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Interplay between musculoskeletal morphology, gait pattern
and bone loads in children with and without cerebral palsy:
Insights gained from an enhanced and validated multi-scale
workflow to predict growth trends

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Abstract

As bones develop during skeletal growth, they not only increase in size but also adapt their shape in response to the loading environment. The shape of lower limb bones, particularly the femur, affects an individual's gait pattern, which modifies bone loads and subsequently influences growth. This highlights the complex interplay between musculoskeletal morphology, gait pattern, bone loading, and bone growth. Femoral deformities are common in children with cerebral palsy (CP), yet the specific loading conditions that result in typical femoral growth trends, as opposed to those leading to pathological developments, remain unknown.

Multi-scale simulations can estimate growth plate stresses and predict growth trends. These simulations integrate musculoskeletal (MSK) modelling, finite element (FE) simulations, and mechanobiological models. However, previous multi-scale studies were limited to small sample sizes ($n < 4$), due to the time-consuming process of creating a personalized FE model for each individual. Nevertheless, the overall femoral geometry, shape and location of the growth plate, and loading conditions significantly influence simulation results, underscoring the necessity of individual personalization. Additionally, the entire multi-scale simulation workflow includes several assumptions and uncertainties. The lack of longitudinal experimental data limits our ability to quantify these uncertainties and validate model assumptions. The primary aim of this thesis was to address these limitations by quantifying uncertainties and enhancing the simulation workflow. These technological advancements have facilitated studies with larger sample sizes, leading to significant scientific and clinical insights.

In the first study, the sensitivity of MSK simulations to misplaced markers during three-dimensional (3D) motion capture were investigated. 3D motion capture data of a child with CP and one typically developing (TD) child was used and systematically modified to mimic experimental marker misplacements. Misplaced knee markers affected MSK simulation results across all joints. However, the orientation of joint contact forces - crucial for predicting growth trends - was only minimally impacted by marker misplacements.

The second study evaluated whether the gait pattern or the femoral morphology is the primary contributor to asymmetric hip joint loads. Magnetic resonance image (MRI) scans and 3D motion capture data of 15 TD children and 12 children with CP were used to create subject-specific MSK models. Additional what-if simulations were conducted to address our research question. The findings showed that the gait pattern is the main contributor to asymmetric hip joint loads in CP and TD children. Therefore, surgical interventions should not only target the correction of the bony morphology but also focus on normalizing the gait pattern, in order to normalize joint loads and prevent the development of future femoral deformities.

The time-consuming process of creating the FE models for the multi-scale simulations was a big bottle-neck for large scale studies. In the third study, I therefore developed a tool, which

enables to create personalized FE models including a hexahedral mesh aligned with the proximal growth plates within minutes. This tool, called “Growth-Prediction-Tool” (GP-Tool), enabled us to conduct mechanobiological simulations with a comparable large sample size ($n=50$ femurs versus $n<4$ femurs in previous studies). We used 3D motion capture data and MRI scans of 12 CP and 13 TD children to create personalized models, perform multi-scale simulations, and analyze the individuals’ femoral growth trends. We obtained physiological plausible results in agreement with experimental observation. Some but not all children with CP showed different growth plate stress distributions compared to the TD children.

Femoral growth occurs at both the proximal and distal growth plate. For the fourth study, I enhanced the GP-Tool to include analysis at the distal growth plate. Using 3D motion capture data and MRI scans of the same participants as in the third study, I quantified stress distributions at the distal growth plate. In children with CP, an increased knee flexion angle during the stance phase altered the stress distribution at the distal growth plate, promoting more growth in the anterior compartment. Over time, this anteriorly promoted growth would lead to greater anterior bending of the femoral shaft, which was confirmed by examining the MRI scans of the participants.

The fifth study focused on validating growth predictions derived from the multi-scale modelling workflow. A longitudinal dataset of 3D motion capture and MRI scans was collected from ten TD children at two time points, approximately two years apart. A linear regression model including predictions from the multi-scale mechanobiological workflow, along with physical activity and anthropometric data from the first data collection session, explained 66% of the changes in femoral anteversion angles. In 18 of 20 femurs analyzed, the direction of the growth (i.e., whether anteversion angle will increase or decrease) was predicted correctly. Considering that bone growth is influenced by mechanical loads, as well as other factors such as genetics and nutrition, this level of predictive accuracy can be regarded as high.

The investigated multi-scale mechanobiological model presents a significant opportunity for early identification of pathological femoral development and can inform clinical decision-making. Recent advancements in streamlined computational simulations and automated segmentation from medical images, combined with the GP-Tool developed in this thesis, could enable personalized multi-scale simulations in clinical settings in the near future. Utilizing mechanobiological growth predictions may facilitate a shift in the clinical treatment strategy for femoral deformities. While currently reactive, invasive procedures such as de-rotation osteotomies, are performed at a late stage, prospective identification of bony deformities at an early stage could allow proactive, non-invasive interventions, such as gait retraining, to normalize loads and prevent the development of deformities.

Zusammenfassung

Knochen nehmen während des Skelettwachstums nicht nur an Größe zu, sondern passen als Reaktion auf die Belastungsumgebung auch ihre Form an. Die Knochengeometrie der unteren Extremität, insbesondere des Oberschenkelknochens, wirkt sich auf das Gangbild einer Person aus. Dadurch wird wiederum die Belastung auf die Knochen verändert, welche maßgeblichen Einfluss auf das Knochenwachstum hat. Ein komplexes Zusammenspiel zwischen muskuloskelettaler Morphologie, dem Gangbild und der daraus resultierenden Knochenbelastung sowie dem Knochenwachstum ist vorhanden. Fehlstellungen des Oberschenkelknochens (Femur) sind bei Kindern mit Zerebralparese (CP) häufig. Die spezifischen Belastungsbedingungen, die zu gesunden femuralen Wachstumstrends führen, sowie jene, die zu pathologischen Entwicklungen führen, sind noch unbekannt.

Mit Hilfe von mehrstufigen Simulationen lassen sich die Belastungen der Wachstumsfuge abschätzen und Wachstumstrends vorhersagen. Diese Simulationen kombinieren muskuloskelettale (MSK) Modellierung, Finite-Elemente-Simulationen (FE) und mechanobiologische Modelle. Bisherige Studien, die diese Simulationen kombinieren, waren jedoch auf kleine Stichprobengrößen ($n < 4$) beschränkt, da die Erstellung eines personalisierten FE-Modells für jedes Individuum sehr zeitaufwändig ist. Die gesamte Geometrie des Femurs, die Form und Lage der Wachstumsfuge, sowie die Belastungsbedingungen beeinflussen die Simulationsergebnisse erheblich, was eine individuelle Anpassung notwendig macht. Darüber hinaus beinhaltet der gesamte Simulationsablauf mehrere Annahmen und Unsicherheiten. Dadurch, dass experimentelle Daten zu mehreren Zeitpunkten fehlen, ist es nicht möglich diese Unsicherheiten zu quantifizieren und die Modellannahmen zu validieren. Das Hauptziel dieser Arbeit war es, diverse Annahmen der Simulationen zu validieren, die Unsicherheiten zu quantifizieren sowie den gesamten Simulationsablauf zu verbessern. Diese technologischen Fortschritte haben Studien mit größeren Stichproben ermöglicht und bedeutende wissenschaftliche und klinische Erkenntnisse vorgebracht.

In der ersten Studie wurde die Empfindlichkeit von MSK-Simulationen gegenüber falsch platzierten Markern bei der dreidimensionalen (3D) Bewegungsanalyse untersucht. Es wurden Daten der 3D Bewegungsanalyse eines Kindes mit CP und eines Kindes mit normaler Entwicklung (TD) verwendet und systematisch modifiziert, um experimentelle Markerverschiebungen zu imitieren. Falsch platzierte Kniemarken beeinflussten die MSK-Simulationsergebnisse in allen Gelenken. Die Orientierung der Gelenkkontaktkräfte - entscheidend für die Vorhersage von Wachstumstrends - wurde jedoch nur minimal durch die Fehlplatzierung der Marker beeinflusst.

In der zweiten Studie wurde untersucht, ob das Gangbild einer Person oder die individuelle Morphologie des Oberschenkels hauptverantwortlich für asymmetrische Hüftgelenkbelastungen

ist. Aufnahmen mittels Magnetresonanztomographie (MRT) und Daten von 3D-Bewegungsanalysen von 15 gesunden Kindern und 12 Kindern mit CP wurden verwendet, um probandenspezifische MSK-Modelle zu erstellen. Zusätzliche „Was-wäre-wenn“-Simulationen wurden durchgeführt, um unsere Forschungsfrage zu beantworten. Die Ergebnisse zeigten, dass das Gangbild die Hauptursache für asymmetrische Hüftgelenksbelastungen bei Kindern mit CP und gesunden Kindern ist. Daher sollten chirurgische Eingriffe nicht nur auf die Korrektur der knöchernen Morphologie abzielen, sondern sich auch auf die Normalisierung des Gangbildes konzentrieren, um die Gelenkbelastungen zu normalisieren und damit die Entwicklung künftiger Deformitäten zu verhindern.

Der zeitaufwändige Prozess der Erstellung der individuellen FE-Modelle mehrstufigen Simulationen war ein großes Hindernis für groß angelegte Studien. In der dritten Studie habe ich daher ein Programm entwickelt, das es ermöglicht, innerhalb weniger Minuten personalisierte FE-Modelle mit einem hexaedrischen Netz, das an der proximalen Wachstumsfuge ausgerichtet ist, zu erstellen. Mit diesem Tool, GP-Tool genannt, konnten wir mechanobiologische Simulationen mit einer vergleichbar großen Stichprobe durchführen (n=50 Femurs gegenüber n<4 Femurs in früheren Studien). Wir verwendeten 3D-Bewegungsanalysedaten und MRT-Bilder von 12 CP- und 13 TD-Kindern, um personalisierte Modelle zu erstellen, mehrstufige Simulationen durchzuführen und die individuellen Wachstumstrends der Oberschenkelknochen zu analysieren. Die Simulationen lieferten physiologisch plausible Ergebnisse, die mit experimentellen Beobachtungen übereinstimmen. Einige, aber nicht alle Kinder mit CP wiesen im Vergleich zu den TD-Kindern eine andere Spannungsverteilung in der Wachstumsfuge auf.

Das Wachstum des Femurs findet sowohl an der proximalen als auch an der distalen Wachstumsfuge statt. Für die vierte Studie habe ich das GP-Tool für die Analyse der distalen Wachstumsfuge erweitert. Anhand von 3D-Bewegungsanalysedaten und MRT-Bildern der gleichen Teilnehmer wie in der dritten Studie habe ich die Spannungsverteilung an der distalen Wachstumsfuge quantifiziert. Bei Kindern mit CP veränderte ein größerer Knieflexionswinkel während der Standphase die Spannungsverteilung an der distalen Wachstumsfuge und förderte somit das Wachstum im vorderen Kompartiment der Wachstumsfuge. Im Laufe der Zeit würde dieses verstärkte anteriore Wachstum zu einer größeren Biegung des Femurschafts führen, was durch die Untersuchung der MRT-Bilder bestätigt wurde.

Die fünfte Studie konzentrierte sich auf die Validierung von Wachstumsvorhersagen, die mit den individuellen mehrstufigen Simulationen prognostiziert wurden. Ein Längsschnittdatensatz von 3D-Bewegungsanalysedaten und MRT-Bildern wurde von zehn TD-Kindern zu zwei Zeitpunkten im Abstand von etwa zwei Jahren erhoben. Ein lineares Regressionsmodell, das Vorhersagen aus dem mehrstufigen mechanobiologischen Simulationsmodell zusammen mit körperlicher Aktivität und anthropometrischen Daten aus der ersten Datenerfassung enthielt, erklärte 66% der Veränderungen der femoral Anteversion. Bei 18 von 20 analysierten Oberschenkelknochen

wurde die Richtung des Wachstums (d. h. ob der Anteversionswinkel zu- oder abnimmt) korrekt vorhergesagt. In Anbetracht der Tatsache, dass das Knochenwachstum durch mechanische Belastungen, aber auch durch andere Faktoren wie Genetik und Ernährung beeinflusst wird, kann der Grad an Vorhersagegenauigkeit als hoch angesehen werden.

Das untersuchte mehrstufige mechanobiologische Simulationsmodell stellt eine bedeutende Möglichkeit zur frühzeitigen Erkennung von pathologischen Entwicklungen des Femurs dar und kann die klinische Entscheidungsfindung unterstützen. Jüngste Fortschritte bei Computersimulationen und automatisierter Segmentierung von medizinischen Bildern, kombiniert mit dem in dieser Arbeit entwickelten GP-Tool, könnten in naher Zukunft personalisierte mehrstufige Simulationen im klinischen Umfeld ermöglichen. Die Verwendung mechanobiologischer Wachstumsvorhersagen könnte eine Änderung der klinischen Behandlungsstrategie für Oberschenkeldeformitäten ermöglichen. Derzeit werden reaktive, invasive Verfahren wie Derotationsosteotomien in einem späten Stadium durchgeführt. Die prospektive Identifizierung von Knochendeformitäten in einem frühen Stadium könnte proaktive, nicht-invasive Interventionen, wie z. B. individuelles Gangtraining, ermöglichen, um die Belastungen auf die Knochen zu normalisieren und damit die Entwicklung von Deformitäten zu verhindern.

1. Introduction

Bones are constantly formed and remodeled. More than a century ago, researchers have shown that these adaptations are guided by the mechanical loading the bones are exposed to (Carter and Beaupré, 2000; Carter and Wong, 1988; Pauwels, 1980; Wolff, 1892). During skeletal growth from childhood to maturity the bones do not only grow in size, but also undergo substantial changes in shape. The femur, which was the investigated bone within this thesis, exhibits a change of femoral anteversion angle (AVA) from approximately 40° to 20° during skeletal growth in healthy people (Bobroff et al., 1999; Fabry et al., 1973). The AVA is a measure that describes the torsion around the longitudinal axis of the bone and is defined as the angle between the neck of the femur and a line passing the distal epicondyles in the transverse plane. This angle alters moment arms of several muscles (Kainz et al., 2023) and is therefore crucial for the biomechanical interaction between the femur and adjacent bones within the hip and knee joints. Pathological AVA, either severe increased anteversion or retroversion can lead to gait abnormalities, i.e. increased internal hip rotation, in-toeing foot progression angle, and further progressive problems like pain and osteoarthritis (Andriacchi et al., 2004; Bruderer-Hofstetter et al., 2015; Hudson, 2016; Sharma, 2001).

While the shape of the lower limb bones influences the walking pattern (Alexander et al., 2019; Bruderer-Hofstetter et al., 2015; Carriero et al., 2009; Hudson, 2016; Mindler et al., 2021), studies have shown that the walking pattern affects muscle forces and joint contact forces and therefore bone loads (Carriero et al., 2014; Kainz and Kranzl, 2022; Steele et al., 2012). These mechanical forces are crucial factors for the development of bones (Carter and Beaupré, 2000; Carter and Wong, 1988; Pauwels, 1980). This highlights the complex circular dependency among a person's musculoskeletal morphology, gait pattern, the mechanical loading on the bones and subsequent bone growth (Figure 1).

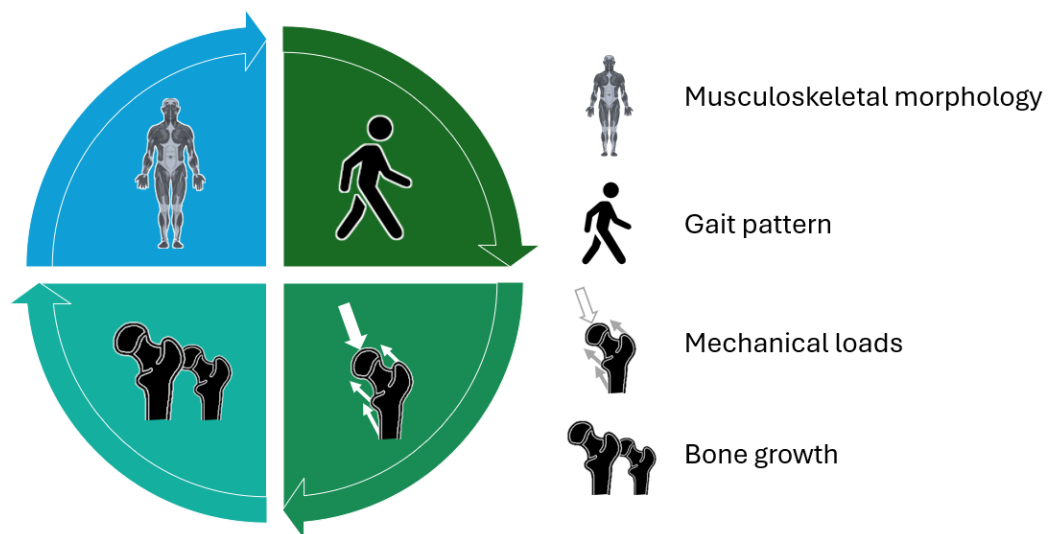


Figure 1: Schematic illustration of the complex interplay between skeletal morphology, gait pattern, mechanical loading on bones and bone growth.

Pathological femoral development frequently occurs in people with neurological problems, like cerebral palsy (CP), but it can also arise in people without neurological disorders (Alexander et al., 2019; Morrell et al., 2002). While CP itself is a non-progressive disease, the disabilities accompanied by CP are typically progressive and worsen over time (Bell et al., 2002). In many children with CP, bony deformities develop during skeletal growth, e.g., pathological AVA (Beals, 1969; Bobroff et al., 1999; Morrell et al., 2002), leading to gait abnormalities (Wren et al., 2005). To date, de-rotation osteotomies are typically performed to correct existing pathological AVA in patients with severe deformities and additional clinical problems such as altered gait pattern or pain (Buly et al., 2018; Dreher et al., 2012).

Advancements in modeling and simulation of the human musculoskeletal system helped to gain more insights into the complex interplay between morphology, gait, loading and growth. Studies have evaluated the effects of femoral morphology on the moment arms of hip-spanning muscles, suggesting that the morphology affects muscle coordination strategies, leading to altered loading conditions of the femur (Alexander et al., 2022; Arnold and Delp, 2001; Kainz et al., 2023; Kainz and Kranzl, 2022; Modenese et al., 2021; Wheatley et al., 2023). However, studies that link mechanical loading of the femur to changes in its morphology are rare, usually include only a limited number of participants, and typically rely on cross-sectional data rather than longitudinally measured shape changes to validate simulations (Carriero et al., 2011; Kainz et al., 2020; Shefelbine and Carter, 2004; Yadav et al., 2017). Therefore, further studies are necessary to fully understand the complex interplay of various factors influencing loads and growth. Eventually, understanding the interaction between gait, loading and bone growth could lead to a paradigm shift in the clinical intervention strategy for patients with pathological femoral development. If pathological femoral loading can be estimated at an early stage, before the development of the deformity, innovative preventive and potentially non-invasive interventions, such as gait-retraining (Kainz et al., 2024; Uhlich et al., 2022), could be used to normalize bone loads and ensure typical growth.

