F^M) and tendon force (F^T).

1.2. Functional anatomy of the lower extremities

The lower extremity includes the hip, knee, and ankle joints, and the bones of the thigh, leg, and foot [62]. The bones of the human leg are femur, tibia, fibula, patella, talus, calcaneus, cuboid, navicular, cuneiforms, metatarsus, and phalanges. Muscles of the lower extremities are presented in Table 1.2 and Table 1.3.

Table 1.2. Function of hip muscles.

Hip movement	Muscles	Hip movement	Muscles
Extension	Gluteus maximus	Lateral rotation	Sartorius
	Gluteus medius		Quadratus femoris
	Gluteus minimus		Obturator internus
	Adductor magnus		Gluteus medius
	Piriformis		Gluteus minimus
	Semimembranosus		Psoas
	Semitendinosus		Iliacus
Biceps femoris long head	Gluteus maximus		
Flexion	Iliacus		Obturator externus
	Psoas		Adductor magnus
	Tensor fascia latae	Semitendinosus	
	Pectineus	Adductor longus	
	Adductor longus	Adductor brevis	
	Adductor brevis	Piriformis	
	Gracilis	Medial rotation	Gluteus medius
	Rectus femoris		Gluteus minimus
Sartorius	Tensor fascia latae		
Abduction	Gluteus medius	Adductor magnus	
	Tensor fascia latae	Pectineus	
	Gluteus maximus		
	Gluteus minimus		
	Piriformis		
Adduction	Obturator internus		
	Adductor magnus		
	Semitendinosus		
	Adductor longus		
	Adductor brevis		
	Gluteus maximus		
	Gracilis		
	Pectineus		
Quadratus femoris			
Obturator externus			

Table 1.3. Function of knee and ankle muscles [62].

Knee movement	Muscles
Extension	Tensor fascia latae
	Vastus lateralis
	Vastus medialis
	Vastus intermedius
Flexion	Rectus femoris
	Semimembranosus
	Semitendinosus
	Biceps femoris
	Gracilis
	Sartorius
Medial rotation	Popliteus
	Gastrocnemius
	Semimembranosus
	Semitendinosus
	Gracilis
Lateral rotation	Sartorius
	Popliteus
	Biceps femoris
	Tensor fascia latae

Ankle movement	Muscles
Dorsiflexion	Tibialis anterior
	Extensor digitorum longus
	Extensor hallucis longus
Plantarflexion	Peroneus longus
	Peroneus brevis
	Flexor digitorum longus
	Tibialis posterior
Eversion	Peroneus longus
	Peroneus brevis
	Extensor digitorum longus
	peroneus tertius
Inversion	Tibialis posterior
	Flexor hallucis longus
	Flexor digitorum longus
	Tibialis anterior

The hip joint with three degree of freedom, is a ball and socket joint consisting of the articulation between the acetabulum on the pelvis and the head of the femur. It can be generally characterized as stable yet mobile. The hip joint allows the thigh to move through a wide range of motion in three directions. The thigh moves through approximately 120° to 125° of flexion, 10° to 15° of hyperextension, 30° to 45° of abduction, 15° to 30° of adduction, 30° to 50° of external rotation, and 30° to 50° of internal rotation [62] (Fig. 1.2).

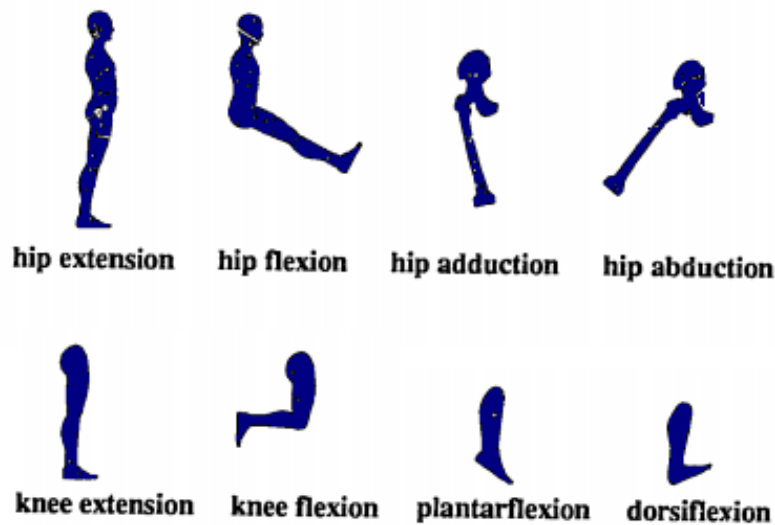


Figure 1.2. The definition of joint motions [34]

The knee joint supports the weight of the body and transmits forces from the ground while allowing a great deal of movement between the femur and the tibia [62]. There are three articulations in the region known as knee joint: the tibiofemoral joint, the patellofemoral joint, and the superior tibiofibular joint. The movements at the knee joint are flexion (130° to 145°) and extension (1° to 7°) [62].

The foot and ankle that make up a complex anatomical structure of 26 irregularly shaped bones and 30 synovial joints. Most of the motion in the foot occurs at three of the synovial joints: the talocrural, the subtalar, and the midtarsal joints. The foot contributes significantly to the function of the whole lower limb. The foot supports the weight of the body in both standing and locomotion. Plantarflexion is the movement in which the bottom of the foot moves down and the angle formed between the foot and the leg increases (the range of motion is approximately 50°). Dorsiflexion occurs at the ankle joint as the foot moves forward the leg or as the leg moves forward the foot (20°) [62].

1.3. Cerebral palsy

About 1 in 500 babies born in Sweden have cerebral palsy [2]. CP is a term used to describe a group of chronic conditions affecting body movements and muscle coordination [116]. It is caused by damage to one or more specific areas of the brain, usually occurring during fetal development or infancy [51].