1.1. Femoral morphology

The morphology of the femur is complex and holds important features for functional hip and knee mechanics. While intact cartilage at the hip and knee joint is a key factor for smooth joint movement without pain (Mansour, 2003), the overall geometry of the femur has multifold influence on biomechanical movement. The bony structure is closely related to the range of motion of the joints (Chadayammuri et al., 2016). Furthermore, numerous muscles directly attach to the femur and several biarticular muscles either cross or attach at the femur. The femoral geometry defines muscle paths and lines of action and therefore, has an impact on the moment arms of muscles around hip and knee joints (Scheys et al., 2008; Scorcelletti et al., 2020). An increased muscle moment arm makes a muscle more efficient as a lower muscle force is necessary to produce a

desired joint moment. Therefore, the femoral morphology has an impact on the muscle coordination strategy for tasks that are usually performed with minimal effort like walking (Anderson and Pandy, 2001; Kainz et al., 2023; Kainz and Kranzl, 2022; Waters et al., 1988).

Atypical femoral shape has been associated with several pathologies like femoroacetabular impingement, osteoarthritis or hip instability as well as with gait impairments and pain (Andriacchi et al., 2004; Bruderer-Hofstetter et al., 2015; Hudson, 2016; Lerch et al., 2018; Rigling et al., 2021; Sharma, 2001). The treatment of these pathologies typically includes surgery to normalize the skeletal alignment of the pelvis, femur, tibia and patella with the overall aim to improve joint kinematics and clinical syndromes. There are several types of surgeries and techniques (e.g., proximal or distal de-rotation osteotomy) used to re-align bones. Currently, the surgeon selects the most promising surgery based on static morphologic and functional assessments (Paley, 2014).

The femoral morphology is mainly defined by two angles that define the orientation of the femoral neck in respect to the shaft and the distal part of the femur (Kaiser et al., 2016; Pick et al., 1941; Sangeux et al., 2015). The AVA is the angle between the neck of the femur and a line passing the distal epicondyles in the transverse plane. The neck-shaft angle (NSA) is the three-dimensional (3D) angle between the neck axis and the shaft axis of the femur (Figure 2). Both angles usually change with skeletal growth in healthy participants (Bobroff et al., 1999; Fabry et al., 1973; O'Sullivan et al., 2021). Angles outside the range of normative values are closely related with several pathologies and impairments (Andriacchi et al., 2004; Bruderer-Hofstetter et al., 2015; Hudson, 2016; Sharma, 2001).

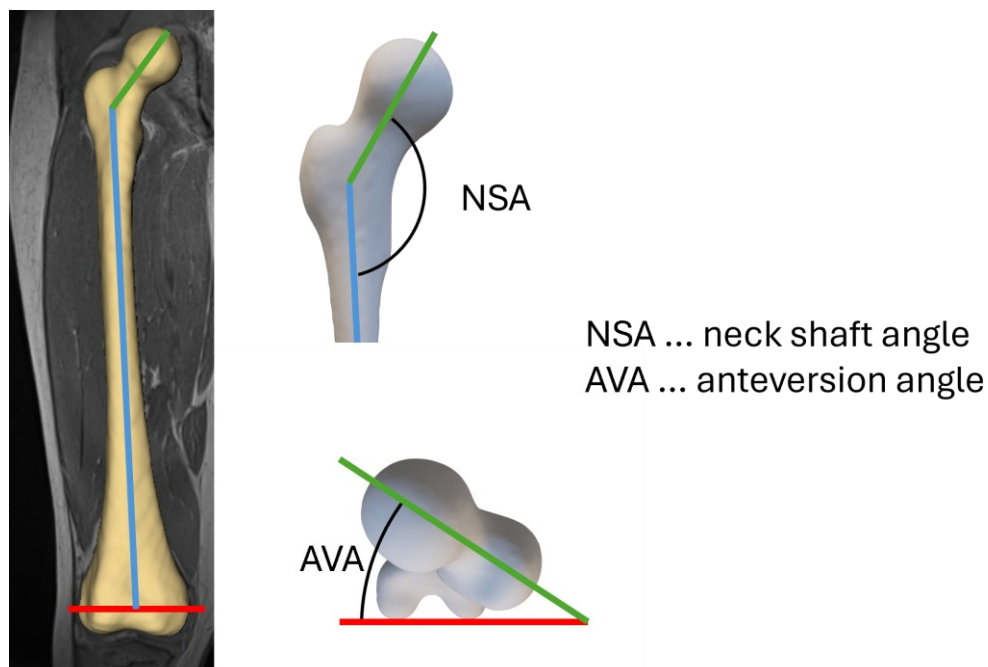


Figure 2: Schematic representation of the neck-shaft angle (NSA) and anteversion angle (AVA). NSA defined by the orientation of the neck (green line) and the shaft axis (blue line). The AVA is defined as the angle between the neck axis and a line passing the epicondyles in transverse plane (red line).

Clinically, the AVA and NSA are usually assessed by either physical examination or measurements in medical images, such as computer tomography (CT) and magnetic resonance image (MRI) scans. Various methodologies to perform these measurements exist, leading to different normative range values (Hernandez et al., 1981; Jarrett et al., 2010; Sangeux et al., 2015; Waidelich et al., 1992; Yoshioka and Cooke, 1987). Furthermore, a relatively high intra- and interobserver variability has been observed in studies for all of these methods (Kaiser et al., 2016; Sangeux et al., 2015; Schmaranzer et al., 2022).

Quantifying femoral NSA and AVA is challenging. With the use of machine learning, automated segmentation of medical images followed by quantification of femoral morphology might soon be used in clinics to get accurate and reliable measures (Milara et al., 2024; Wasserthal et al., 2023). However, to date, the established manual measurements (Hernandez et al., 1981; Jarrett et al., 2010; Murphy et al., 1987) are still used to inform clinical decision-making and surgical planning.

To summarize, the femoral morphology is complex, has a severe impact on a person's movement pattern and is associated with several pathologies and pain. Despite the difficulties in quantification of the morphology, it is often used to inform clinical interventions, such as de-rotation osteotomies.

1.2. Mechanobiological tissue response

The development of femoral morphology, similar as other bones, is influenced by the mechanical loading it is experiencing. More than a century ago, the theory that biological structures respond to mechanical loads has been proposed and it is continuously refined and adapted (Frost, 2001; Stevens et al., 1999; Wolff, 1892). Mechanobiological responses are multi-scale phenomena that occur at the organ, tissue, and cellular levels. These responses are present not only in bones but also in soft tissues such as muscles, tendons or cartilage (Wang et al., 2019). Cells are sensitive to mechanical loads and respond with biochemical actions that induce tissue remodeling, growth or absorption (Niebur, 2019). In bones, these biochemical signals trigger osteocytes, osteoblasts and osteoclasts to maintain bone health, absorb bone in unused areas and form new bone to ensure strength and functionality. Studies observed that low mechanical loads, e.g., when astronauts experience zero-gravity or due to immobilization, lead to reduced bone density (Lau and Guo, 2011; Sievänen, 2010). On the other hand, increased mechanical loading, e.g., due to physical activity, promotes mineralization and remodeling (Haapasalo et al., 2000). These remodeling and adaptation processes are crucial to withstand mechanical loading. In addition to mechanical loads, other factors such as genetics and nutrition affect bone growth (Stevens et al., 1999). The mechanical loads, however, guide the direction of growth and are therefore crucial for the shape of bones.

Finite element (FE) simulations are used to investigate the mechanobiological response of tissues. Bone is a heterogenous structure with wide varying material properties across different

regions (Linde et al., 1985; Rho et al., 1993). Inverse bone remodeling approaches to predict the bony structure based on the predominant loading conditions showed good agreement with experimental data (Bachmann et al., 2023; Barak et al., 2011; Campoli et al., 2012). Furthermore, FE simulations across multiple scales can be utilized to predict the mechanobiological response of biological structures to the mechanical loading (García-Aznar et al., 2021). Stresses and strains estimated from macro-scale FE simulations of the whole bone can be transferred to micro-scale FE models to estimate tissue and cell loading. Subsequently, biological responses can be modeled to predict adaptations on the tissue and organ level (Figure 3). These adaptations and resulting biological structures can be validated by imaging techniques such as CT or microCT scans. However, to obtain accurate results, realistic loading conditions need to be quantified in activities of daily living.

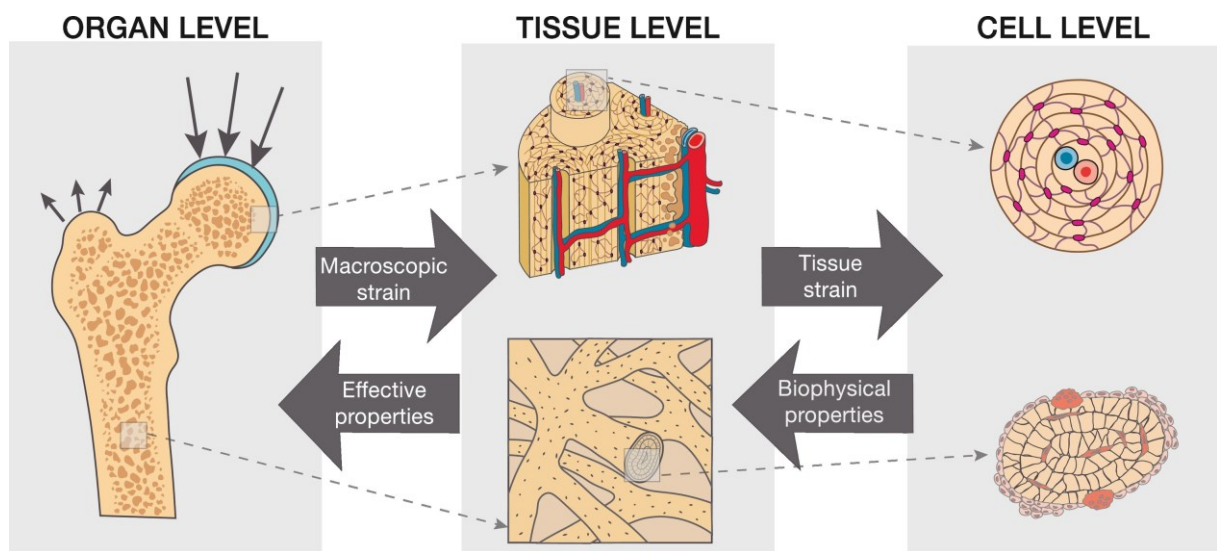


Figure 3: Finite element (FE) simulations at a macro scale can be used to estimate the mechanical loads at tissue level due to muscle and joint contact forces acting on the bone. Similarly, the consideration of a volume that incorporates detailed tissue enables estimations of stresses and strains on bone cells. According to the signals perceived, cells can update the bone tissue properties which in turn alters the bone structure at the macro scale. Figure adapted from García-Aznar (2021).

1.3. Estimation of mechanical loading on bones

Measuring mechanical loads that act on bones in vivo is not feasible in a non-invasive way. Joint loads measured with instrumented implants in patients that underwent joint arthroplasty are only available from a limited number of elderly people (Bergmann et al., 2001, 1993). Fortunately, musculoskeletal (MSK) simulations can be used to estimate muscle and joint contact forces based on experimentally measured motion capture data (Delp et al., 2007). A MSK model including bones, joints and muscles, is scaled to the participant's anthropometry and used to replicate the motion of the participant, quantified by a 3D motion capture system. Ground reaction forces are simultaneously recorded which allow to calculate external joint moments acting at the joints.

Subsequently, the muscle forces that are necessary to counteract these external joint moments to produce the recorded motion, can be estimated. Furthermore, the forces acting between bones within the joints can be calculated. Results of these MSK simulations have been shown to agree with experimentally measured joint contact forces (Buehler et al., 2021; Modenese et al., 2021; Steele et al., 2012).

Most MSK simulations are based on generic models which are derived from cadaveric or medical imaging data. The first step in a standard MSK simulation workflow based on generic models is the scaling of the model to the anthropometry of the participant. Typically, this is done based on the location of surface markers recorded in a static position during the 3D gait analysis (Kainz et al., 2017; Lund et al., 2015). How scaling errors influence simulation results on different levels has not been investigated in a comprehensive way so far. Nevertheless, this is relevant information for multi-scale studies, which use MSK simulation results as an input for further simulations.

MSK models can also be created from scratch based on CT or MRI scans of the participant (Kainz et al., 2021b; Modenese and Renault, 2021; Scheys et al., 2008; Valente et al., 2014). This process is, however, very time consuming and requires additional resources to collect the required medical images. Most researchers therefore rely on generic MSK models. However, generic models do not replicate the participant's MSK system exactly. Recently, the TorsionTool (Veerkamp et al., 2021) and the bone-deformation toolbox (Modenese et al., 2021) have been developed which enable personalization of lower limb bones in these generic musculoskeletal models. Both tools enable the modification of the model's femoral (i.e., AVA) and tibial torsional profiles, while the TorsionTool also enables adjustments to the femoral neck-shaft angle (NSA). Changes of the bony geometry not only alters the attachment sites of muscles but also moment arms of muscles across joints (Arnold and Delp, 2001; Scheys et al., 2008). Therefore, the optimization approach used to calculate muscle forces might lead to different muscle coordination strategies to produce the same motion in individuals with different femoral morphology. Personalization of the femoral geometry in MSK models has been shown to improve the agreement between simulation results and values obtained from instrumented implants (Modenese et al., 2021).

Due to the redundancy of the MSK system (i.e., each joint is spanned by multiple muscles) there are infinite muscle coordination strategies to counteract the external joint moments to produce the participant's motion. Therefore, optimization algorithms are used within these MSK simulations to estimate the muscle activations. A widely used approach is static optimization (SO) that minimizes the sum of squared muscle activations, which is a representative value for the effort of a muscle. Walking in humans is a very efficient task and therefore low co-contraction and minimal effort can be assumed (Anderson and Pandy, 2001; Waters et al., 1988). While SO does not account for subject-specific motor control and coordination strategy, there are other

approaches that use muscle activations recorded by electromyography (EMG) to inform the optimization algorithm (De Groote et al., 2016; Dembia et al., 2020; Pizzolato et al., 2015). It has been shown that EMG-informed approaches increase the agreement between simulated and experimentally measured joint contact forces (Bennett et al., 2022; Hoang et al., 2019). This is of importance especially in participants with neurological disorders, as their motor control is impaired. Nevertheless, a study on children with CP has shown that the personalization of femoral geometry outweighs the effect of personalized motor control (Kainz et al., 2021b).

Muscle and joint contact forces depend on an individual's bony geometry, the subject-specific motor control and the gait pattern (i.e. joint kinematics and ground reaction forces). Whether the gait pattern or the person's bony geometry is the main contributor to altered joint contact forces in pathological cohorts has not been assessed comprehensively. Though, this information would be important to identify if clinical interventions should mainly target static, anatomical impairments, i.e. bony deformities, or dynamic, functional impairments, i.e. pathological gait pattern, to normalize loading conditions.

To summarize, MSK simulations provide a good estimation of muscle and joint contact forces as loading condition on the MSK system. However, certain steps like scaling the model should be taken with special care to reduce potential errors. The MSK models' bony geometry should be personalized with the use of medical images to improve the accuracy of estimated joint loads. Furthermore, EMG-informed MSK simulations might provide more accurate results, especially in participants with neurological disorders, as they account for subject-specific motor control.

In each part of the circular dependency of the musculoskeletal morphology, gait pattern, mechanical loading and growth, specific measurements – such as medical imaging and 3D gait analysis – alongside simulations like MSK and FE simulations can be utilized to assess the current state (e.g. bony structure, walking pattern) and to estimate the influencing factors within these interactions (e.g. muscle force, joint contact forces, tissue stresses that influence bone growth). Combining all these could help to improve our insights into this complex interplay and might enable early detection of pathological bone growth. A person's femoral morphology can be quantified and incorporated into a personalized MSK model. MSK simulations based on the person's experimentally recorded movement data can be performed to estimate muscle as well as joint contact forces acting on the femur. In turn, the obtained mechanical loading can be used to inform mechanobiological FE simulations to predict the femoral development.

1.4. Multi-scale mechanobiological workflow to predict femoral growth trend

Multi-scale simulations in combination with a mechanobiological bone growth model have been used to estimate bone loads and predict proximal femoral growth trends based on cross-sectional data (Carriero et al., 2011; Kainz et al., 2020; Shefelbine and Carter, 2004; Yadav et al., 2021, 2017, 2016). Within this multi-scale workflow, the loadings on the participant's femur during

walking are derived from MSK simulations based on subject-specific models and 3D gait analysis data. Subsequently, the muscle and joint contact forces from the MSK simulations are applied to a FE model of the femur created from MRIs to estimate the stresses within the growth plate. Based on these stresses, a growth rate and growth direction are calculated for each element within the growth plate representing the mechanobiological response of the structure at tissue level. Finally, growth of the femur is simulated in a second FE analysis and the development of certain angles (i.e., change in AVA or NSA) can be quantified by comparing the final with the baseline geometry (Figure 4). Previous studies using this workflow to calculate growth plate stresses and predict femoral growth revealed plausible growth patterns for healthy and pathological populations (Carriero et al., 2011; Kainz et al., 2020; Shefelbine and Carter, 2004; Yadav et al., 2021, 2017, 2016).

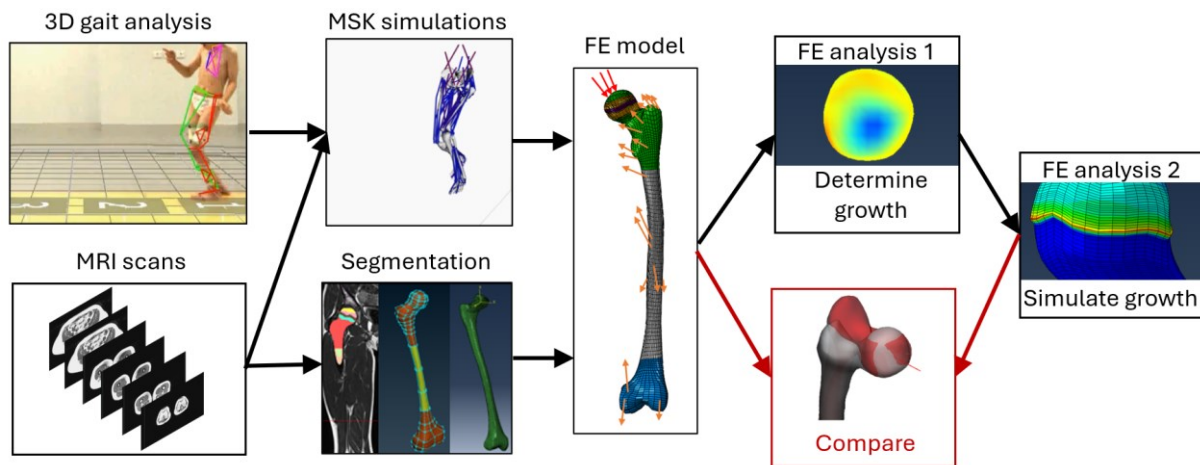


Figure 4: Schematic illustration of the mechanobiological multi-scale workflow to predict femoral bone growth. Data from three-dimensional (3D) gait analysis and magnetic resonance image (MRI) scans is used to perform personalized musculoskeletal (MSK) simulations to estimate muscle and joint contact forces acting on the femur. MRI scans are segmented to create a subject-specific mesh of the femur with hexahedral elements aligned with the growth plate. In finite element (FE) analysis 1, the stresses within the growth plate are assessed. In FE analysis 2, the biological response to these mechanical loads is simulated. Predicted growth changes can be quantified by comparing the grown with the baseline geometry.