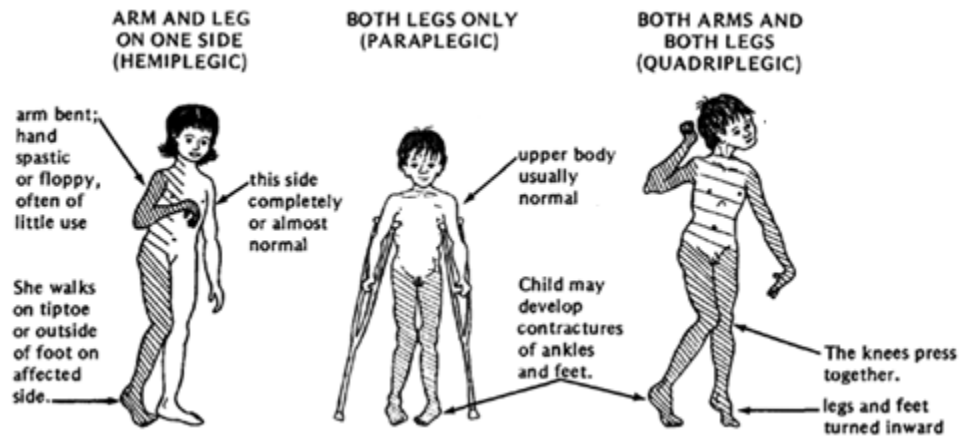


Figure 1.3. Types of cerebral palsy [1].

In a case of spastic cerebral palsy (Fig. 1.3) the affected muscles are more stiff than normal [3]. The degree of spasticity in an affected arm or leg can vary greatly from case to case. Movements of an affected arm or leg are less flexible [50]. The stiffness of the muscles in spastic cerebral palsy can gradually lead to permanent fixed contractures of joints in arms and legs. Some joints may eventually become 'fixed' in a flexed position as a child becomes older. The main aim of treatment for spastic cerebral palsy is to keep to a minimum the effects of the muscle stiffness [51;105].

Unilateral CP, traditionally called hemiplegic CP, is a form of spastic CP, in which one arm and leg on either the right or left side of the body are affected [5]. Individuals with unilateral CP exhibit asymmetry between the affected and the non-affected sides [85], e.g. decreased muscle volume in the affected side [71;77] and significant leg length discrepancy [95].

1.4. Motion analysis

Locomotion is the process of self-propulsion by which one moves from one geographic position to another [98]. The human body integrates the motions of the various segments of the body during walking and controls the activity of the muscles so that the metabolic energy required for a given distance walked is minimized. Different gaits are characterized by differences in limb movement patterns, overall velocity, forces, kinetic and potential energy cycles, and changes in the contact with the ground [93].

The gait cycle describes the motions from initial placement of the supporting heel on the ground to when the same heel contacts the ground for a second time. The gait cycle (Fig. 1.4) is divided into stance phase, which is an interval in which the foot is on the ground (60% of the gait cycle), and swing phase, which is the interval when the foot is not in contact with the ground (40% of the gait cycle).

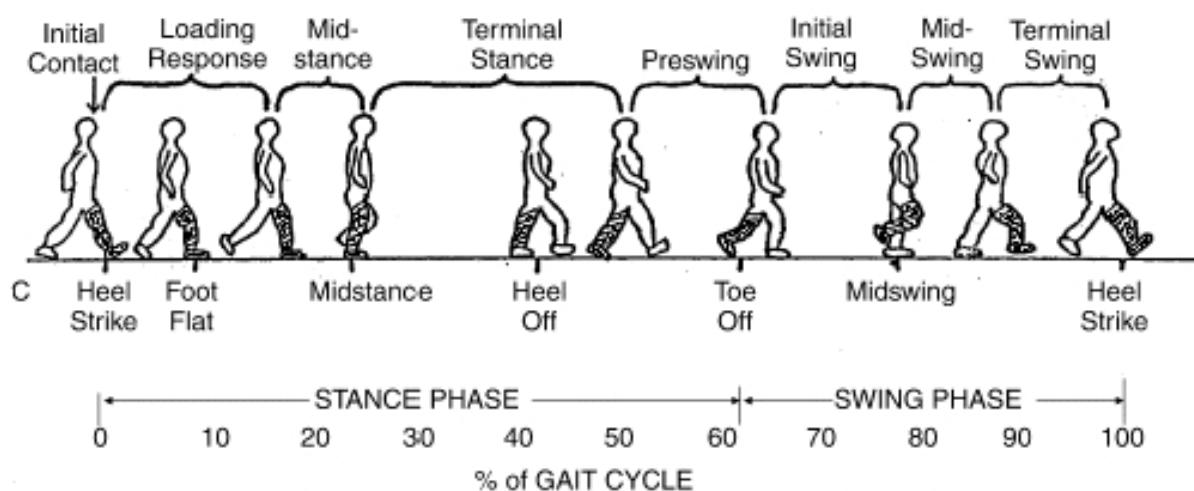


Figure 1.4. Gait cycle. Modified from Cuccurullo[32].

Motion capture is used to describe the process of recording motion and translating that movement into a digital model. Most motion capture systems detect the movement by the use of reflective skin markers placed on anatomical landmarks. Force platforms are used to accurately acquire ground reaction forces during gait, dynamic electromyography (EMG) in

evaluating and recording the electrical activity in skeletal muscles [26;45]. Gait analysis, often consisting of joint kinematics, kinetics and dynamic EMG data [33;80], is the major application of a motion capture in orthopedics [16;49;52], and is used to define movement deviations and the various functional deficits related to complex neuromuscular conditions such as CP [107]. Postoperatively, it provides an accurate assessment of outcome [53] that enables objective evaluation of surgeries [48]. However, instrumental errors, anatomical landmark misplacement [70], and soft tissue artefacts may lead to inaccurate conclusions made by gait analysis [28;30]. Novel methods have been applied to minimize the effect of skin movement on the accuracy of recorded markers trajectories on space [4;27;74].

The data from gait analysis (GA) not only should be collected in a standardized way but also must be calculated with appropriate methods. This requires an accurate underlying computational musculoskeletal model.

1.5. Generic musculoskeletal models

Computational musculoskeletal models allow quantifying factors (e.g. muscle moment arms, joint motions) that affect musculoskeletal function, and may help clinicians to improve clinical outcomes of the necessary treatments [8;10;11;11;14;38;61]. Musculoskeletal models have been used to study stroke [65], spinal cord injury [88], osteoarthritis [55;56] and neurological deficits such as CP [35]

However, the existing musculoskeletal models in use have limitations. Most of the software packages for biomechanical analysis of muscle function are based on biomechanical studies of cadaveric specimens [13;36], and use the musculoskeletal geometry of a healthy, average-sized adult male with normal musculoskeletal geometry [10;36;38]. These generic models apply variations in subject size by scaling [40;43;76], based on three-dimensional positions of markers placed on selected anatomical landmarks and measured during a static, standing trial. Generic models were used to simulate bone deformities[8], osteotomies [44;104], and tendon transfer surgeries [40]. However, a recent study has proved that such models provide inaccurate analysis of muscle function even for a healthy adult male [102].

The musculoskeletal system is very intricate and large anatomical variations exist among individuals. The musculoskeletal geometry determines moment arm and thereby the moment about a joint produced by a given musculotendon force [68;117;118]. Duda et al [41] have studied how variability of muscle attachments affects muscle moment arms (MALs). The effects of bone geometry on the moment-generating capacity of the muscles has been shown by Delp et al.[39] Thus, the different musculoskeletal geometry due to size

or pathology can also affect the accuracy of results derived from generic models. A recent study [100] has demonstrated the inaccuracy of gait kinematics calculated by the scaled generic models in subjects with increased femoral anteversion. It was reported that the muscle-tendon length (MTLs) calculated with a generic model are erroneous if compared with subject-specific models in children with CP and crouch gait [7]. It was shown that scaled generic models provide inaccurate analysis of MALs and MTLs in CP children with altered femoral geometry [103].

Since the results of simulations are often sensitive to the accuracy of the functional musculoskeletal model, individualized musculoskeletal models may be a better alternative [73;113].

1.6. Subject-specific musculoskeletal models

Defining the geometry of a complex musculoskeletal system is challenging. Medical imaging techniques such as magnetic resonance imaging (MRI) or computer tomography (CT) are used to create images of the human body, and to study *in vivo* the complex geometric relationships among the muscles, bones, and other structures [14;15;18;24;46;47;57-59;63;71;96;97;99;106;108;110;111]. The volumes of muscles, which can be derived from segmented MRIs, are important in examining the atrophy or hypertrophy resulting from different pathologies, treatments, and strength training [17;46;67;71;77].

An accurate reconstruction of the functional anatomy of the body, required for modern whole-body biomechanical models, is not trivial [114]. The musculoskeletal geometry for a specific subject can be extracted from MRI [11;12;15;21;71] or CT-scan images [114]. Three-dimensional reconstructions from CT scans have been used to design orthopedic implants [60;89;112] and plan orthopedic surgeries [81]. Subject-specific 3D models of muscles have been created from MRIs to study muscle volumes [57;71;78;87]. Muscle moment arms have been estimated *in vivo* from static MRIs [99], however it is time-consuming and requires extensive imaging protocols to capture the muscle and joint geometry at different limb positions. Arnold et al. [12] were the first to build subject-specific models using MRI to analyse the MALs over the range of joint motion.

Subject-specific musculoskeletal modelling also addresses the problem of image segmentation, which consists of extracting anatomical structures from medical image data such as MRI. Semiautomatic or fully automatic segmentation methods are fast but inaccurate since muscle distinction is often difficult or impossible to assess with currently

used methods. Thus, muscles volumetric representations are most often and most accurately acquired by defining muscle contours manually [11;86].

Blemker et al. [22] created volumetric finite-element representations of a muscle and built the surface data from manually segmented MRIs, combined with description of the nonlinear stress-strain behaviour of muscle tissue, and developed a new formulation for representing muscles shape, geometry, and force. Arnold et al. [12] created MRI-based musculoskeletal models of three lower extremity cadaveric specimens, which included pelvis, femur, tibia, psoas, semimembranosus, and semitendinosus, from manually segmented MRIs. Scheys et al. [101] generated a subject-specific musculoskeletal model of the lower extremities of an able-bodied subject, which included femur, tibia and fibula and 25 muscles' lines of action using a centroid approach, i.e. the attachment points of the muscle to the bone were identified by scrolling through the image slices and picking an appropriate point in the last slice where the muscle is visible.

Automatic segmentation and a 3D region-growing algorithm were applied by Scheys et al. [103] to define the bone structures. These methods were also used to build the person-specific models of CP children with presence of femoral anteversion and study the effect of bone deformities on the accuracy of hip muscles moment arms [12;103]. However, the entire process of MRI-based modeling is still time-consuming because semi-automatic segmentation of the muscles has failed thus far.

Since the extensive variations in musculoskeletal geometry exist among individuals, there is no public software which can perform acquisition of individual musculoskeletal geometry from medical imaging data and analyse muscle function.

SCOPE AND AIMS

The scope of this thesis is focused on the developing and applying subject-specific musculoskeletal models of the lower extremities to study muscle volumes and biomechanics parameters of muscles in subjects with unilateral CP.

Study I

The first aim was to develop a workflow to build highly detailed, subject-specific musculoskeletal model of the lower extremities from MRIs of a person with unilateral CP that can be exported in software for musculoskeletal computing (SIMM).

The second aim was to calculate MTLs and MALs during gait using the developed musculoskeletal model.

The third aim was to determine the accuracy of hip, knee and ankle MALs and MTLs during gait calculated from the scaled generic model by comparing them to those computed from the subject-specific musculoskeletal model.

Study II

Study II was designed as a wider scale application of the methods developed in Study I.