Performing this workflow with subject-specific MSK and FE simulations is very time consuming. The mesh used for FE simulations requires to have hexahedral elements perfectly aligned in layers with the growth plate to allow modeling layer-wise ossification (Shefelbine and Carter, 2004). Therefore, previous studies were either based on a generic FE model of the femur (i.e., generic femoral morphology and growth plate shape and location) (Carriero et al., 2011; Kainz et al., 2021a) or included not more than three individuals (Kainz et al., 2020; Yadav et al., 2021, 2017, 2016). This limits the generalizability of findings of previous studies as it has been shown that the geometry of the growth plate substantially alters stresses within the growth plate (Yadav et al., 2016). Furthermore, this workflow includes many model parameters that are based on

assumptions. The lack of longitudinal data in previous studies hindered refinements of the mechanobiological model and validation of subject-specific growth predictions, thereby limiting clinical applications. Despite that approximately 70% of total growth happens at the distal growth plate (Anderson et al., 1963), it was not included in these subject-specific multi-scale simulations. Simulating growth at the distal growth plate could help to investigate pathological knee varus or valgus alignment or femoral shaft bending. Furthermore, subject-specific simulations for large cohorts might reveal insights how specific gait patterns influence femoral growth trends.

1.5. Thesis aims

The general aim of this thesis was to enhance the multi-scale modelling workflow to estimate MSK loads and predict bone growth in typically developing children and children with CP, and use it to gain novel scientific and clinical insights. The specific aims of this thesis were to:

1. Quantify the impact of scaling errors on MSK simulation results (Paper 1, Chapter 2.1).
2. Assess the influence of a person's gait pattern and femoral morphology on asymmetric hip joint contact forces (Paper 2, Chapter 2.2).
3. Quantify subject-specific stresses at the proximal growth plate in typically developing children and children with CP (Paper 3, Chapter 2.3).
4. Quantify subject-specific stresses at the distal growth plate in typically developing children and children with CP (Paper 4, Chapter 2.4).
5. Validate the multi-scale modelling workflow to predict growth trends (Paper 5, Chapter 2.5).

This thesis is based on analysis of retrospective 3D motion capture data and MRI scans of typically developing children and children with CP. Additionally, a unique longitudinal dataset including 3D gait analysis data and MRIs was collected at two timepoints approximately two years apart (Figure 5), and used to validate the growth predictions.

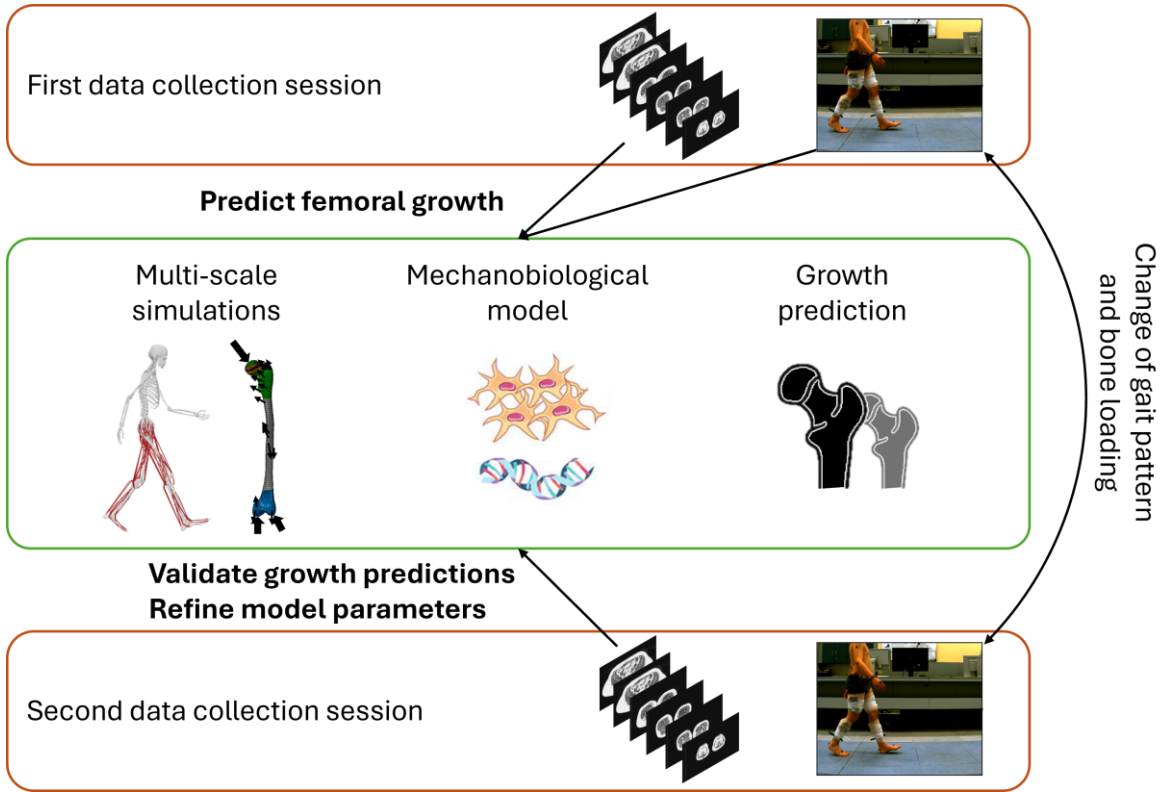


Figure 5: Schematic illustration of longitudinal study design used in Chapter 2.5. Data of magnetic resonance image (MRI) scans and three-dimensional gait analysis was used to perform multi-scale simulations and model the mechanobiological response to predict femoral growth. MRI scans of the second data collection session were used to validate the predicted development.

1.5.1. Technological developments

The previously released version of the TorsionTool (Veerkamp et al., 2021) was able to alter lower limb geometries of a single generic MSK model (i.e., gait2392 model). However, many other models are available which include more representative muscle properties of healthy individuals and higher complexity (e.g. include more degrees of freedom at the knee joint or enable a differentiation between medial and lateral knee joint contact force). Hence, we extended the TorsionTool to allow modification of additional MSK models and subsequently published the updated scripts on SimTK (<https://simtk.org/projects/torsiontool>). The updated tool was used in Paper 3, 4 and 5 of this thesis.

Alterations of the bony geometry change moment arms of muscles. Therefore, modifications of the femur and tibia might result in unphysiological moment arms during movement. A MATLAB (MathWorks, Massachusetts, USA) script was developed to check moment arms of all lower limb muscles for given kinematics. If discontinuities in moment arms are detected, corresponding wrap objects, that guide muscle paths around bony structures, are automatically altered to ensure smooth moment arms and realistic simulations. We published the script open source (https://github.com/WilliKoller/OpenSim_MuscleMomentArmsChecker) and used it in all five papers of this study.

Furthermore, the workflow to perform multi-scale simulations to predict femoral bone growth was enhanced. Up to now, the creation of subject-specific hexahedral meshes with elements aligned in layers within the growth plate was very time consuming and required substantial knowledge. The GP-Tool was developed and released open source (<https://github.com/WilliKoller/GP-Tool>), which enables semi-automatic creation of such meshes in short time with a comprehensive graphical user interface. Additionally, it enables to use loading conditions given as output of OpenSim (Delp et al., 2007) to calculate stresses within the growth plate and predict femoral bone growth. This enables subject-specific mechanobiological analysis based on the participants' femoral morphology and mechanical loading in large cohorts and short time (see Paper 3, Chapter 2.3). In Paper 4 of this thesis (Chapter 2.4), I extended the GP-Tool to include analysis of the distal growth plate. All tools and workflows developed within this thesis were published open-access to foster and accelerate further research.

1.5.2. Clinical insights

In Paper 2 (Chapter 2.2), we assessed the influence of a person's gait pattern and the femoral morphology on asymmetric hip joint contact forces. This study revealed that the individual's gait pattern is the main contributor to asymmetric hip loads. Our findings highlighted that clinical interventions should target functional improvements, i.e. improve the pathological gait pattern, additionally to correcting bone alignments, to ensure a normalization of the loading conditions and prevent further pathological developments.

In Paper 3 (Chapter 2.3), we quantified growth plate stresses at the proximal femoral growth plate within large cohorts of 24 femurs of children with CP and 26 femurs of typically developing (TD) children. The paper provided reference values of growth plate loads from TD children and showed that some children with CP experience very different loads of the growth plate, which might be the reason for the pathological femoral developments.

In Paper 4 (Chapter 2.4), we showed that children with CP, who walk with an increased knee flexion, experience more anterior promoted growth at the distal femoral growth plate. In the long run, the anterior promoted growth could lead to a more anterior bending of the femoral shaft which was confirmed by the analysis of the MRI scans of our participants.

In Paper 5 (Chapter 2.5), we showed that predictions from the multi-scale workflow, together with physical activity information and anthropometric data correlate significantly with the development of femoral anteversion quantified from MRI scans which were two years apart. These predictions based on 3D gait analysis and medical images could help to identify pathological femoral development at an early stage and therefore, support clinical decision making for torsional deformities.

1.6. Overview of included publications

Paper 1: Impact of scaling errors of the thigh and shank segments on musculoskeletal simulation results

MSK simulations are widely used in the research community. The locations of surface markers are often used to scale a generic model to the participant's anthropometry. Marker-based scaling approaches include errors due to inaccuracies in marker placements. Scaling errors of the thigh and shank segment were systematically induced and its' effect on MSK simulations results quantified comprehensively. Scaling errors mainly changed the magnitude but not the shape and function of most analyzed parameters. The results of this study can be used to estimate potential errors due to marker-based scaling approaches in previous and future studies.

Paper 2: The gait pattern and not the femoral morphology is the main contributor to asymmetric hip joint loading

Gait asymmetry and skeletal deformities are common in many children with and without neurological disorders. Changes of the hip joint loading, i.e. hip joint contact force (HJCF), can lead to pathological femoral growth. An individual's gait pattern and the femoral morphology affect HJCFs. Differences between left and right HJCF magnitude and orientation were computed and compared between participant groups (CP versus TD). Additionally, the influence on HJCF asymmetries solely due to the femoral morphology and solely due to the gait pattern was quantified using fictive what-if simulations. Our findings demonstrated that the gait pattern is the main contributor to asymmetric HJCFs in CP and TD children. Clinical interventions should, therefore, focus on normalizing the gait pattern additionally to correcting the femoral morphology.

Paper 3: Intra- and inter-subject variability of femoral growth plate stresses in typically developing children and children with cerebral palsy

This paper was published as one of the Highlights from the 27th Congress of the European Society of Biomechanics, 2022.

Within this study, the GP-Tool was developed and used to analyze intra- and inter-subject variability in growth plate stresses in a large cohort of CP and TD children. Additionally, the influence of the musculoskeletal model and the chosen material properties on simulation results was investigated. Intra-subject variability in growth plate stresses was higher in CP than in typically developing children. A representative reference growth distribution heatmap generated from data of 26 TD children's femurs showed a ring shape with low values in the center region and high values at the border of the growth plate. This was a plausible result as previous studies based on medical images show that the shape of the growth plate changes from a convex to a flatter disc with age (Kandzierski et al., 2012). Furthermore, some children with CP showed similar growth patterns as the TD cohort while the distribution of some others was completely different,

potentially leading to pathological proximal femoral growth. Our findings agree with clinical observation where some children with CP experience normal, while others experience pathological femoral developments.

Paper 4: ESMAC Best Paper Award 2023: Increased knee flexion in participants with cerebral palsy results in altered stresses at the distal femoral growth plate compared to a typically developing cohort

In 2023, I won the *Best Paper Award* at the annual meeting of the European Society for Movement Analysis in Adults and Children (ESMAC) in Athens (Greece). Hence, we were invited to publish this paper. Importantly, despite being an Award Paper, the paper was still peer reviewed.

We analyzed growth trends within the distal femoral growth plate in TD and CP children. Limbs of participants with CP were grouped depending on their knee flexion kinematics during stance phase as this potentially changes the stresses induced by knee and patellofemoral joint contact forces. Higher growth rates were observed in the anterior compartment in CP limbs with high knee flexion while CP limbs with normal knee flexion showed high similarity to the group of healthy participants. This indicates that the knee flexion angle during the stance phase is of high relevance for typical bone growth at the distal femur. The observed growth rates were plausible, as long-term promoted growth in the anterior compartment leads to anterior bending of the femur which was confirmed for the group with high knee flexion through analyses of the femoral geometry with medical images.

Paper 5: Femoral bone growth predictions based on personalized multi-scale simulations: Validation and sensitivity analysis of a mechanobiological model

This study aimed to experimentally investigate the growth predictions from multi-scale mechanobiological simulations using MRIs and motion capture data – collected longitudinally – from ten growing children. Additionally, a sensitivity analysis was conducted to refine model parameters. A linear regression model based on predictions from the refined mechanobiological model, physical activity information and anthropometric data was able to explain 66% of femoral anteversion development. Notably, the direction of femoral development was accurately predicted in 18 out of 20 femurs, suggesting that growth predictions could help to identify the potential for pathological femoral development at an early stage and therefore, support clinical decision making for torsional deformities.

1.7. Additional co-authored publications not included in this thesis

- Buehler, C.†, **Koller, W.**†, De Comtes, F., Kainz, H., 2021. Quantifying Muscle Forces and Joint Loading During Hip Exercises Performed With and Without an Elastic Resistance Band. Front. Sports Act. Living 3, 695383. <https://doi.org/10.3389/fspor.2021.695383>
- Exel, J., Deimel, D., **Koller, W.**, Werle, C., Baca, A., Maffiodo, D., Sesana, R., Colombo, A., Kainz, H., 2023. Neuromechanics of finger hangs with arm lock-offs: analyzing joint moments and muscle activations to improve practice guidelines for climbing. Front. Sports Act. Living 5. <https://doi.org/10.3389/fspor.2023.1251089>
- Kainz, H., **Koller, W.**, Wallnöfer, E., Bader, T.R., Mindler, G.T., Kranzl, A., 2024. A framework based on subject-specific musculoskeletal models and Monte Carlo simulations to personalize muscle coordination retraining. Sci Rep 14, 3567. <https://doi.org/10.1038/s41598-024-53857-9>
- Kaufmann, P., **Koller, W.**, Wallnöfer, E., Goncalves, B., Baca, A., Kainz, H., 2024a. Increased trial-to-trial similarity and reduced temporal overlap of muscle synergy activation coefficients manifest during learning and with increasing movement proficiency. Sci Rep 14. <https://doi.org/10.1038/s41598-024-68515-3>

† shared first author

1.8. Overview of conference presentations related to the research of this thesis

- Koller, W.**, Kranzl, A., Mindler, G., Baca, A., Kainz, H., 2024. Advanced multi-scale mechanobiological simulations enable the distinction between healthy and pathological bone growth patterns. <https://doi.org/10.36950/2024.4ciss007>
Oral presentation at the 19th Congress of the Austrian Sport Science Society (ÖSG)
Winner of the “Young Investigator Award”
- Koller, W.**, Mindler, G., Kranzl, A., Svehlik, M., Baca, A., Kainz, H., 2024. Multi-scale mechanobiological growth simulations can differentiate between individuals with different femoral growth patterns. <https://doi.org/10.1016/j.gaitpost.2024.07.136>
Oral presentation at the Annual Meeting of the European Society for Movement Analysis in Adults and Children (ESMAC)
- Koller, W.**, Zwicker, M., Baca, A., Kainz, H., 2024. Femoral growth predictions based on multi-scale models: which model leads to the most accurate predictions?
Oral presentation at 29th congress of the European Society of Biomechanics (ESB)
Runner-Up of the “ESB Student Award”

Koller, W., Wallnöfer, E., Holder, J., Kranzl, A., Baca, A., Kainz, H., 2023. Femoral growth plate stresses in children with cerebral palsy compared to typically developing children.
<https://doi.org/10.1016/j.gaitpost.2023.07.128>

Oral presentation at the Annual Meeting of the ESMAC

Winner of the “Best Paper Award”

Koller, W., Gonçalves, B., Baca, A., Kainz, H., 2023. Femoral growth plate stresses in children quantified with a semi-automated multi-scale modeling workflow.

Oral presentation at the 18th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering (CMBBE)

Koller, W., Kranzl, A., Baca, A., Kainz, H., 2023. Net joint moments versus internal joint loading: Can we trust correlations between joint moments and contact forces from generic-scaled models? <https://doi.org/10.1016/j.gaitpost.2022.11.022>

Oral presentation at 4th Conference of the “Gesellschaft für die Analyse menschlicher Motorik und ihre klinische Anwendung” (GAMMA)

4th place “Best Presentation Award”

Kainz H., **Koller, W.**, Kaufmann, P., Unglaube, F., Kranzl, A., Baca, A., 2022. Impact of Bony Geometry on Static Optimization Based Estimations of Muscle Activations and Forces.
<https://doi.org/10.11128/arep.17.a17042>

Oral presentation at 10th Vienna International Conference on Mathematical Modelling

Koller, W., Baca, A., Kainz, H., 2022. Intra-subject variability of femoral growth simulations based on personalized finite element models.

Oral presentation at 27th congress of the ESB

Koller, W., Baca, A., Kainz, H., 2021. Asymmetric gait pattern versus femoral morphology – What is the main reason for asymmetric hip joint loading?
<https://doi.org/10.1016/j.gaitpost.2021.09.065>

Oral presentation at the annual meeting of the ESMAC

Koller, W., Baca, A., Kainz, H., 2021. Impact of femur length scaling errors on estimate muscle and joint contact forces at all joints.

Poster presentation at 28th congress of the International Society of Biomechanics (ISB)

2. Publications

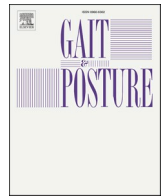
2.1. Impact of scaling errors of the thigh and shank segments on musculoskeletal simulation results

Authors: Willi Koller, Arnold Baca and Hans Kainz

Status: The manuscript was published in *Gait & Posture* Volume 87, 65–74 in 2021.