The first aim was to develop subject-specific musculoskeletal models of the hip joints in both sides of the lower extremities based on MRIs of nine subjects with unilateral CP.

The second aim was to examine MALs and MTLs over hip abd/adduction, hip flexion/extension and hip rotation, and muscle volumes calculated by the subject-specific model.

The third aim was to study the accuracy of MALs calculated by the scaled generic model.

2. MATERIALS AND METHODS

2.1. SUBJECTS

Nine subjects (Table 2.1) with unilateral CP (GMFCS level 1) participated in a study at Karolinska University Hospital. They were able to walk independently without the aid of orthotic or supporting devices and none had received surgical interventions prior to this study.

Table 2.1. Characteristics of the subjects with unilateral CP.

	Gender	Affected leg	Age, yrs	Height, cm	Weight, kg
Subject 1	Male	left	20	169.5	66.0
Subject 2	Female	right	20	161.0	61.3
Subject 3	Male	left	16	176.5	90.0
Subject 4	Female	left	17	162.5	59.7
Subject 5	Female	left	16	172.0	66.6
Subject 6	Female	left	20	170.5	73.1
Subject 7	Male	left	18	175.5	54.2
Subject 8	Male	right	15	166.5	54.7
Subject 9	Male	right	21	185.5	102.5

2.2. IMAGING CAPTURE

MRIs of the lower extremities of subjects were taken using T2-weighted tra×5 MRI scanner (Philips Medical Systems). The field of view was the entire region of the lower extremities. Slice thickness was 5 mm and spacing between axial slices was 10 mm. Each subject was scanned in a supine position with both legs stretched and parallel to the long axis of the body. Ethics approval for this study has been obtained.

2.3. MOTION CAPTURE

Motion capture was performed using a 8-camera motion analysis system (Vicon, Oxford, England) with two force plates (Kistler). Markers were placed on anatomical landmarks (Fig. 2.1) according to a conventional gait marker protocol (Vicon Plug-In-Gait). A series of trials were collected with one representative trial used for further analysis.

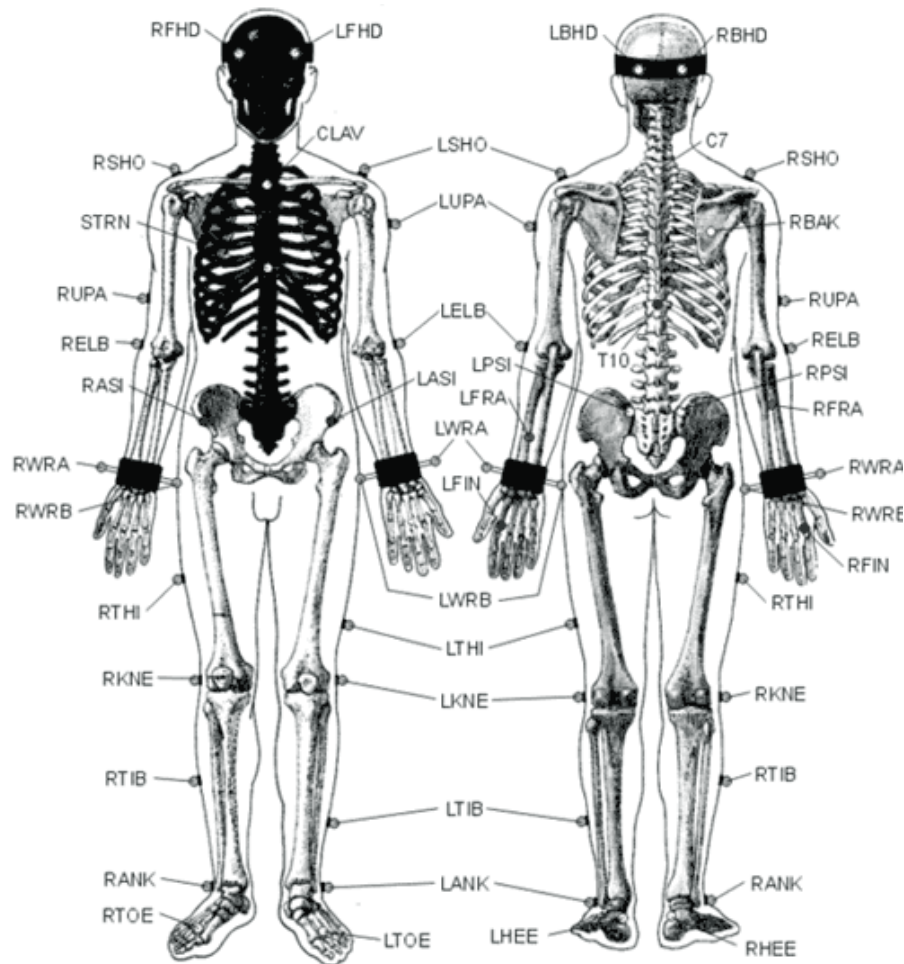


Figure 2.1. Plug-In-Marker Placement.

2.4. SCALED GENERIC MODEL

The generic model [36] was scaled in SIMM (Musculographics Inc., Santa Rosa, CA) based on three-dimensional positions of markers attached to the pelvis, femur, tibia and foot during a standing trial.

2.5. SUBJECT-SPECIFIC MUSCULOSKELETAL MODEL

2.5.1. Study I

The subject-specific model of the lower extremities was developed from MRIs of **Subject 8** (Table 2.1). It included muscles, bones (Table 2.2), and kinematic descriptions of hip, knee and ankle joints.

Table 2.2. List of muscles and bones in the musculoskeletal model of the lower extremities.

Bones	Muscles		
pelvis	gluteus maximus	adductor magnus	extensor digitorum longus
femur	gluteus medius	adductor longus	extensor hallucis longus
patella	gluteus minimus	adductor brevis	peroneus longus
tibia	quadratus femoris	semimembranosus	peroneus brevis
fibula	iliacus	semitendinosus	flexor hallucis longus
talus	psoas	biceps femoris long head	flexor digitorum longus
calcaneus	gracilis	biceps femoris short head	tibialis anterior
	pectineus	rectus femoris	tibialis posterior
	piriformis	vastus medialis	soleus
	sartorius	vastus lateralis	popliteus

2.5.2. Study II

The subject-specific models of the hip regions were developed from MRIs of nine subjects (Table 2.1). Each of the model included hip muscles (gluteus maximus, gluteus medius, gluteus minimus, psoas, iliacus, semimembranosus, semitendinosus, biceps femoris long head, adductor longus, adductor brevis, and tensor fascia latae), bones (pelvis, femur, patella, tibia, and fibula) and kinematic descriptions of the hip joint.

2.5.3. Three-dimensional reconstruction of muscles and bones models

Bones and muscles contours were manually outlined by assigning label maps, where each voxel is a number indicating the type of tissue at that location in 3D Slicer (www.slicer.org), which is a free open- source software for visualization and image computing and can perform different medical image processing activities including surface reconstruction from MRI [54;90;91].

Three-dimensional surface models of muscles and bones were automatically reconstructed from manually segmented axial MRIs (Fig.2.2). The volumes of bones and muscles were calculated after reconstruction. Segmentation repeatability was evaluated by comparing the volumes of muscles from repeated segmentations and three-dimensional reconstructions of MRIs of three random subjects.

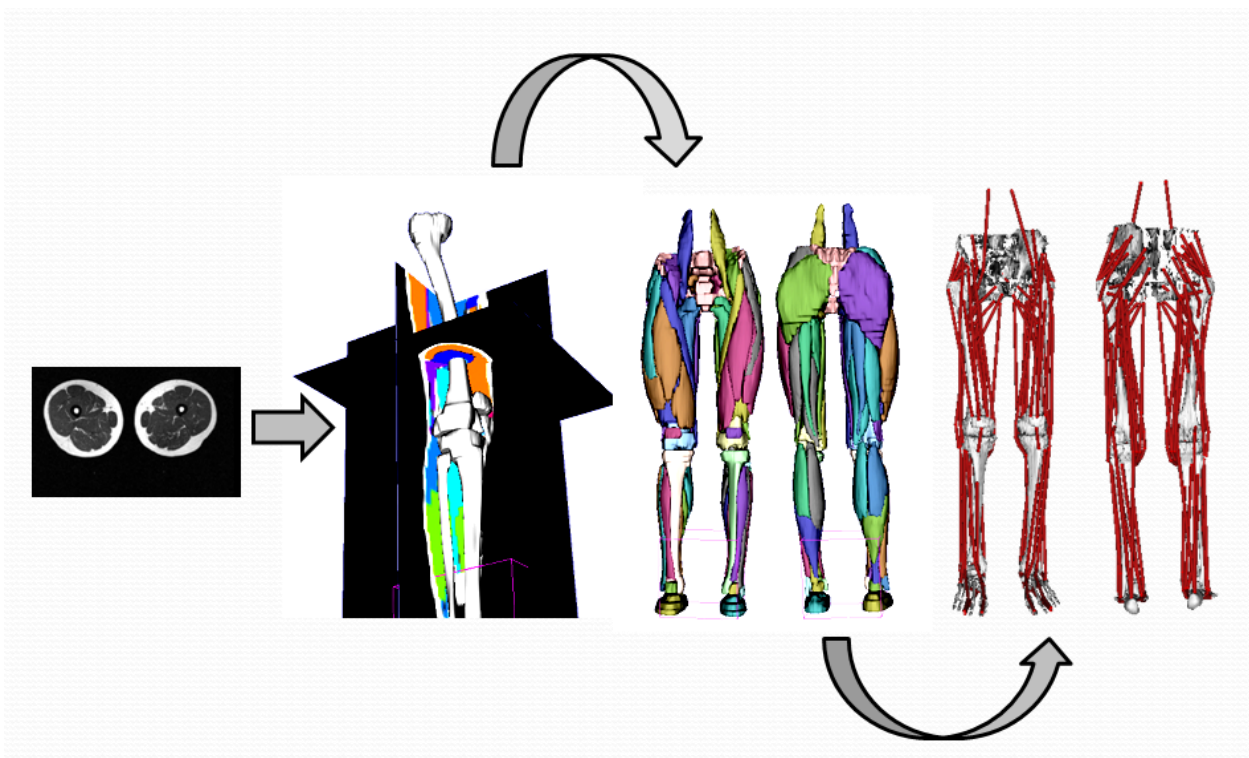


Figure 2.2. The workflow of building subject-specific musculoskeletal model of the lower extremities from MRIs.

2.5.3. Specification of joint kinematics and representation of muscle-tendon paths

Using a musculoskeletal modeling package [36], we defined the joint kinematics, and muscle–tendon paths of the model.

Kinematic descriptions of hip, knee and ankle joint were defined based on the patient’s bone surface geometry in the scanned position. The transformations that relate the position and orientation of one body segment to another consisted of three translations and three rotations.

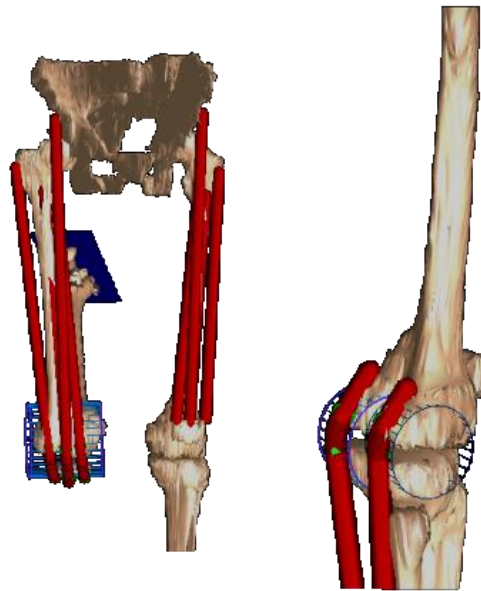


Figure 2.3. Definition of muscle wrapping surfaces.