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Authors' contribution: All authors contributed to the conceptualization of the study. The data was collected by Hans Kainz. The analyses were performed by Willi Koller. All authors contributed to the interpretation of the data. Willi Koller wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript and approved the submission.



Full length article

Impact of scaling errors of the thigh and shank segments on musculoskeletal simulation results

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Musculoskeletal simulation
Scaling
Cerebral palsy
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ABSTRACT

Background: Musculoskeletal simulations are widely used in the research community. The locations of surface markers are mostly used to scale a generic model to the participant's anthropometry. Marker-based scaling approaches include errors due to inaccuracies in marker placements.

Research question: How do scaling errors of the thigh and shank segments influence simulation results?

Methods: Motion capture data and magnetic resonance images from a child with cerebral palsy and a typically developing child were used to create a subject-specific reference model for each child. These reference models were modified to mimic scaling errors due to inaccurately placed lateral epicondyle markers, which are frequently used to scale the thigh and shank segments. The thigh length was altered in 1 % steps from the original length and the shank length was accordingly adjusted to keep the total leg length constant. Thirty additional models were created, which included models with an altered thigh length of ± 15 %. Subsequently, musculoskeletal simulations with OpenSim were performed with all models. Joint kinematics, joint kinetics, muscle forces and joint contact forces (JCF) were compared between the reference and altered models.

Results: The investigated scaling error influenced joint kinematics and joint kinetics by up to 9.4° (hip flexion angle) and 0.15 Nm/kg (knee flexion moment), respectively. Maximum muscle and JCF differences of 46 % (medial gastrocnemius) and 72 % (hip JCF) bodyweight, respectively, were observed between the reference and altered models. Scaling errors mainly changed the magnitude but not the shape of most analyzed parameters. The influence of scaling errors on simulation results were similar in both participants.

Significance: Scaling errors of the thigh segment influence simulation results at all joints due to the global optimization approach used in musculoskeletal simulations. Our findings can be used to estimate potential errors due to marker-based scaling approaches in previous and future studies.

1. Introduction

Musculoskeletal simulations based on commercial (i.e. Anybody, [1]) and open-source software packages (e.g. OpenSim [2],) are widely used in the research community [3]. Over the last decade, musculoskeletal simulations are increasingly used to answer clinical-relevant questions [4–7]. Furthermore, musculoskeletal simulations in combination with finite-element simulations enable to conduct multi-scale studies to estimate tissue stresses [8] or predict bone growth [9].

The first step in the musculoskeletal simulation workflow is to generate the subject-specific model. The gold standard for personalizing a musculoskeletal model is to create the model based on the segmentation of medical images [10–14]. This, however, requires the collection of medical images (i.e. magnetic resonance images or computer

tomography), which is expensive and demanding on the participants, especially in children or pathological populations. Alternatively, biplane x-rays or 3D ultrasound measurements could be used to determine subject-specific anatomical landmarks for personalizing a model [15]. X-rays and computer tomography, however, are invasive and therefore are barely used in children without a clinical reason. Furthermore, creating a model from medical images is very time-consuming and requires a lot of expertise. Hence, this approach is not used in clinical practice and barely used in the research community.

In most cases, a generic musculoskeletal model is scaled to the anthropometry of the participant based on the location of surface markers on the model and the participant. Several marker-based scaling approaches have been proposed to adjust the segment lengths of the model [16,17]. However, all approaches include errors. Scaling is the

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first step of a musculoskeletal simulation workflow. Hence, scaling errors will impact on all further calculations.

The lateral femoral epicondyle marker is difficult to place and therefore the intra- and inter-examiner precision is only around 10 mm and 19 mm, respectively [18]. This marker, however, is frequently used to scale the thigh and shank segments. Inaccurately placed lateral epicondyle markers can lead to increased femur and decreased tibia length or vice versa. Furthermore, it is very common to scale the thigh segment based on the distance between the lateral femoral epicondyle marker and the anterior superior iliac spine marker. Additionally, to the marker position, this distance, however, depends on the hip flexion angle and therefore can lead to increased errors, especially in people who have difficulties to stand in the anatomical neutral position (e.g. many children with cerebral palsy (CP)). In children, the typically used linear scaling methods lead to errors up to 15 % of femur length [16]. The purpose of this study was to quantify the impact of scaling errors of the thigh and shank on the musculoskeletal simulation results in children. A reference model from a typically developing (TD) child and a child with CP was modified to mimic scaling errors of the thigh segment. Joint kinematics, joint kinetics, muscle forces and joint contact forces of the lower limbs during walking were compared between the reference models and models with different amount of scaling errors. It was expected that scaling errors of the thigh and shank segments will influence simulation results at all joints due to the global optimization approach used in musculoskeletal simulations.

2. Methods

Magnetic resonance imaging data and motion capture data (marker trajectories and ground reaction forces) of a child with CP and one TD child were retrospectively analyzed for this study. The data was captured during a previous study [16] and ethics approval was obtained from the local ethics committee. These two male children were chosen to have the same age (both 8 years), nearly the same body mass (22 kg and 20 kg) and height (125 cm and 124 cm). Detailed information about the participants can be found in supplementary Table S1.

2.1. Musculoskeletal models

The torso body and associated muscles were removed from the generic 'gait2392' OpenSim model [2], which included 92 muscles and 23 degrees of freedom. Furthermore, the metatarsophalangeal joints were locked. Subsequently a reference model was created for every participant based on measurements from the MRI images. Pelvis width, height and depth as well as femur and tibia length were calculated from the MRI images as described in detail by Kainz et al. [16]. These 'gold standard' measures were used to scale the musculoskeletal model to create the reference model for each participant. The maximum isometric muscle forces were scaled by Eq. (1) [19,20].

$$F_{scaled} = F_{generic} * \left(\frac{m_{scaled}}{m_{generic}} \right)^{\frac{2}{3}} \quad (1)$$

The reference model was systematically modified to create models, which included different amounts of scaling errors. The thigh length was altered in 1 % steps from the original length and the shank length was accordingly adjusted to keep the total leg length constant. Furthermore, the marker positions of the musculoskeletal model were adjusted to match the position of the markers of the 3DGA using a customized MATLAB script. Thirty additional models were created, which included models with an altered thigh length of ± 15 %. This error range was

chosen based on the data of a previous study which evaluated the accuracy of marker-based scaling approaches reporting femur length scaling errors of approximately ± 10 % in TD children and up to 12.4 % in children with CP [16]. This error span includes errors due to misplaced surface markers and deviation in joint angles from the anatomical position (i.e. hip flexion angle will influence scaling if a pelvis and knee marker is used to scale the thigh segment).

2.2. Musculoskeletal simulations

For the musculoskeletal simulations three and four gait trials were used for the TD and the CP child, respectively. The motion capture data was based on the Plug-in-Gait marker set with additional clusters of three markers on each thigh and shank segment and an additional marker at the 5th metatarsal head of each foot. The reference models and the corresponding gait analysis data were used to run inverse kinematics followed by inverse dynamics, static optimization by minimizing the sum of squared muscle activations and joint reaction load analyses [21] with MATLAB R2020a (Mathworks Inc., Natick, MA, USA) and OpenSim 4.1 [3]. Markers close to joint axes were excluded during inverse kinematics. The remaining markers were weighted equally as detailed in the supplementary Table S2. Afterwards, the same workflow was used to run the simulations for the 30 modified models of each participant.

2.3. Data analysis

Joint kinematics, joint kinetics, muscle forces, joint contact forces and joint contact force orientations of the lower limbs during walking were compared between the reference models and models with different amount of scaling errors. First, all results were time normalized to a full gait cycle from initial contact to the following initial contact of the same foot. Subsequently for every model and analyzed parameter, the mean waveform for all gait trials were calculated. Afterwards, the root-mean-square-error (RMSE) between the reference model and every single other model was computed. The orientation of the joint contact forces was defined as the mean value of the contact force during the whole gait cycle.

3. Results

All plots in Figs. 1–6 show the results for the left leg, results for the right leg can be found in the supplementary material. Detailed numeric results are available as a MATLAB file in the electronic appendix. In general, the RMSE due to scaling error were similar between the TD and CP participant (Fig. 1).

3.1. Joint kinematics

Errors due to altered femur and tibia length mainly altered joint kinematics in sagittal and frontal plane while effects on transversal plane kinematics were negligible (Fig. 2). Maximum absolute differences between the reference and modified models were 9.4° and 7.8° for the hip flexion angle in the TD and the CP child, respectively. All tracking errors of the inverse kinematic simulations were below the OpenSim's best practice recommendations (Supplementary Table S3).

3.2. Joint kinetics

Scaling errors had a minor impact on joint moments (Fig. 3). The largest differences were 0.15 Nm/kg and 0.12 Nm/kg (right leg) for the

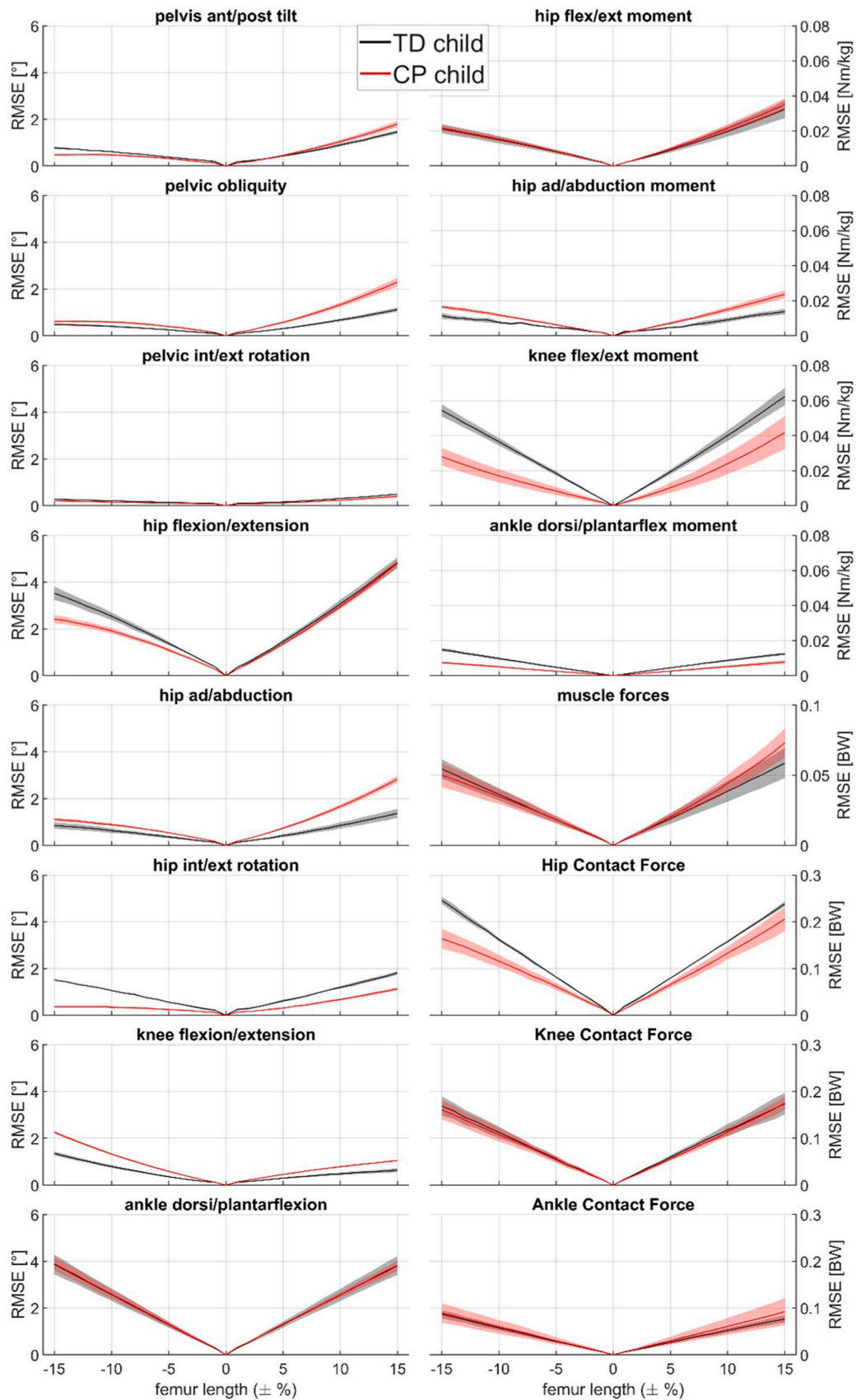


Fig. 1. Comparison of the root mean square errors (RMSE) between the reference model and the adapted models. The RMSE of the muscle forces were calculated as the mean RMSEs over all observed muscles. The RMSEs for the CP child are shown in red and the RMSEs for the TD child are black. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

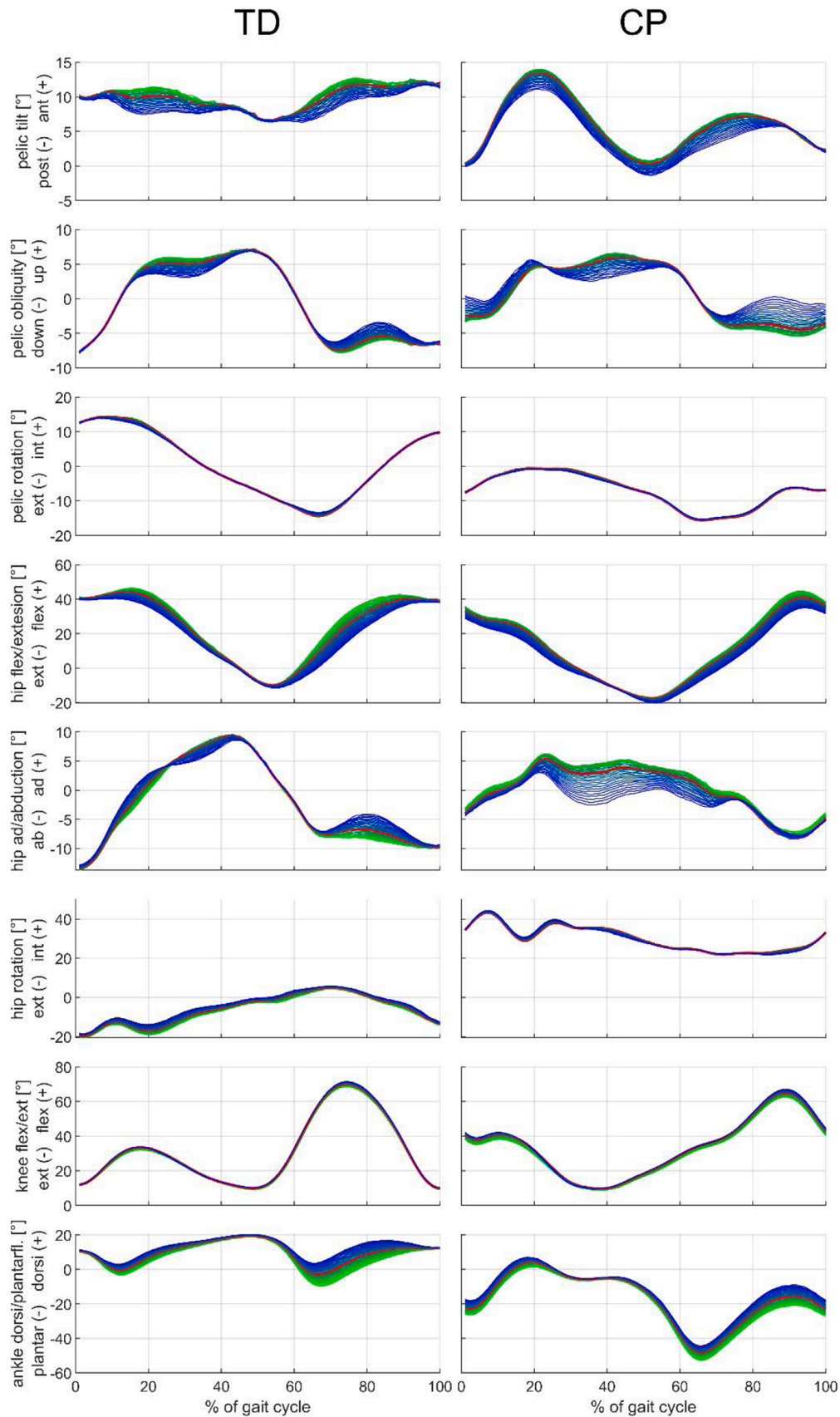


Fig. 2. Joint kinematics of the TD (left column) and the CP child (right column) obtained with the reference and modified models. The red line shows the mean kinematic waveforms of the reference model. Green lines represent the models with shorter femur length while blue lines show the models with increased femur length. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

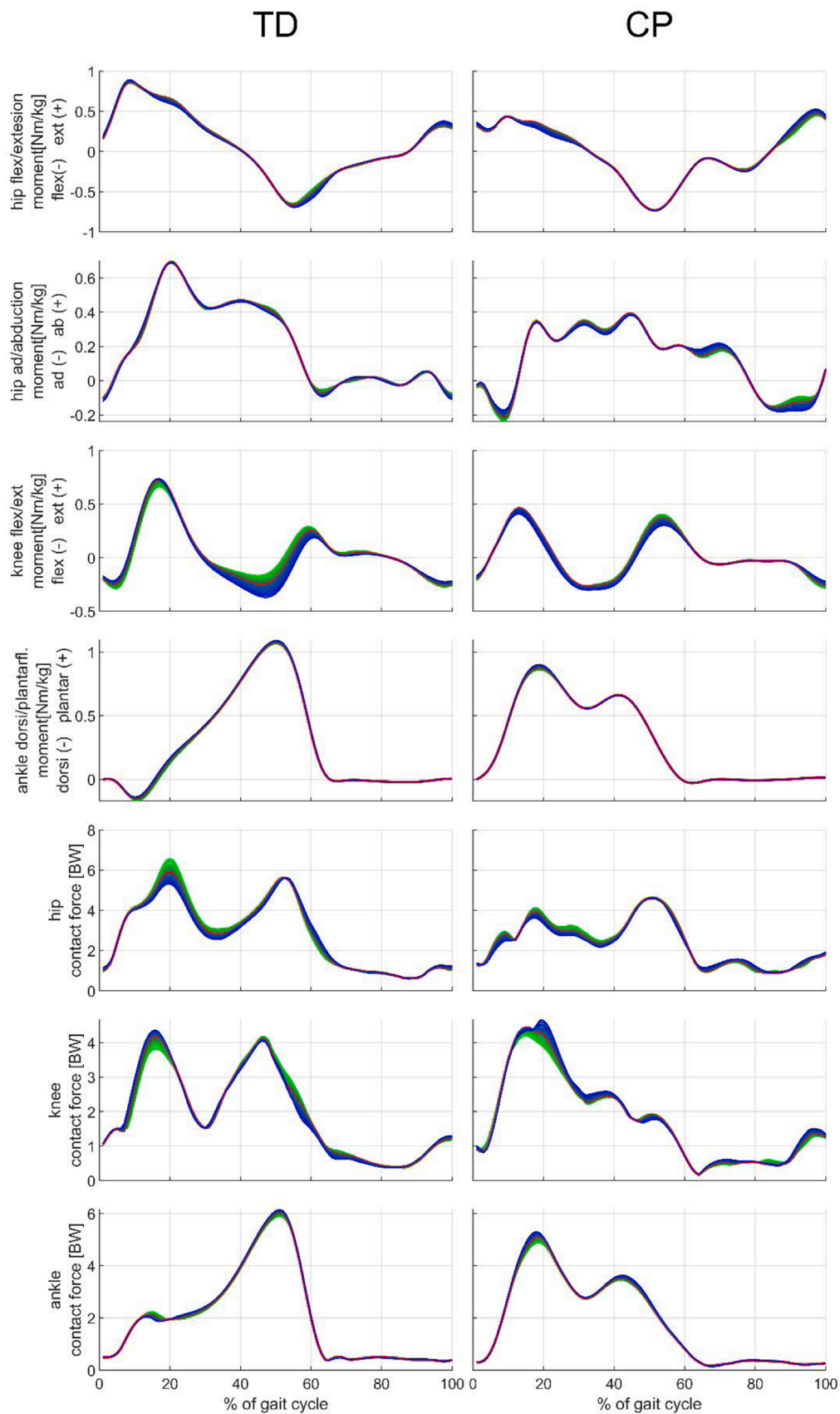


Fig. 3. Comparison of joint kinetics and joint contact forces of the TD (left column) and the CP child (right column) including all modified models. The red line shows the mean waveforms of the reference model. Green lines represent the models with shorter femur length while blue lines show the models with increased femur length. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

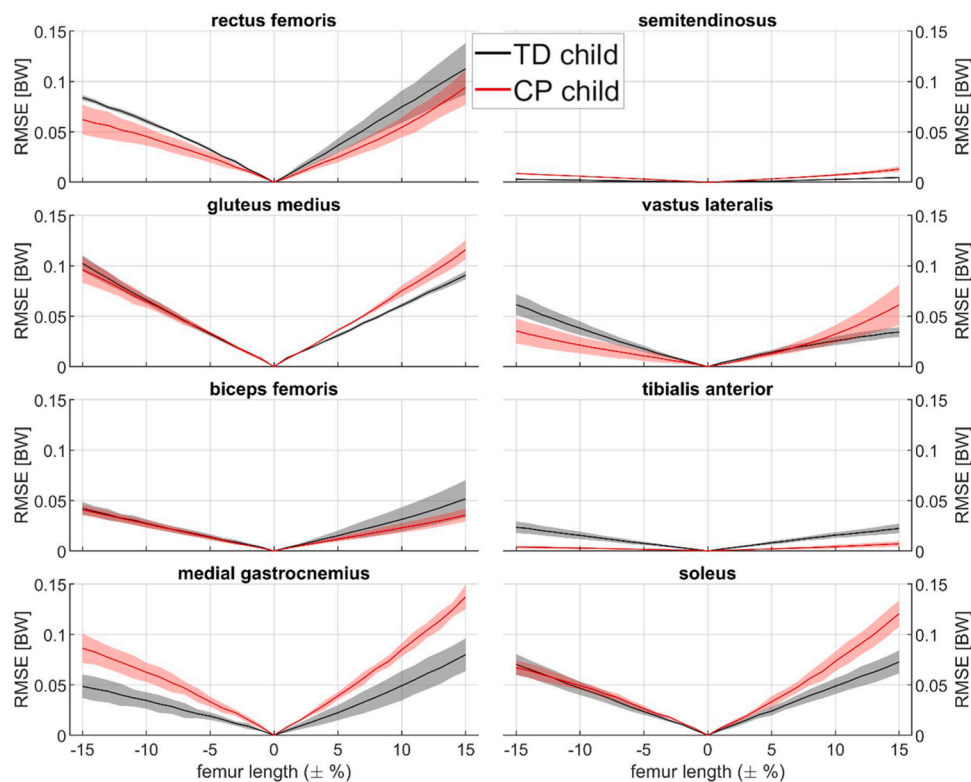


Fig. 4. Comparison of the root mean square errors of an example of muscle forces between the reference model and the modified models. The RMSEs for the CP child are shown in red and the RMSEs for the TD child are black. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

knee flexion moment of the TD and the CP child, respectively. All other joint moments showed errors lower than 0.08 Nm/kg for both participants.

3.3. Muscle forces

The influence of scaling errors on estimated muscle forces varied between muscles (Figs. 4 and 5). In the TD child the largest error occurred at the rectus femoris muscle with a value of 34 % of the bodyweight (Fig. 5). In the child with CP, the biggest influence of the scaling error was observed in the medial gastrocnemius muscle with an error of 46 % of the bodyweight.

3.4. Joint contact forces (JCF)

A decreased femur length and increased tibia length led to higher hip JCF and lower knee JCF in both participants (Fig. 3). The errors in ankle JCF were small compared to the errors in hip and knee JCF.

Maximum differences in JCF of 72 % bodyweight and 35 % bodyweight were observed for the TD and the CP child, respectively. These values corresponded with an increase of 12 % and 14 % of the first peak of the hip JCF for the TD child and CP child, respectively.

3.5. JCF orientations

Scaling error had an impact on the JCF orientation in transversal plane while the differences in the frontal and sagittal plane were minor (Fig. 6). For both participants, the largest errors were observed for ankle JCF orientations in the transverse plane.

4. Discussion

The purpose of this study was to investigate the impact of scaling errors on simulation results. In general, we found that scaling errors of the thigh segment influence all simulation results, which was in agreement with our assumption. Furthermore, our findings showed that the impact of scaling errors on simulation results is similar for pathological and typical gait.

Simulation results of the reference models were in agreement with previous studies. Joint kinematics and kinetics were comparable to Schwartz et al. [22] and muscle and JCF were in agreement with Modenese et al. [13] and Bergmann et al. [23]. The simulation results from our participant with CP were similar to previous studies in children with CP, which reported joint kinematics and kinetics [24], muscle forces [20] and JCF [21].

In most analyzed parameters, scaling errors led to a shift of the waveforms and did not change the shape or function of the parameter. This, however, was not the case for the hip adduction angle. Interestingly, increased femur length changed the hip movement strategy from hip adduction to abduction during terminal stance and pre-swing in the participant with CP.

Scaling errors mainly influenced joint moments at the knee joint. Femur and tibia length were altered contrary; therefore, the leg length was constant over all models. This barely affected the ankle and hip joint center locations; hence, the impact was small on these joint moments.

The influence of scaling errors on muscle forces varied between muscles. Due to changed joint kinematics the muscle moment arms were influenced. Hence, this led to altered muscle forces. Furthermore, because of the changed knee joint moment, some muscles had to

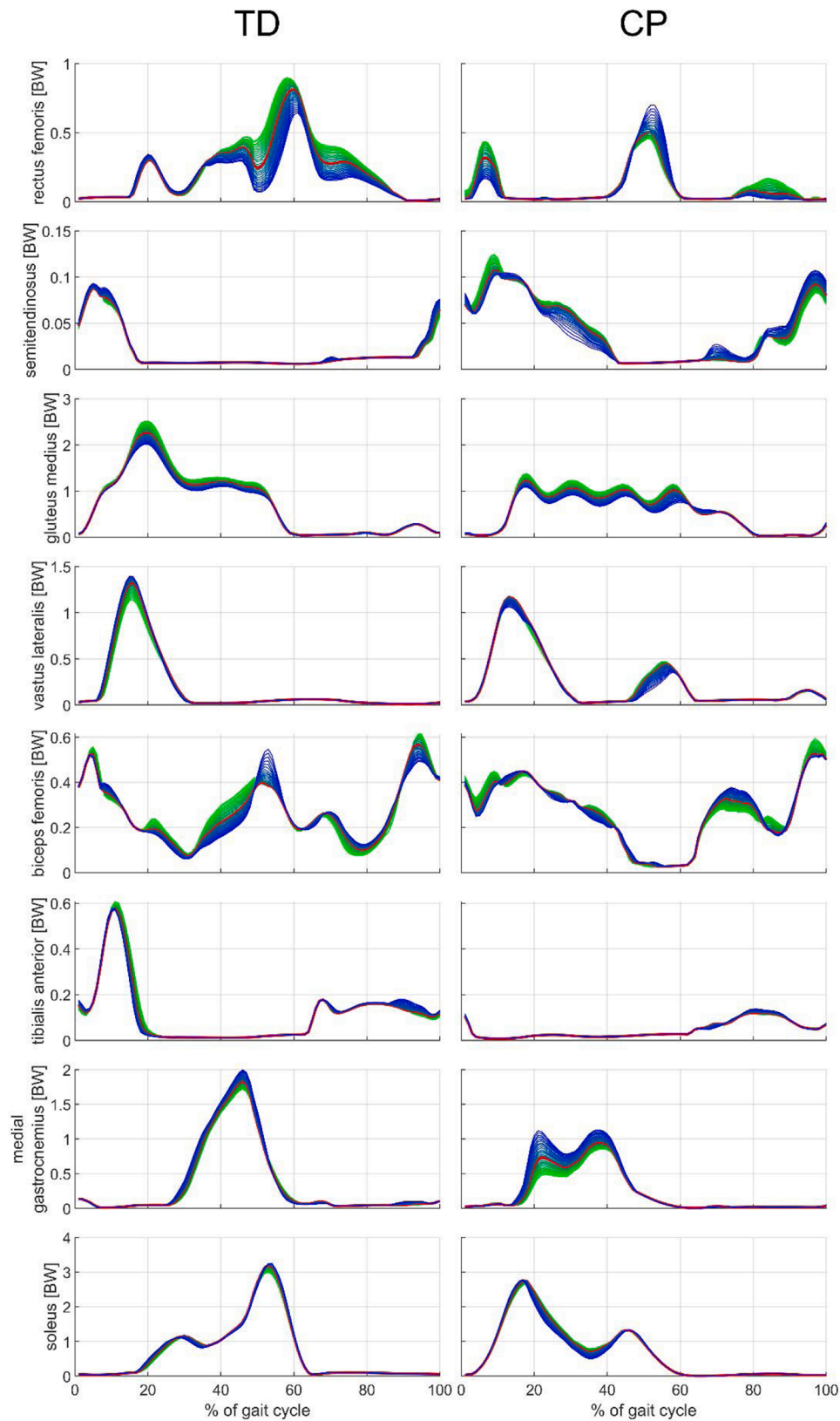


Fig. 5. Comparison of an example of muscle forces obtained with the reference and modified models. The red line shows the mean waveforms of the reference model. Green lines represent the models with shorter femur length while blue lines show the models with increased femur length. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

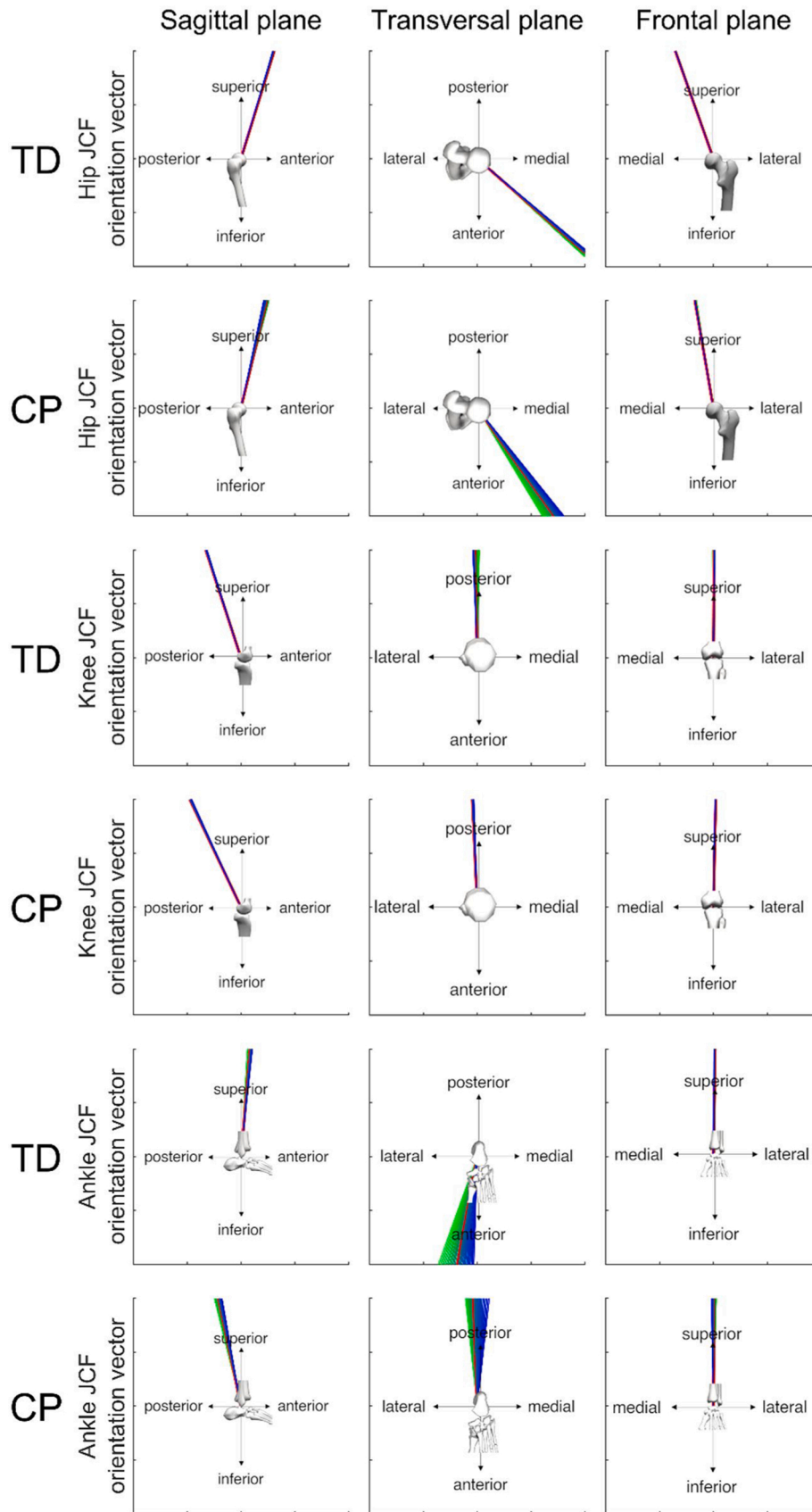


Fig. 6. Joint contact force orientations obtained with the reference and modified models. The red line shows the orientation of the reference model. Green lines represent the models with shorter femur length while blue lines show the models with increased femur length. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

generate a different force to provide the altered joint moment.

Maximum errors in JCF were observed at the hip joint. The used joint reaction analysis of OpenSim implements an inverse approach [21]. Hence, JCF were calculated from the ankle moving upwards. Therefore, altered ankle JCF influenced the knee JCF which, furthermore, affected the hip JCF. The cumulated error from the ankle to the hip JCF might explain why the maximum error was found at the hip joint.

JCF orientations, especially at the hip and knee joint, barely changed although the magnitude of the JCF were influenced by the scaling errors. Therefore, the magnitude changed in a similar way in all three anatomical directions. This is an important finding for multi-scale studies which use the JCF orientations as an input for further calculations (e.g. bone growth simulations [25]).

In a recent study the influence of a misplaced knee marker on joint kinematics was investigated using the Conventional Gait Model [26]. The Conventional Gait Model, however, uses a direct kinematics instead of an inverse kinematic approach to calculate joint angles and does not allow estimating muscle forces or JCF. Hence, to the best of the authors' knowledge, this is the first study, which investigated the impact of scaling errors on simulation results of musculoskeletal models in a systematic and comprehensive way.

Our error span included worst case scenarios due to misplaced markers and deviation in joint angles from the anatomical position. Scaling errors solely due to misplaced knee markers would likely result in a change in thigh length of less than 2 cm [18], which would be approximately 7 % of the thigh length of our participants.

Marker-based scaling approaches usually induce errors at every segment, which is scaled based on the location of surface markers. In (lean) children, however, the placement of pelvic, ankle and foot markers are relatively easy compared to the placement of the knee markers. Hence, we did not investigate the concurrent errors due to scaling inaccuracies of different segments.

Several model assumptions and simplifications influence musculoskeletal simulation results, whereas we only investigated the impact of thigh and shank scaling errors on the results. For example, we did not consider the age-specific bony geometry (e.g. femoral neck-shaft angle) in our participants because previous studies already quantified the impact of subject-specific geometry on simulation results in TD and CP children [9,14,27]. Furthermore, we did not consider soft tissue artifacts [28] and different optimization methods to estimate muscle forces [29,30] because we solely wanted to quantify the impact of scaling errors on simulation results independent of any confounding factors.

In summary, this is the first study which quantified the impact of scaling errors due to misplaced lateral epicondyle markers on musculoskeletal simulation results with OpenSim in a systematic and comprehensive way. Scaling errors mainly changed the magnitude but not the shape and function of most analyzed parameters. Our RMSE plots can be used to estimate potential errors due to marker-based scaling approaches in previous and future studies. Furthermore, the gained insights are relevant for multi-scale studies, which use musculoskeletal simulation results as an input for further simulations (e.g. hip JCF magnitude and orientation for femoral growth simulations [25]).

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We, further, confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.gaitpost.2021.02.016>.

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2.2. The gait pattern and not the femoral morphology is the main contributor to asymmetric hip joint loading

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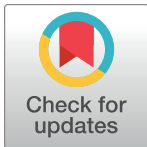
RESEARCH ARTICLE

The gait pattern and not the femoral morphology is the main contributor to asymmetric hip joint loading

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Data Availability Statement: The following material will be made publicly available on https://simtk.org/projects/bone_gait_load: (i) musculoskeletal models and (ii) MSK simulation results. MRI images are not publicly available due to restriction on sharing medical images (i.e. health information) and are not necessary to replicate the findings of the study.