The geometry of a muscle–tendon unit was considered as line segments (Fig.2.2). The positions of the muscle attachments were consistent with three-dimensional surfaces of the muscles and bones created from MRIs. Muscles with large or multiple attachment areas (gluteus maximus, gluteus medialis, gluteus minimus, adductor magnus) were divided into three partitions. Via points and wrapping surfaces (Fig. 2.3) were used to describe a muscle-tendon path that was constrained by bones.

2.5.4. Simulation of gait

Three-dimensional marker’s positions were defined in software for musculoskeletal modeling. Gait trial data was imported and motion pattern was created based on reordered marker’s coordinates in 3D space.

2.6. DATA ANALYSIS

Study I

The hip, knee and ankle MALs and MTLs of 70 muscles in affected and non-affected sides during gait were calculated using both the subject-specific model and the scaled generic model.

Study II

For each subject MALs over hip adduction/abduction, extension/flexion and rotation ranges of motion in the both affected and the non- affected sides were calculated using both the scaled generic and the subject-specific models. We calculated the ratio, standard deviation (SD) between the average values of the MALs, over the range of hip motion, in both sides of the lower extremities in the generic scaled model and subject-specific model. The Wilcoxon matched pairs test (significance level of $p < 0.05$) was implemented in Matlab (MathWorks Inc.) to evaluate the differences in muscle volumes, MALs and MTLs in the affected side vs. the non-affected side calculated by the subject-specific models, and to evaluate systematic differences between average hip MALs calculated by the scaled generic modes and subject-specific models.

3. RESULTS AND DISCUSSIONS

Study I

We developed the workflow to build a highly detailed, subject-specific model of the entire lower extremities from MRIs, which can be exported into the software for biomechanical analysis of muscle function during gait. The study provided a comprehensive evaluation of muscle volumes, MTLs and MALs of 70 muscles in the entire lower extremities in a subject with unilateral CP.

During the process of subject-specific modeling we created 3D models of muscles and bones from axial MRIs, calculated muscle volumes and evaluated the repeatability of MRI segmentation. The maximum volume error was 12% for tensor fascia latae, since it was difficult to see muscle-tendon transition. The volume error for other muscles was approximately 1-4% (the low resolution artifacts and noise in images led to difficulty in identifying borders between muscles in some of the axial MRIs, which influenced the precision of calculation of muscle volumes).

All muscle volumes in the affected limb were found to be smaller than in the non-affected limb, with atrophy being more significant in the shank than in the thigh, with an average muscle volume discrepancy of 28% and 13% respectively. Our findings confirm those of Elder et al. [42], Malaiya et al. [77], and Lampe et al. [72]. We also found that maximal MTLs during gait calculated by the subject-specific model were shorter in the affected side in adductor longus, adductor brevis, adductor magnus, pectineus, and quadratus femoris muscles. The decreased muscle volumes in the affected leg may therefore be attributable in part to shorter muscles, corresponding to findings by Lieber et al.[75].

Muscle tendon lengths during gait

In general, the scaled model delivered accurate enough values for changes in MTLs during gait for all muscles except adductor magnus, adductor longus, adductor brevis, pectineus, iliacus, psoas, and quadratus femoris.

Muscle moment arm lengths in the affected side during gait

We found that scaled generic model extremely overestimated MALs for hip medial (gluteus medius, gluteus minimus, adductor longus, psoas, tensor fascia latae, biceps femoris) and lateral rotation; for hip abduction and adduction (in semitendinosus, sartorius, biceps femoris); for hip flexion in adductor brevis; for knee flexion in semimembranosus and semitendinosus; for ankle flexion in peroneus tertius.

Muscle moment arm lengths discrepancies between the affected and the non-affected sides

Average hip rotation MAL discrepancies between affected and non-affected lower extremities during gait were underestimated by the scaled generic model in most hip rotator muscles, except gluteus medialis, by an average of 73%

Average hip abd/adduction MAL discrepancies between affected and non-affected lower extremities during gait were underestimated by the scaled generic model in most hip add-/abductors muscles by an average of 62%; and were overestimated in gluteus minimus, adductor brevis, tensor fascia latae, gracilis, semitendinosus by an average of 53%.

Average hip flexion/extension MAL discrepancies between affected and non-affected lower extremities during gait were underestimated by the scaled generic model in most hip flexors/extensors muscles, except semitendinosus, by an average of 71%; and were overestimated in gluteus medius, gluteus maximus, adductor longus, piriformis, tensor fascia latae, sartorius by more than 100%.

Average knee flexion/extension MAL discrepancies between affected and non-affected lower extremities during gait were underestimated by scaled generic model in most knee flexors/extensors muscles, except sartorius, by 83%; and were overestimated in semimembranosus and semitendinosus by an average of 33%

Average ankle plantar/dorsiflexion MAL discrepancies between affected and non-affected lower extremities during gait were underestimated by the scaled generic model in most ankle flexion muscles by an average of 84%; and were overestimated in peroneus longus by 18%,

Study II

We created the subject-specific musculoskeletal models of the lower extremities from MRIs of nine teenagers and young adults with mild unilateral CP to study muscle volumes, hip MALs and MTLs.

Since all studied subjects in the present study were highly functioning, the MTLs in the affected and non-affected sides were very similar. No significant differences between sides were observed in MTLs of gluteus maximus, gluteus medius, gluteus minimus, psoas, iliacus, adductor longus and adductor brevis. Average hip adduction/abduction MALs of rectus femoris, the medial part of gluteus medius, the anterior parts of gluteus medius and gluteus minimus in the affected side were slightly smaller by an average of 5 ± 1 mm; MALs iliacus, psoas and the medial part of gluteus maximus in the affected side were slightly larger by an average of 3 ± 1 mm.