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Abstract

Gait asymmetry and skeletal deformities are common in many children with cerebral palsy (CP). Changes of the hip joint loading, i.e. hip joint contact force (HJCF), can lead to pathological femoral growth. A child's gait pattern and femoral morphology affect HJCFs. The two-fold aim of this study was to (1) evaluate if the asymmetry in HJCFs is higher in children with CP compared to typically developing (TD) children and (2) identify if the bony morphology or the subject-specific gait pattern is the main contributor to asymmetric HJCFs. Magnetic resonance images (MRI) and three-dimensional gait analysis data of twelve children with CP and fifteen TD children were used to create subject-specific musculoskeletal models and calculate HJCF using OpenSim. Root-mean-square-differences between left and right HJCF magnitude and orientation were computed and compared between participant groups (CP versus TD). Additionally, the influence on HJCF asymmetries solely due to the femoral morphology and solely due to the gait pattern was quantified. Our findings demonstrate that the gait pattern is the main contributor to asymmetric HJCFs in CP and TD children. Children with CP have higher HJCF asymmetries which is probably the result of larger asymmetries in their gait pattern compared to TD children. The gained insights from our study highlight that clinical interventions should focus on normalizing the gait pattern and therefore the hip joint loading to avoid the development of femoral deformities.

Introduction

Gait asymmetry [1] and skeletal deformities [2–4] are common in many children with cerebral palsy (CP). Children with CP are born with typical bony geometry, but in many patients the femoral neck shaft angle (NSA) and anteversion angle (AVA) does not decrease during growth as in typically developing (TD) children [2, 5, 6]. In TD children the NSA and the AVA approximately decrease from 150° to 120° [7] and from 40° to 15° [2, 8] during childhood, respectively. The pathologic femoral geometry in children with CP affects moment arms of muscles [9], which might have an impact on the patient's gait pattern [10]. CP gait differs widely between

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patients and can be classified based on the joint kinematics of the lower limbs e.g. equinus drop foot gait, jump gait or crouch gait [11]. Gait asymmetries are higher in patient with hemiplegic CP compared to patients with diplegic CP. However, many children with diplegic CP have a more affected leg, which can also lead to an asymmetric gait pattern [1].

Bone is adaptive to mechanical loading [12, 13] and the hip joint contact force (HJCF) is one of the main biomarkers, which determines femoral bone growth [14–16]. Musculoskeletal simulations can be used to estimate subject-specific HJCF [17]. In a recent simulation study, Kainz et al. [18] showed that the orientation of the HJCF in the sagittal plane can differentiate between children with CP who are likely to have typical and pathological femoral growth. Asymmetric HJCF can alter growth plate loading [19] and therefore lead to asymmetric development of bones in length and shape resulting in altered biomechanics. Previous studies showed that not only the subject-specific gait pattern but also the femoral geometry has a big impact on the estimation of the HJCF [16, 20–22].

Single event multi-level surgeries, including de-rotation osteotomies, are frequently performed in children with CP to address femoral deformities, enhance their gait pattern, hinder the progression of additional impairments and normalize joint loadings [23–25]. The femoral geometry and the gait pattern interrelate with each other, i.e. the geometry influences muscle moment arms, altered moment arms might change muscle forces and/or the gait pattern resulting in altered loading which subsequently modifies the femoral growth and geometry. Considering that both, the gait pattern and femoral geometry, influence joint loads, it is difficult to assess any cause-effect relationships with traditional experimental studies. Hence, it is not known if the child's gait pattern or the subject-specific femoral geometry is the main contributor to asymmetric HJCFs in children with CP. Furthermore, it is unknown if the asymmetry in HJCFs is higher in children with CP compared to TD children.

The twofold aim of this study was to (1) evaluate if the asymmetry in HJCFs is higher in children with CP compared to TD children and (2) identify, if the bony femoral morphology or the subject-specific gait pattern is more associated with asymmetries of HJCFs. We conducted what-if simulations to identify whether normalizing the gait pattern or correcting the bony geometry is of utmost importance in clinical interventions to normalize joint loadings. Considering that CP is a disease where both legs can be affected by different severity leading to gait variations and induced compensation mechanisms on the less affected leg, we hypothesized that the asymmetry in hip loading, i.e. HJCF magnitude and orientation, is higher in children with CP compared to TD children. Furthermore, we assumed that the gait pattern has a bigger impact on asymmetries in HJCF than the subject-specific femoral geometry because the gait pattern alters ground reaction forces and therefore joint moments at each joint whereas the femoral geometry, i.e. NSA and AVA, only alters the moment arms of a small number of muscles.

Methods

Magnetic resonance imaging (MRI) data and three-dimensional gait analysis (3DGA) data including marker trajectories and ground reaction forces of twelve children diagnosed with CP (10.4±3.7 years old, height: 133.6±14.9 cm, mass: 30.1±10.1 kg) and fifteen TD children (10.3±2.6 years old, height: 146.3±11.9 cm, mass: 40.1±14.8 kg) were analyzed for this study. The data of all CP children and five TD children was captured during a previous study [26] while the data of the remaining ten TD children was additionally collected for the purpose of this study. The sample of the newly recorded dataset was planned to match the age of the CP cohort and to ensure a comparable number of participants in the TD and CP groups. Walking without an assistant device in daily life was the main inclusion criteria for participants with

CP. Three and nine of these children were classified as level 1 and 2 based on the Gross Motor Function Classification System (GMFCS), respectively. Five and seven of the participants were diagnosed with hemi- and diplegic CP, respectively. Our participants with CP walked with a variety of pathological gait patterns including true equinus, equinus jump gait, apparent equinus and crouch gait. Further details are provided in S1 Table in the [S1 File](#). None of the TD participants had any previous major injuries, surgeries or pain at the lower limbs. Ethics approval was obtained from the local ethics committees (University of Vienna, reference number 00578). Written informed consent to participate in this study was provided by the participants' legal guardian.

Data collection

Data collection of the retrospective analyzed data (CP children and 5 TD children) is described in detail in Kainz et al. [26]. In short, MRIs of the pelvis and lower limbs were collected using a 1.5 Tesla MRI scanner (MAGNETOM Avanto, Siemens, Berlin/Munich, Germany) with a voxel size of 1.1x1.1x1.1 mm. Motion capture data were collected using an 8-camera 3D motion capture system (Vicon Motion Systems, Oxford, UK) with an extended Plug-in-Gait marker set with additional clusters of three markers on each thigh and shank segment and an additional marker at the 5th metatarsal head of each foot [27–29]. MRI images of the additionally recorded data (ten TD children) were collected using a 3T magnetic resonance scanner (MAGNETOM Vida, Siemens, Berlin/Munich, Germany) with a T1 vibe sequence with a voxel size of 0.8x0.8x0.7 mm. 3DGA-data for these ten TD children were captured on the same day as the MRI images using a 12 camera motion capture system (Vicon Motion Systems, Oxford, UK) with a camera sampling frequency of 200 Hz. The used marker set during the motion capturing was the same as in the retrospective dataset. Simultaneously, ground reaction forces were acquired with 1000 Hz using five force plates (Kistler Instrumente, Winterthur, Switzerland). All children performed several gait trials with a self-selected walking speed. Marker trajectories were captured, labelled, and filtered (Butterworth 4th order, 6Hz low-pass filter) in Nexus 2.12.1 (Vicon Motion System, Oxford, UK). The retrospective and prospective datasets included the same types of experimental data and all further simulations and analyses were performed with the same workflow for both datasets.

Segmentation of MRIs

All MRIs were segmented using 3D Slicer [30] and each femur was exported as a STL-file. The STL mesh was subsequently used to compute the NSA and AVA with a customized MATLAB (Mathworks Inc., Natick, MA, USA) script, described in detail in the supplementary material of Kainz et al. [16].

Musculoskeletal models

The generic 'gait2392' OpenSim model [31] with locked metatarsophalangeal joints was used as the base model for the subject-specific models. The recently developed Torsion Tool [32] was used to personalize the femoral geometry of each model to match the child's NSA and AVA (personalized model). One additional model (mirrored model) was created for each participant where the models' femoral morphology of the right femur was modified according to the NSA and AVA of the participants' left femur and vice versa. This allowed us to calculate the impact on the asymmetry solely due to the gait pattern and solely due to the femoral morphology, separately (Fig 1).

The personalized models were scaled to the participants anthropometry based on calculated joint centers (hip: equation from Sangeux [33]; knee: midpoint between medial and lateral

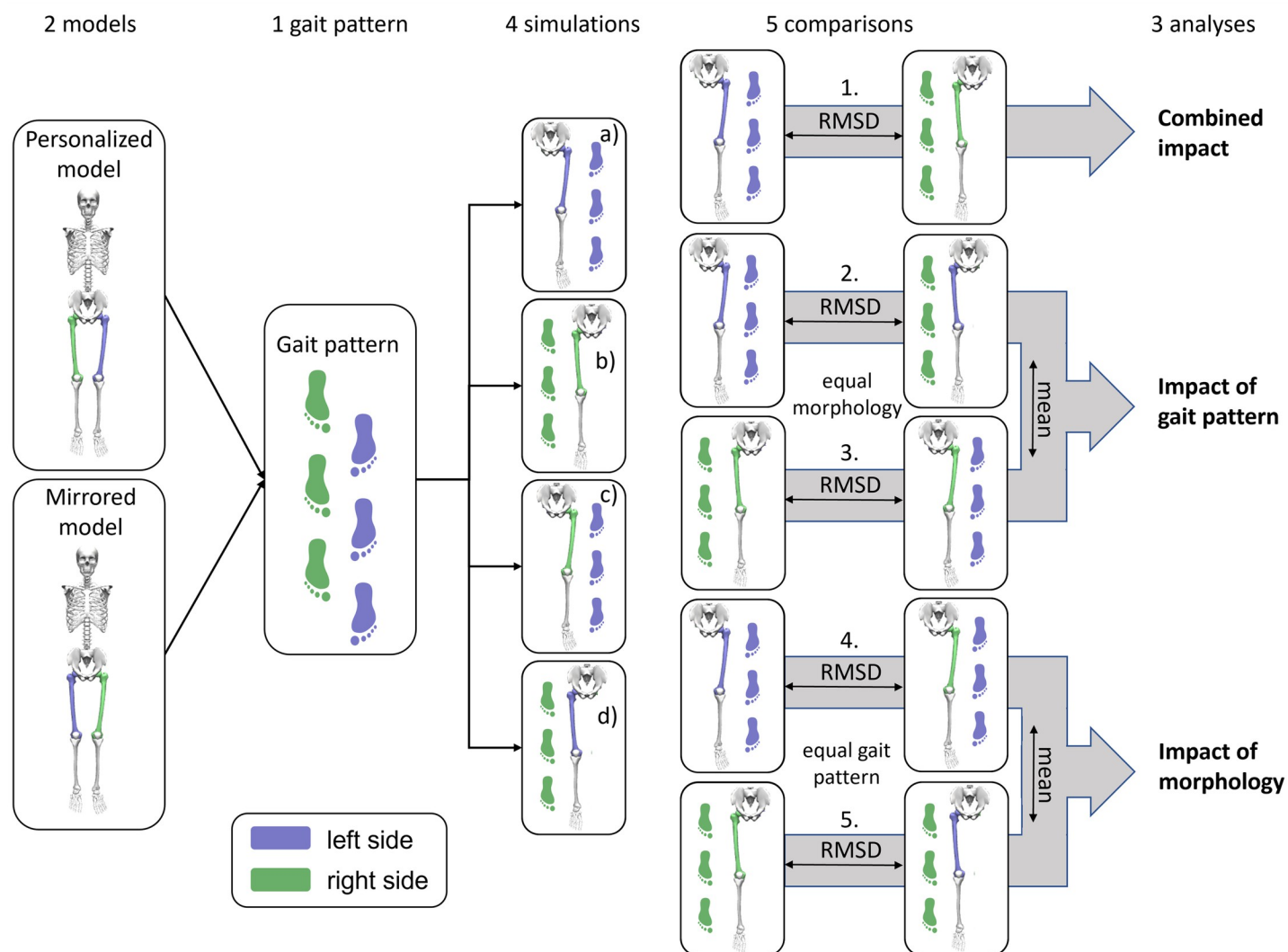


Fig 1. Combination of models and input data for four different simulations (a–d) and five comparisons (1–5.) to identify the influence on the asymmetry of HJCF magnitude and its orientation solely due to the participants' gait pattern (mean of comparison 2. and 3.), solely due to the participants morphology (mean of 4. and 5.) and the combination of both factors (comparison 1.).

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knee markers; ankle: equation from Bruening [34]) and the location of surface markers [26]. Each leg was scaled independently to account for potential length discrepancies between the left and right leg. The mirrored model was scaled with the same scale settings. Hence, we had two models, which were exactly the same except for the femoral morphology and the corresponding muscle paths. The maximum isometric muscle forces of all models were scaled by Eq 1 to improve muscle force estimations [35, 36].

$$F_{scaled} = F_{generic} * \left(\frac{m_{scaled}}{m_{generic}} \right)^{(2/3)} \quad (1)$$

Musculoskeletal simulations

All models and the corresponding gait analysis data were used to calculate joint angles, joint moments, muscle forces and joint contact forces using inverse kinematics, inverse dynamics, static optimization (minimizing the sum of squared muscle activations) and joint reaction load analyses [37], respectively. Knee and ankle joint markers were only used for scaling and excluded during inverse kinematics. The remaining markers were weighted equally. Maximum marker errors and root-mean-square errors were accepted if less than 4 cm and 2 cm, respectively, as recommended by OpenSim's best practice recommendations [38]. On average the mean waveforms of 8.4 ± 4.1 steps (minimum of 3 steps for each side) were computed for each parameter and further analyzed. All simulation were performed with MATLAB R2021a and OpenSim 4.2 [39].

Data analysis

The intra-subject differences of the NSA (Δ NSA) and AVA (Δ AVA) were calculated as the absolute difference between the values of the left and right side (Eqs 2 and 3). A score to quantify the asymmetry of the intra-subject femoral morphology was calculated by the sum of the differences in AVA and NSA between the left and right femur (Eq 4) and is further referred to as morphology asymmetry score (MAS).

$$\Delta NSA = |NSA_{left} - NSA_{right}| \quad (2)$$

$$\Delta AVA = |AVA_{left} - AVA_{right}| \quad (3)$$

$$MAS = |AVA_{left} - AVA_{right}| + |NSA_{left} - NSA_{right}| \quad (4)$$

Walking speed was calculated, normalized to participants' leg lengths [40] and compared between both groups. A gait asymmetry score (GAS) was used to quantify differences in joint angles between left and right leg of each participant. The GAS was calculated similar to the gait profile score [41] except that we compared joint angles between each participant's right and left leg and not between a patient and a healthy control group.

All results of the musculoskeletal simulations were time normalized to the stance phase. Joint kinematics were reported according to the International Society for Biomechanics' (ISB) recommendations [42]. HJCF magnitudes and orientations acting on the femur were calculated in the sagittal, transversal and frontal plane of the femurs' coordinate system [43] and then compared between each participant's left and right side. Performing the musculoskeletal simulations for the personalized and the mirrored model resulted in the following four simulations for each participant:

- a. left kinematics and left femoral morphology (left steps of personalized model)
- b. right kinematics and right femoral morphology (right steps of personalized model)
- c. left kinematics and right femoral morphology (left steps of mirrored model)
- d. right kinematics and left femoral morphology (right steps of mirrored model)

Subsequently, for each participant HJCF asymmetries were quantified by calculating root-mean-square-difference (RMSD) between the extracted waveforms (HJCF magnitude and orientation during stance phase) of different simulations. The following five comparisons between the different simulations were used to quantify HJCF asymmetries and the impact of each child's gait pattern and femoral morphology on HJCF asymmetries (Fig 1):

1. RMSD of simulations a) and b) to identify the combined impact of morphology and gait pattern on HJCF asymmetries
2. RMSD of simulations a) and d) to identify the impact of the gait pattern on HJCF asymmetries
3. RMSD of simulations b) and c) to identify the impact of the gait pattern on HJCF asymmetries
4. RMSD of simulations a) and c) to identify the impact of the morphology on HJCF asymmetries
5. RMSD of simulations b) and d) to identify the impact of the morphology on HJCF asymmetries

Statistics

One-sided independent samples t-tests were used to compare the NSA, AVA, the intra-subject difference of NSA (Δ NSA) and AVA (Δ AVA) and MAS between the CP and TD group.

Two between-within 2x3x2 ANOVAs were performed with SPSS Statistics 28.0 (IBM, New York, USA) to answer our research questions, i.e. identify significant differences in HJCF asymmetries (i) between CP and TD children and (ii) caused by the morphology versus the gait pattern. The cohort (CP versus TD) and the contribution (due to morphology versus due to gait pattern) were independent variables and the component/angle in 3 directions/planes of the HJCF were dependent variables. For pairwise comparisons, post-hoc Bonferroni correction was applied and Greenhouse-Geisser corrected values were used, if sphericity was violated. Additional independent t-tests were used to compare the combined influence of the morphology and the gait pattern on HJCF asymmetries between CP and TD children. For all tests, the significance level was set to $p < 0.05$. Post-hoc power analyses were performed with GPower 3.1.9.7 [44] to quantify the statistical power of our main findings related to our research questions.

Furthermore, we evaluated if there are significant linear regression correlations between the asymmetry in femoral morphology (Δ NSA, Δ AVA and MAS) and the asymmetry of HJCF magnitude and/or orientation. Results and discussion of these additional analysis can be found in the [S1 File](#).

Results

Femoral morphology

The NSA ($134.3 \pm 6.9^\circ$) and Δ NSA ($4.9 \pm 3.5^\circ$) of the CP group were significantly higher ($p < 0.05$) than the values of the TD group (NSA $130.9 \pm 3.5^\circ$, Δ NSA $2.6 \pm 1.5^\circ$). The AVA was significantly higher ($p < 0.01$) in TD ($29.7 \pm 8.8^\circ$) compared to CP children ($22.3 \pm 10.2^\circ$), but Δ AVA did not differ between both groups. The MAS was significantly lower ($p < 0.05$) in TD participants ($7.0 \pm 4.1^\circ$) compared to participants with CP ($11.9 \pm 9.1^\circ$) ([Fig 2](#)).