However muscle volumes in gluteus maximus ($p=0.008$), adductor longus ($p=0.014$), tensor fascia latae ($p=0.006$), biceps femoris long head ($p<0.001$), rectus femoris ($p=0.005$), semimembranosus ($p=0.022$), semitendinosus ($p=0.020$) in the affected side were significantly smaller than in the non-affected side by an average of 16%, correlating with previous findings [71;94].

Fukunaga et al. [46] found a correlation between muscle torque and muscle volume or PSCA, and smaller torque around hip joint in the affected side. It was reported that the loss of muscle strength [115] correlates with the volumetric loss of the spastic musculature. Spastic muscles have also shown power reduction during gait [71;94]. Gluteus medius and gluteus minimus with smaller muscle volumes and hip abduction MALs in the affected side therefore can be expected to have lower hip abduction strength comparing with the non-affected side. Similarly, we can expect iliacus to have lower hip flexion; and, finally, gluteus maximus to have lower hip rotation strength [19;92].

Comparison of MALs from the scaled generic and the subject-specific models

Hip abduction/adduction MALs of gluteus medius, gluteus minimus, tensor fascia latae and biceps femoris long head and the anterior part of gluteus maximus were significantly overestimated by the scaled generic model by an average of 46% ($p<0.001$, $p<0.001$, $p=0.001$, $p=0.001$ and $p=0.02$) in the affected side and by 34% ($p=0.04$, $p=0.005$, $p=0.006$, $p=0.006$ and $p=0.01$) in the non-affected side. Hip abduction/adduction MALs of adductor longus and semimembranosus were significantly underestimated by the scaled generic

model by an average of 15% ($p=0.01$ and $p=0.02$) side in the affected, and by 44% ($p=0.01$ and $p=0.02$) in the non-affected side. Adduction MALs of psoas in the affected side were also significantly ($p=0.04$) underestimated by the scaled generic model by 81%.

Hip flexion/extension MALs of the medial part and the posterior part of gluteus maximus, the anterior part of gluteus medius, the medial part of gluteus minimus were significantly underestimated by the scaled generic model by an average of 44% ($p=0.02$, $p=0.02$, $p=0.02$ and $p=0.006$) in the affected side, and by 47% ($p=0.004$, $p=0.002$, $p=0.03$ and $p=0.001$) in the non-affected side. Hip flexion/extension MALs of the medial and the posterior parts of gluteus medius, adductor brevis and psoas were significantly overestimated by the scaled generic model by an average of 99% ($p=0.004$, $p=0.01$, $p=0.01$ and $p=0.01$) in the affected side and by 113% ($p<0.001$, $p<0.001$, $p=0.03$ and $p=0.03$) in the non-affected side. Hip flexion/extension MALs of adductor longus and rectus femoris in the non-affected side were significantly overestimated by the scaled generic model by an average of 44% with $p=0.03$ and $p=0.008$ respectively.

Hip rotation MALs of the posterior part of gluteus minimus and semitendinosus were significantly underestimated by the scaled generic model by an average of 65% (with $p=0.004$ and $p<0.001$) in the affected side and by 68% ($p<0.001$ and $p<0.001$) in the non-affected side. Hip rotation MALs of the medial part of gluteus maximus ($p=0.02$) and semimembranosus ($p=0.02$) in the non/affected side were significantly underestimated by the scaled generic model by 22% and 57%. Hip rotation MALs of the posterior part of gluteus maximus and gluteus medius, the anterior part of gluteus medius and biceps femoris long head were significantly ($p=0.008$, $p=0.002$ and $p<0.001$) overestimated by the scaled generic model in the affected side by an average of 65%.

Our results also confirmed that the scaled generic model significantly underestimated hip MALs differences between the affected and the non- affected sides in most muscles.

Consequently, the scaled generic models may lead to erroneous conclusions about individual muscle contributions to joint moments.

4. GENERAL DISCUSSION

The results of the performed studies have important implications for the accuracy of assessing muscle function of persons with unilateral CP using the scaled generic model. Our findings showed that the scaled generic and the subject-specific lower extremity musculoskeletal models showed substantial dissimilarities in hip, knee and ankle MALs and MTLs calculated during gait of a subject with unilateral CP and significant differences in MALs over the range of hip motion in a group of subjects with very mild unilateral CP.

Differences between the subject-specific and the scaled generic models were caused by the variability in muscle attachment locations [102] and bone geometry that is not taken into account in the scaling of the generic model. Persons with unilateral CP often have asymmetric musculoskeletal geometry in the affected side and the non-affected side[49], e.g. decreased muscle volume in the affected side[71;77] and significant leg length discrepancy[95]. Nevertheless, the both sides of the lower extremities are symmetrical in the generic model; axial scaling makes its bones longer/shorter or wider/narrower, but changes in muscle attachment positions were not taken into account. As a result, the scaled generic model failed to identify variability of muscle attachments and bone geometry between the affected and the non-affected sides in subjects with unilateral CP.

The inaccuracies of the generic scaled model were very pronounced in femur, because it was impossible to assess femoral shape parameters (e.g. neck length, femoral length, femoral neck angle etc.) in individuals using only scaling based on markers placed on skin. As a result, muscle attachments and via points were defined by the scaled generic model with a large error.

It is important to keep in mind some of the limitations of this study. We described muscle-tendon paths as a series of line segments; because the main goal was to import the subject-specific model in software that can calculate muscle moments arms and tendon lengths during motion based on such simplified representation of muscle geometry. This is a reasonable simplification for muscles with small areas of origin and insertion (e.g. tibialis posterior). However, it was challenging to use a series of line segments to represent muscles with broad attachments, like the gluteus maximus. In SIMM models such muscles are separated into compartments, and multiple paths to represent the muscle [36] are used. However, it was unclear how many paths to define, where the paths should be

located, and how to define via points (and/or wrapping surfaces) so that the models accurately represent the anatomy. The resulting muscle moment arms may be highly sensitive to how the constraints are defined. In a future, muscles with large areas of attachment, multiple origins, or curved paths could be advantageously modelled as volumetric objects [14;22;23].

The outcome of orthopedic surgery aimed to correct movement abnormalities of persons with CP [3;29;31;60;81] can be difficult to predict and is sometimes unsuccessful [25;29;31;105]. Musculoskeletal simulations are needed to analyse the biomechanical causes of movement abnormalities since this information is important for developing better treatment plans [9;10]. Despite limitations of this study, we believe that the methods presented here offer the potential to improve the accuracy of models of the musculoskeletal system for development of more effective treatment plans of persons with movement disorders. Based on inaccuracies of scaled generic model reported in our studies and in recent articles [7;100;102], the scaled generic models that are used to study persons with CP must be tested and interpreted with care, in the knowledge of the underlying limitations of the models and the conditions that determine when, and for which patients subject-specific models are the better alternative.

Future work

The accuracy of a simulation depends on the accuracy of the defined musculoskeletal model. The subject-specific musculoskeletal models, based on *in vivo* measurements of musculoskeletal geometry and joint kinematics, can help in understanding the causes of movement deviations [13;37] and assessing treatment options [43].

It is challenging to simulate, explore and predict the biomechanical effects of orthopedic surgeries using subject-specific musculoskeletal models and dynamic simulations of individuals with pathological gait [9]. Further advancements in image-based musculoskeletal modeling will expand the accuracy and utility of models used to study musculoskeletal and neuromuscular impairments, and to improve the treatment outcome.

Modeling muscle using a series of line segments allows only one length and moment arm to be estimated for each muscle path. However, variation in moment arms lengths among fibers within a muscle could greatly influence the muscle's capacity to generate force: previous study [64] has demonstrated that such simplified musculoskeletal models do not

accurately predict *in vivo* force–joint angle behaviours of muscles with complex architectures. By creating volumetric finite-element representations of muscle from the 3D muscle surface derived from static MRIs, combined with description of the nonlinear stress-strain behaviour of muscle tissue, a new formulation for representing muscle shape, geometry, and force can be developed.

The internal architecture of muscles can be also derived from diffusion tensor imaging combined with tractography methods as it was implemented in recent studies [24;63;108]. Models that represent the 3D arrangement of muscle fibers and allow for variations in fiber lengths and moment arms [22;23] are needed to more closely represent *in vivo* muscle behaviour.

Subject-specific musculoskeletal models can be evaluated by comparing muscle tissue deformations predicted by volumetric muscle models with tissue deformations derived from dynamic MRI, and by comparing MALs predicted by models with MALs measured from dynamic MRIs. Joint kinematics can be prescribed from *in vivo*, dynamic, loaded measurements of individual subjects. Acquisition of static MRIs at multiple joint positions has been applied to studying the mechanics of the many joints [58;59;106].

OUTLINE OF PAPERS

Paper 1

The purpose of this paper was to develop methods to build a subject-specific musculoskeletal model of the lower extremities based on MRIs of a subject with unilateral CP, and to determine whether a scaled generic musculoskeletal model is accurate enough to characterize MTLs and MALs of 70 muscles in both lower limbs during gait in a subject with unilateral cerebral palsy.

We found, that the generic models produced accurate values for changes in MTL during gait for almost all muscles, except adductor longus, adductor magnus, adductor brevis, quadratus femoris, pectineus, extensor digitorum longus, soleus, lateral gastrocnemius, and medial gastrocnemius.

MALs computed from the scaled generic model, however, differed considerably from those computed from the subject-specific model. Upon comparison of hip, knee and ankle MALs in affected and non-affected sides of the lower extremities, the scaled generic model generally failed to identify level arm dysfunction in the subject with unilateral CP.

Paper II

The aim of this paper was to create the subject-specific modes of the lower extremities based on MRIs of nine youth adults with unilateral CP to study hip muscle volumes, MTLs and MALs. Muscle volumes and hip abduction MALs in gluteus medius and gluteus minimus, hip flexion MALs in iliacus, and hip rotation in gluteus maximus were smaller in the affected side of lower extremities. Yet, MTLs were very similar in the involved and the non-involved sides.

We also studied the accuracy of MALs of 36 muscles over the range of hip motion calculated from generic scaled models, and its ability to identify discrepancy in MALs between the affected and the non- affected sides. The hip MALs of almost all muscles in the affected leg were overestimated by the scaled generic. The MALs discrepancies between the affected and the non- affected sides of the lower extremities were significantly underestimated by the scaled generic model.

ACKNOWLEDGEMENTS

This work was supported by Stiftelsen Promobilia and The Swedish Research Council.

I am sincerely thankful to Professor Anders Eriksson and Svetlana Bauer, who gave me the chance to do a research as a PhD student at Royal Institute of Technology, Department of Mechanics.

Lanie Gutierrez-Farewik for presenting me the world of orthopedics, biomechanics, and simulations of the musculoskeletal system. As my principal supervisor, Lanie has been a constant source of enthusiasm and creativity. Thank you, Lanie, for your steadfast encouragement to complete this thesis.

Professor Anders Eriksson, my co-supervisor, for introducing me to biomechanics, for great kindness and support of my studies.

Peter Loan and Steve Piper have been of tremendous assistance in developing the subject-specific musculoskeletal model. Without their help this project would not have been possible.

Jacques Riad and Eva W. Broström for sharing their insights into hemiplegic cerebral palsy.

Carolina, Nina and Heide for constant friendship and invaluable help in solving problems connected with documentation and applications.

I have enjoyed daily interactions with colleagues at Mechanical Department in The Royal Institute of Technology. Thanks to Eva, Natalia, Rouli and Zeinab for friendship atmosphere and interesting conversations about life during daily coffee breaks.

Finally, and most importantly, I thank my parents, sister Maria, grandmother Valentina for their love and support during all my life. Спасибо тебе, мама, что была рядом в трудные минуты моей жизни и не позволила сломаться под гнетом обрушившихся несчастий. Тебе я посвящаю эту диссертацию.

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