Gait pattern and HJCF

The CP group walked significantly slower ($p < 0.01$) than the TD group but walking speed normalized to leg length was not significantly different between both groups ([Fig 3](#)). Joint angles and HJCF during the gait cycle of TD participants were similar between both legs, whereas in some children with CP joint angles as well as HJCF differed vastly between the left and right

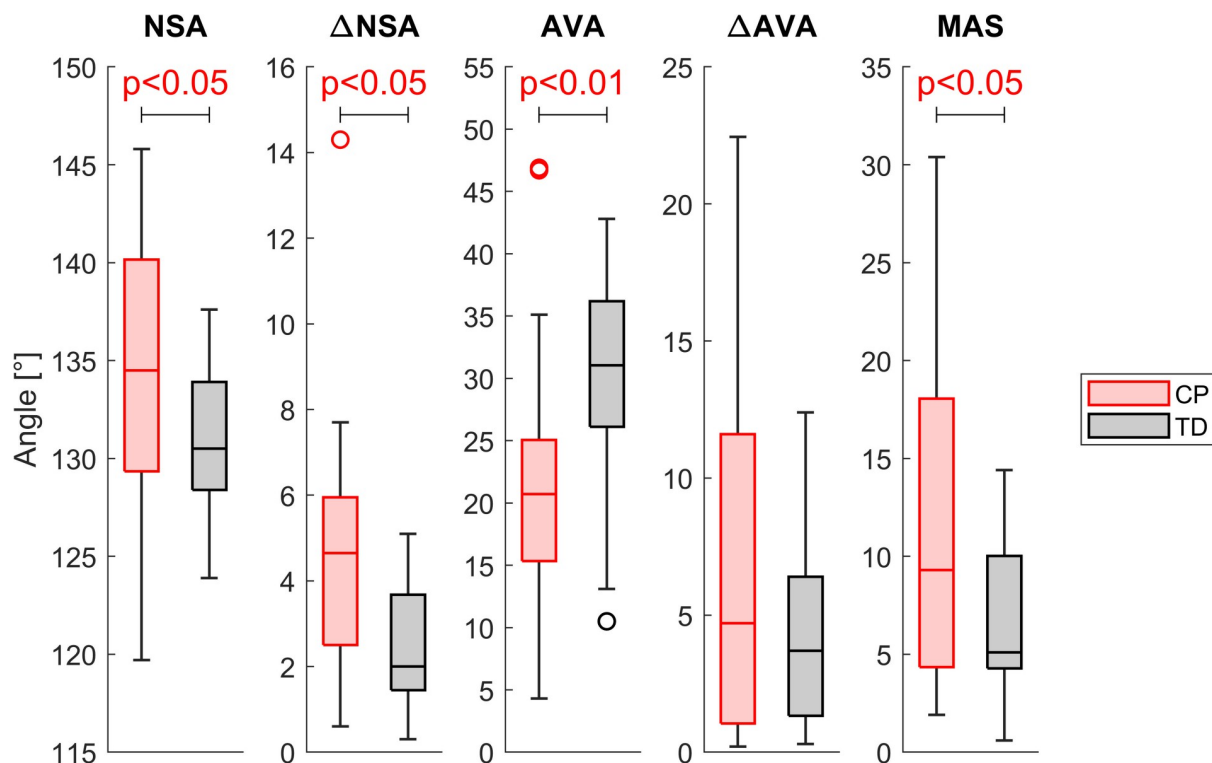


Fig 2. Comparison of the NSA, the AVA, the corresponding asymmetries (ΔNSA and ΔAVA) and the MAS between the CP and the TD group.

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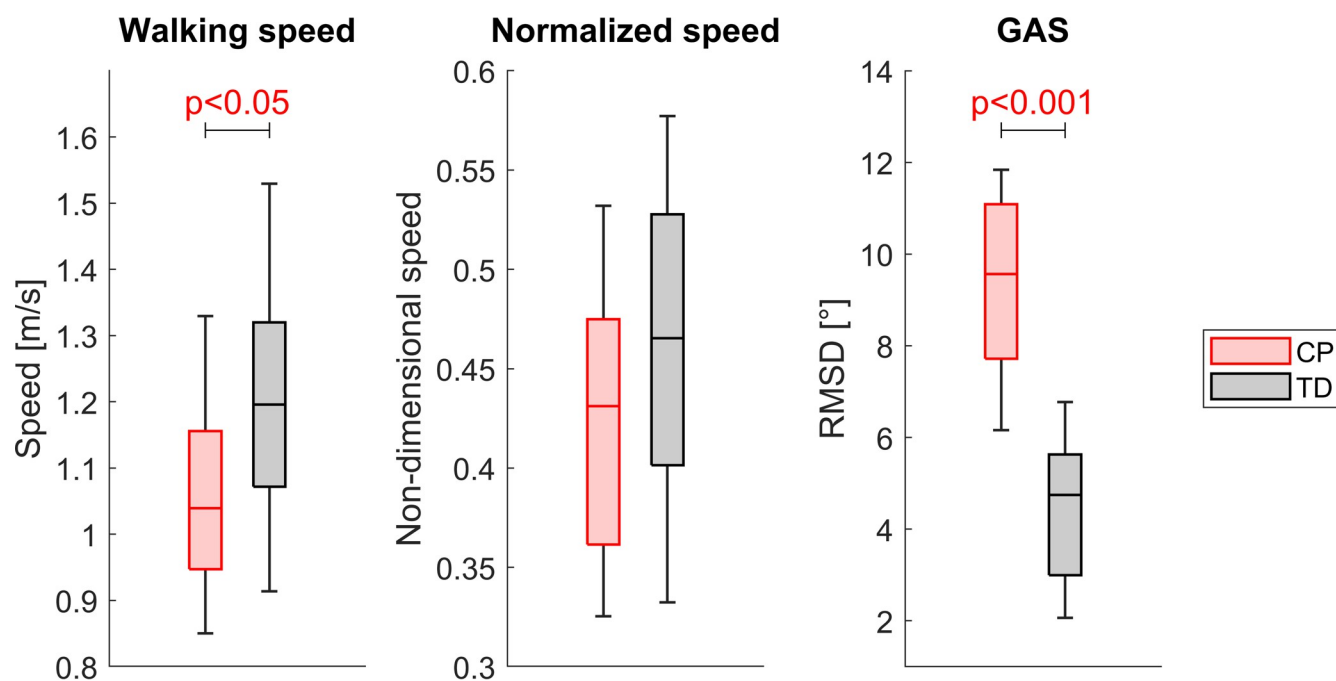


Fig 3. Comparison of the walking speed and the GAS between the CP and the TD group.

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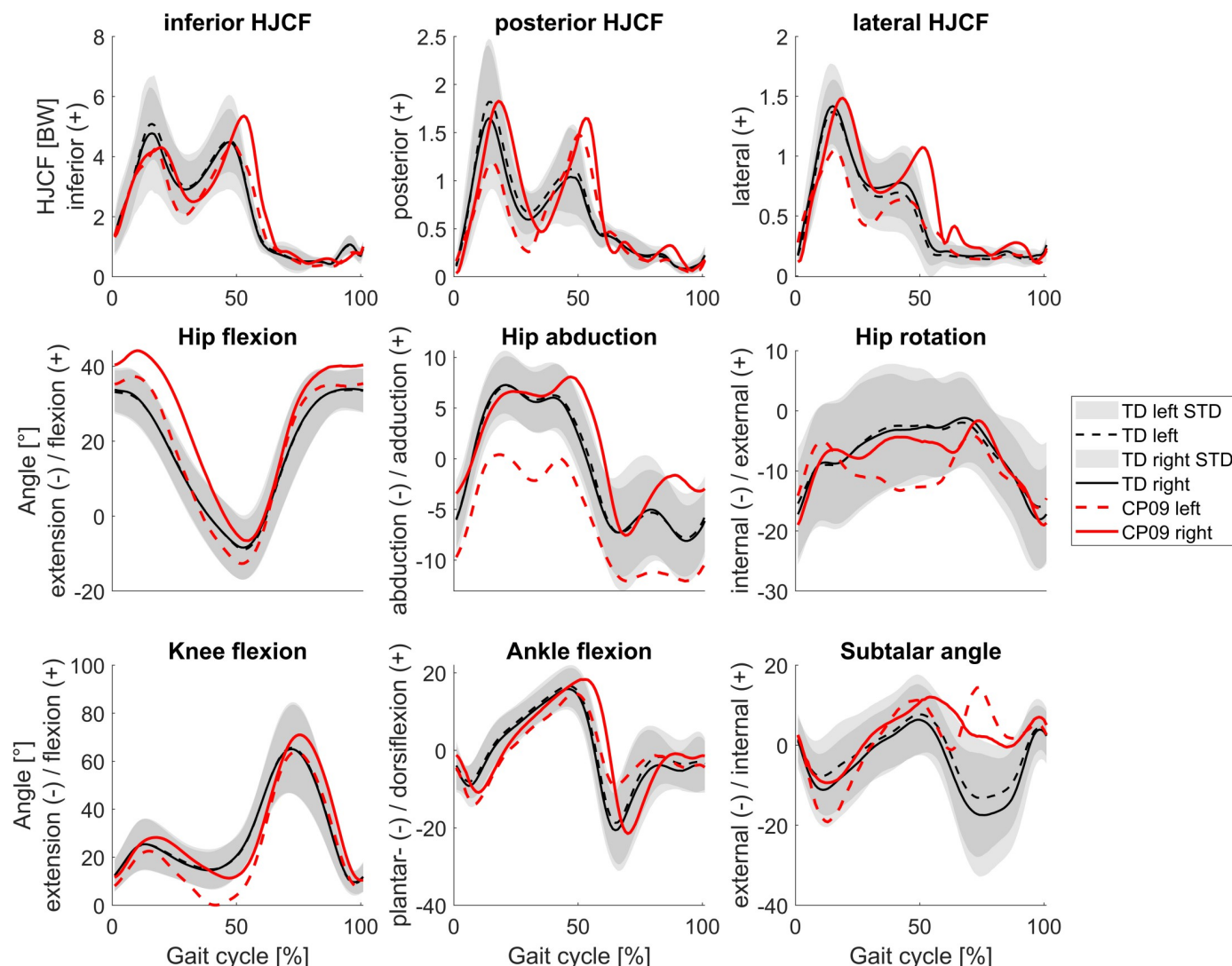


Fig 4. Mean HJCF represented in femurs' coordinate system and joint angles during the gait cycle presented for TD children and HJCF and joint angles of a representative child with CP. CP01 was the participant with the lowest GAS. Figures with the gait kinematic waveforms of each participant with CP are included in the [S1 File](#).

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side (Figs 4 and 5). The GAS was significantly higher ($p < 0.001$) in CP ($10.4 \pm 4.7^\circ$) compared to TD participants ($4.5 \pm 1.5^\circ$).

Asymmetries in HJCF magnitude (anterior, inferior and resulting) and orientation (all planes) were significantly larger ($p < 0.05$, effect size = 0.9 ± 0.26 , power = 0.69 ± 0.17 for HJCF magnitude; $p < 0.05$, effect size = 1.26 ± 0.17 , power = 0.92 ± 0.06 for HJCF orientation) in CP compared to TD participants (Fig 6). In both groups (TD and CP), the gait pattern had a significantly larger ($p < 0.001$, effect size = 2.48, power > 0.99 for HJCF magnitude; $p < 0.05$, effect size = 0.73, power > 0.99 for HJCF orientation) impact on asymmetries in HJCF magnitudes and orientations compared to the morphology. For the HJCF orientation, a significant interaction effect ($p < 0.05$) was observed showing that in the CP group the gait pattern has an even higher contribution to the HJCF asymmetry than the femoral morphology.

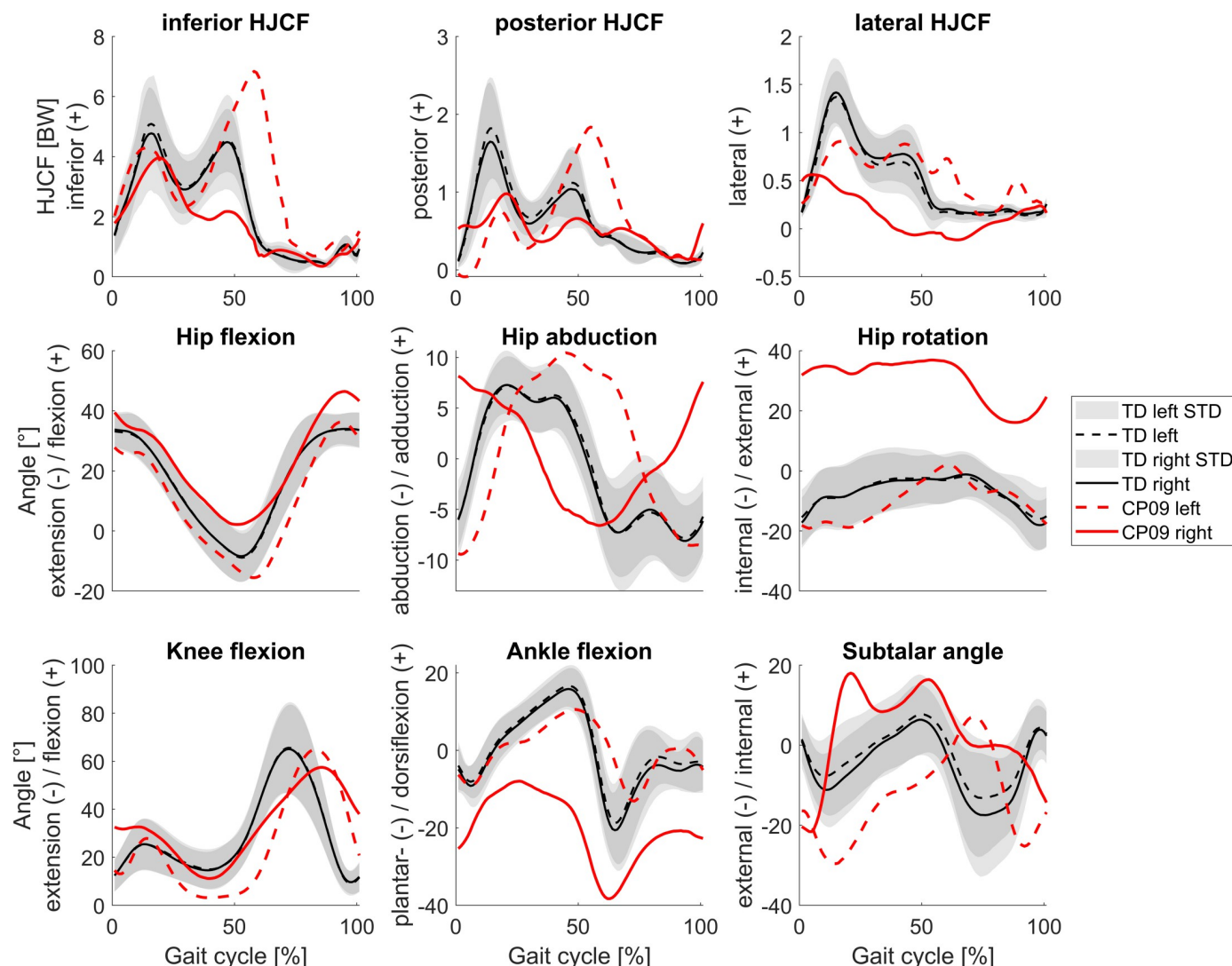


Fig 5. Mean HJCF represented in femurs' coordinate system and joint angles during the gait cycle presented for TD children and HJCF and joint angles of a representative child with CP. CP09 was the participant with the highest GAS. Figures with the gait kinematic waveforms of each participant with CP are included in the [S1 File](#).

<https://doi.org/10.1371/journal.pone.0291789.g005>

Discussion

The purpose of this study was to comprehensively analyze HJCF asymmetries in children with CP and TD children and to evaluate if the subject-specific gait pattern or the femoral morphology is the main contributor to these asymmetries. In general, HJCF asymmetries were significantly higher in CP compared to TD children except for the medial/lateral component. In agreement with our hypothesis, the gait pattern had a larger influence on the HJCF asymmetry than the femoral morphology in both groups.

As anticipated, our findings showed that HJCF asymmetries are higher in CP compared to TD children. We expected this finding due to higher gait asymmetries in CP compared to TD children [11]. The standard deviations in HJCF asymmetries in the CP group were very high which indicates that some participants were similar to the TD group and others were far outside the TD range. This is in agreement with previous work [18], which showed that some

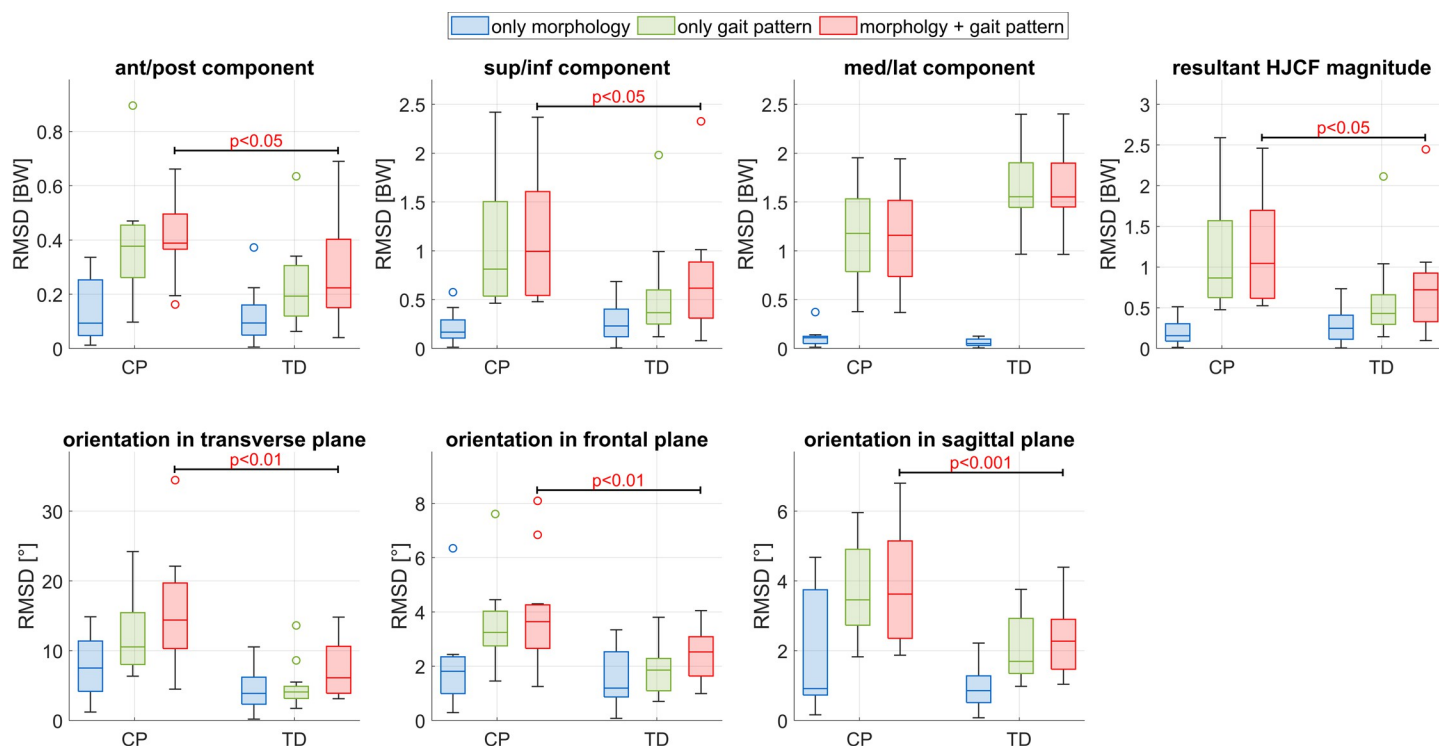


Fig 6. Contribution of the femoral morphology (blue), the gait pattern (green) and the combined contribution of morphology and gait pattern (red) on the asymmetry of HJCF magnitude and orientation during the stance phase.

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children with CP have typical HJCF, whereas others have HJCF outside the TD range. Future work based on a larger cohort of CP participants is needed to identify how different pathological gait pattern, e.g. in-toeing gait or crouch gait, or CP diagnosis, e.g. hemiplegic or diplegic CP, affect HJCF asymmetries.

The overall femoral asymmetry, i.e. MAS, was as expected higher in children with CP compared to TD children. Furthermore, the NSAs were significantly higher in CP compared to TD participants. However, against our expectation based on previous studies [2, 45], the AVAs were significantly lower in our CP compared to our TD participants. Typically, the AVA decreases with age in TD children and remains higher in children with CP [2, 45]. There was no significant difference in age between our CP and TD groups, which could explain the observed difference. The AVAs of our TD participants were within the range of TD values reported in a study based on 508 participants [46]. Hence, we assume that the low number of participants in our study is responsible for the observed higher AVAs in our TD compared to our CP participants.

In children with CP single event multi-level surgeries including de-rotation osteotomies and muscle-tendon-lengthening surgeries are often used to correct femoral deformities, improve the child's gait pattern and prevent the development of further deformities [23–25]. The gained insights from our study suggest that normalizing the gait pattern should be a high priority of clinical interventions and might be even more important than correcting the bony deformities. However, de-rotation osteotomies normalize the lever arms of muscles [23, 24], which might be necessary to enable a typical walking pattern. Hence, clinical interventions should target static, anatomical impairments, i.e. bony deformities, and dynamic, functional impairments, i.e. pathological gait pattern. Based on our findings, solely the correction of bony

deformities is unlikely to stop the development of further deformities. Therefore, an intervention should only be judged successful if the gait pattern improves additionally to the anatomical correction. Yadav et al. (2021) performed predictive simulations based on a mechanobiological model and concluded that the posterior and the lateral HJCF components highly affect the change of the NSA and AVA. Hence, a normalization of these HJCF components seems to be of high importance. Further studies are needed to identify which gait modifications and clinical interventions could achieve the desired normalization of the HJCF.

Our study included the following limitations. First, only the femoral morphology was personalized in our musculoskeletal models. Tibial morphology could not be personalized because MRI images of the tibia were not available for all participants. Changes of tibial geometry alters the moment arms of the shank muscles and consecutively has an impact on the estimation of muscle and knee joint contact forces. Due to the bottom-up approach used to estimate joint contact forces in OpenSim [37], changes in the knee joint contact force would also affect HJCF. However, tibial torsion only affects lever arms of a limit number of muscles and therefore we assume the impact on HJCF is negligible. Further studies which investigate the impact of tibial torsion on HJCF should be carried out to verify our assumption. Second, the HJCF could not be measured in-vivo and therefore were estimated with musculoskeletal simulation. The shape and magnitude of our HJCF were, however, in agreement with previous studies [16, 18, 47–49]. Third, although we showed that the gait pattern has a larger influence on HJCF than the femoral morphology, it has to be mentioned that the femoral geometry itself influences the moment arms of several hip muscles [9, 50, 51] and therefore might be the reason why some children are not able to walk with a typical walking pattern [10]. Fourth, mean kinematic and kinetic waveforms were calculated based on a different number of trials between participants due to a low number of valid force plate strikes in some children with CP. Although this is standard practice in clinical and research settings [52], it potentially had a small impact on the obtained mean waveforms. Fifth, our intention was not to find the cause of femoral deformities but to identify the main contributor to asymmetric HJCFs. Pathological gait patterns alter the HJCF which is the main biomarker that determines femoral bone growth [14–16, 18]. Future studies including predictive musculoskeletal and mechanobiological simulations [18, 53] are needed to comprehensively evaluate the impact of femoral morphology on the walking ability and investigate the reasons for femoral deformities.

To conclude, this study comprehensively analyzed HJCF asymmetries in CP and TD children and identified the contribution of subject-specific femoral morphology and gait pattern to the asymmetry of hip loading. The asymmetric gait pattern had a larger influence on HJCF asymmetries than the asymmetric femoral morphology. Gait asymmetries and therefore also HJCF asymmetries were larger in CP compared to TD participants. Bone is adaptive to mechanical loading [12, 54–56] and pathological HJCF will likely lead to pathological femoral growth [18]. Hence, in patients with femoral deformities it is of utmost importance to correct the functional impairment, i.e. patient-specific gait pattern, with the aim to normalize loading and femoral growth. Whether normalization of the gait pattern can be achieved solely with physical therapy (e.g. gait retraining) or in combination with surgical interventions depends on the individual patient and was beyond the scope of our study. However, our findings highlight that pre- and post-intervention gait analysis should be performed to evaluate the success of an intervention.

All musculoskeletal models and the simulation results are published on https://simtk.org/projects/bone_gait_load to allow peers to further investigate the data.

Supporting information

S1 File. This file contains CP participants' details, additional plots on the correlation between asymmetry of femoral morphology and asymmetry of HJCF and each CP participants' kinematic.

(DOCX)

Author Contributions

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Methodology: Willi Koller, Hans Kainz.

Project administration: Hans Kainz.

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Supervision: Arnold Baca.

Validation: Hans Kainz.

Visualization: Willi Koller, Hans Kainz.

Writing – original draft: Willi Koller, Hans Kainz.

Writing – review & editing: Willi Koller, Arnold Baca, Hans Kainz.

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2.3. Intra- and inter-subject variability of femoral growth plate stresses in typically developing children and children with cerebral palsy

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Intra- and inter-subject variability of femoral growth plate stresses in typically developing children and children with cerebral palsy

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Little is known about the influence of mechanical loading on growth plate stresses and femoral growth. A multi-scale workflow based on musculoskeletal simulations and mechanobiological finite element (FE) analysis can be used to estimate growth plate loading and femoral growth trends. Personalizing the model in this workflow is time-consuming and therefore previous studies included small sample sizes ($N < 4$) or generic finite element models. The aim of this study was to develop a semi-automated toolbox to perform this workflow and to quantify intra-subject variability in growth plate stresses in 13 typically developing (TD) children and 12 children with cerebral palsy (CP). Additionally, we investigated the influence of the musculoskeletal model and the chosen material properties on the simulation results. Intra-subject variability in growth plate stresses was higher in cerebral palsy than in typically developing children. The highest osteogenic index (OI) was observed in the posterior region in 62% of the TD femurs while in children with CP the lateral region was the most common (50%). A representative reference osteogenic index distribution heatmap generated from data of 26 TD children's femurs showed a ring shape with low values in the center region and high values at the border of the growth plate. Our simulation results can be used as reference values for further investigations. Furthermore, the code of the developed GP-Tool ("Growth Prediction-Tool") is freely available on GitHub (<https://github.com/WilliKoller/GP-Tool>) to enable peers to conduct mechanobiological growth studies with larger sample sizes to improve our understanding of femoral growth and to support clinical decision making in the near future.

KEYWORDS

femoral growth plate, cerebral palsy, femoral deformities, growth plate, musculoskeletal simulation, finite element analysis, osteogenic index, personalized modelling

1 Introduction

During growth, bones of mammals do not only grow in size but also the geometry adapts according to the predominant loading conditions (Arkin and Katz, 1956; Rauch, 2005; Carter and Beaupré, 2007; Mirtz et al., 2011; Mellon and Tanner, 2012). Altered forces acting on bones can lead to various skeletal deformities. In humans, femoral deformities are common in children with cerebral palsy (CP) but also in children without neurological disorders

(Bobroff et al., 1999; Morrell et al., 2002; Beals, 2008). These children are born with typical bony geometry, but in many patients the femoral neck shaft angle (NSA) and anteversion angle (AVA) does not decrease during growth as in typically developing (TD) children (Fabry et al., 1973; Bobroff et al., 1999; Robin et al., 2008). The pathological femoral geometry alters moment arms of muscles (Arnold et al., 2008) which influences muscle recruitment strategy (Kainz et al., 2021b), resulting in altered joint contact forces which are often associated with joint pain (Mackay et al., 2021). Altered movement strategies and joint loading subsequently lead to further progressive disabilities with walking impairments being one of the most profound (Rethlefsen et al., 2017). The altered loading on the growth plate is assumed to be responsible for the pathological femoral growth, yet this assumption remains to be confirmed.

Multi-scale simulations based on musculoskeletal (MSK) simulations and mechanobiological finite element (FE) analysis are used to estimate growth plate loading and femoral growth trends, i.e. the change of the femoral NSA and the AVA due to the forces acting on it (Shefelbine and Carter, 2004; Carriero et al., 2011; Yadav et al., 2016; Yadav et al., 2017; Kainz et al., 2020). First, three-dimensional gait analysis data is collected and MSK simulations are performed to estimate muscle and joint contact forces. Subsequently, these forces are used as loading conditions in a FE model of the femur to quantify the stresses at the growth plate. Based on the estimated shear and hydrostatic stresses at the growth plate the osteogenic index (OI) can be defined, which determines the subject-specific growth rate due to mechanical loading (Carter and Wong, 1988). The mechanical growth rate is added to the biological growth rate which is determined by biological factors, e.g. genetics and nutrients (Stevens et al., 1999). In regions with high OI, bone growth is more likely to occur, whereas in regions with negative OI, growth will be inhibited (Yadav et al., 2016). With these analyses, the development of pathological femoral growth could be identified at an early stage and simple and non-invasive interventions (e.g., orthoses, physical therapy) could potentially normalize bone growth and prevent the necessity of severe corrective osteotomies at a later stage.

Hip joint contact forces (HCF) and subject-specific growth plate geometry are the two main factors influencing growth plate stresses and femoral growth predictions. HCF have been shown to be the main biomarker which determines femoral bone growth (Carriero et al., 2011; Kainz et al., 2020; Yadav et al., 2021). Kainz et al. (2021a) recently showed that the orientation of the HCF in the sagittal plane can differentiate between children with CP who are likely to have typical and pathological femoral growth. HCF are influenced by the subject-specific gait pattern and femoral geometry (Kainz et al., 2020; Kainz et al., 2021b; Modenese et al., 2021). Yadav et al. (2016) showed that the growth plate shape and location affect the stress distribution within the growth plate and therefore change the OI. These studies highlight the importance of accounting for the subject-specific gait pattern and using subject-specific MSK and FE models for mechanobiological growth simulations.

All previous femoral mechanobiological growth studies were based either on a generic FE model of the femur (i.e., generic femoral morphology and growth plate shape and location) (Carriero et al., 2011; Kainz et al., 2020; 2021a) or include very small sample sizes ($N < 4$) (Yadav et al., 2016; Yadav et al., 2017; Yadav et al., 2021). The

reason for this might be the time-consuming generation of personalized FE models. The mechanobiological model requires hexahedral elements aligned with the growth plate. The creation of such a hexahedral mesh from irregular 3D volumes of the femur is challenging and time-consuming. Furthermore, the measured material properties reported in literature (Linde et al., 1985; Rho et al., 1993) for bone vary substantially. Previous studies (Carriero et al., 2011; Yadav et al., 2016; Yadav et al., 2017; Kainz et al., 2020; Kainz et al., 2021a; Yadav et al., 2021) used material property values on the lower bounds of the reported range. Moreover, the generalization of the findings from previous studies was limited due to small sample sizes and the lack of comprehensive reference dataset for TD children. Hence, a reference data set of OI values from TD children obtained with subject-specific MSK and FE models is needed to quantify the typical OI variability within TD children and facilitate an appropriate interpretation of the findings for future femoral growth studies.

This study included the following two clinical aims: 1) quantify and compare the OI in a reference dataset of TD children and children with CP, 2) quantify the intra- and inter-subject variability of the OI. Additionally, our study included the following two technical aims: 3) evaluate the influence of the chosen MSK model, i.e. generic-scaled versus personalized femoral geometry, and 4) evaluate the effect of the chosen material properties on the simulation results. Furthermore, we analyzed and compared the shape, the location and the orientation of the growth plates between groups (CP and TD). Considering that the variability in CP gait is higher compared to TD gait (Kurz et al., 2012; Davies and Kurz, 2013), we hypothesized that the intra-subject variability in the OI is higher in children with CP compared to TD children. In addition, we hypothesized that the chosen MSK model will influence the OI distribution, whereas the material properties will mainly alter the magnitude but not the distribution of the OI. A toolbox based on freely available software, which enables the generation of the personalized FE model and perform the multi-scale simulations in a simple and comprehensive way was developed and used to address our aims. Magnetic resonance imaging (MRI) and three-dimensional gait analysis (3DGA) data of twelve children with CP and thirteen TD children were used to generate subject-specific FE models and quantify the OI based on different input data and model properties.

2 Materials and methods

2.1 Data collection

MRI and 3DGA data including marker trajectories and ground reaction forces of twelve children diagnosed with CP (10.4 ± 3.8 years old, height: 133.6 ± 16.1 cm, mass: 30.1 ± 10.8 kg) and thirteen TD children (10 ± 2.2 years old, height: 144.5 ± 8.5 cm, mass: 36.8 ± 9.5 kg) were analyzed for this study. All participants walked without walking aids and with a self-selected speed. The data of all CP children and three TD children was captured during a previous study (Kainz et al., 2017) while the data of the remaining ten TD children was additionally collected for the purpose of this study. Ethics approval was obtained from the local ethics committees (University of Vienna, reference number 00578).

Data collection of the retrospective analyzed data (CP children and three TD children) is described in detail in Kainz et al. (2017).

MRI images of the additionally recorded data (ten TD children) were collected using a 3T magnetic resonance scanner (MAGNETOM Vida, Siemens, Berlin/Munich, Germany) with a T1 viba sequence with a voxel size of $0.8 \times 0.8 \times 0.7$ mm. 3DGA-data for these ten TD children were captured on the same day as the MRI images using a 12 camera motion capture system (Vicon Motion Systems, Oxford, UK). The used marker set during the motion capturing was based on the Plug-in-Gait marker set (Kadaba et al., 1990; Davis et al., 1991) with additional clusters of three markers on each thigh and shank segment and an additional marker at the 5th metatarsal head of each foot. Simultaneously, ground reaction forces were acquired using five force plates (Kistler Instrumente, Winterthur, Switzerland). All children performed several gait trials with a self-selected walking speed. Marker trajectories were captured, labelled, and filtered (Butterworth 4th order, 6 Hz low-pass filter) in Nexus 2.12.1 (Vicon Motion System, Oxford, United Kingdom).

2.2 Segmentation of MRIs and quantification of geometrical features

3D Slicer 4.13 (Fedorov et al., 2012) was used to segment MRI images. Each femur was split into five parts similar to previous studies (Kainz et al., 2020)—the proximal trabecular bone, the growth plate, the cortical bone of the shaft, the bone marrow and the distal trabecular bone. STL-files of all parts and additionally a file containing the full femur were exported. The STAPLE-Toolbox of Modenese and Renault (2021) was used to identify the femoral head and the epicondyles representing the hip and the knee joint axis using the “GIBOC-Femur” and “GIBOC-Cylinder” algorithms, respectively. If “GIBOC-Cylinder” algorithm failed to fit a cylinder through both epicondyles, “GIBOC-Ellipsoids” algorithm was used to fit ellipsoids through medial and lateral epicondyles. The hip joint center and knee joint axis were required to transform the femur into the OpenSim coordinate system.

The diaphysis of the femur was defined by removing 20% off the top and bottom of the femur. Then, the principal inertia axis of the remaining part was calculated to identify the shaft axis. The neck axis was defined by fitting a least-squares cylinder through surface nodes of the femoral neck. The longitudinal axis of this cylinder was constrained to pass through the femoral head center. The AVA was calculated as the angle between the neck axis and the medial-lateral knee axis obtained from STAPLE-Toolbox (Modenese and Renault, 2021) in the transverse plane. The NSA was computed as the angle between the neck axis and shaft axis in 3D space.

2.3 MSK simulations and loading for FE models

Two models, i.e., generic-scaled and personalized, were created for each participant and used to perform MSK simulations with OpenSim 4.2 to estimate muscle and joint contact forces acting on the femur (Delp et al., 2007; Steele et al., 2012). For the generic-scaled models, the generic ‘gait2392’ OpenSim model (Delp et al.,

2007) with locked metatarsophalangeal joints was linearly scaled to fit to the participants’ anthropometry based on the location of surface markers (Kainz et al., 2017). For the personalized model, the Torsion Tool (Veerkamp et al., 2021) was used to modify the femoral geometry in the ‘gait2392’ model to match each child’s NSA and AVA before scaling the model. The maximum isometric muscle forces of all models were scaled based on the ratio of the body mass between the participant’s model and unscaled reference model (Eq. (1)) (van der Krogt et al., 2016; Kainz et al., 2018). In summary, we had two models for each participant which were exactly equivalent except for the femoral geometry and corresponding muscle paths and attachments of muscles.

$$F_{scaled} = F_{generic} * \left(\frac{m_{scaled}}{m_{generic}} \right)^{(2/3)} \quad (1)$$

All models and the corresponding gait analysis data were used to calculate joint angles, joint moments, muscle forces and joint contact forces using inverse kinematics, inverse dynamics, static optimization by minimizing the sum of squared muscle activations and joint reaction load analyses, respectively. Knee and ankle joint markers were only used for scaling and excluded during inverse kinematics. The remaining markers were weighted equally. Maximum marker errors and root-mean-square errors were accepted if less than 4 cm and 2 cm, respectively, as recommended by OpenSim’s best practice recommendations (Hicks et al., 2015). Additional analyses were performed to identify muscle attachments on the femur and obtain the effective directions of muscle forces (van Arkel et al., 2013). The mean waveform of the resultant HCF from all trials was calculated and the trial with the lowest root mean square difference to the mean waveform was selected as a representative loading condition. Similar to previous studies (Yadav et al., 2016; Kainz et al., 2020) nine load instances were selected based on the HCF peaks and the valley in-between during the stance phase. The HCF and muscle forces acting on the femur during the nine load instances were used as loading conditions for FE analysis.

2.4 Creation of hexahedral mesh

The mechanobiological model requires hexahedral elements aligned within the growth plate stacked in several layers to define transition zones and enable progressive growth simulations for each layer of the growth plate. We developed the GP-Tool to automatically create hexahedral meshes based on the subject-specific femoral geometry. The STL-files obtained from the segmented femurs were used as input for the GP-Tool. A visual overview of the steps to create a mesh with the GP-Tool is shown in Figure 1.

Using MATLAB’s (MathWorks, Natick, MA, United States) principal component analysis (“pca”-function) the main orientation of the growth plate was determined. All parts of the femur were rotated so that growth plates’ main orientation was parallel to the XY plane. The growth plate itself was removed and the part above the growth plate of the proximal trabecular bone was positioned on the part which is below the growth plate. Smoothing of the intersection region was performed with MeshLab (Cignoni et al., 2008). These steps were necessary to create a continuous mesh

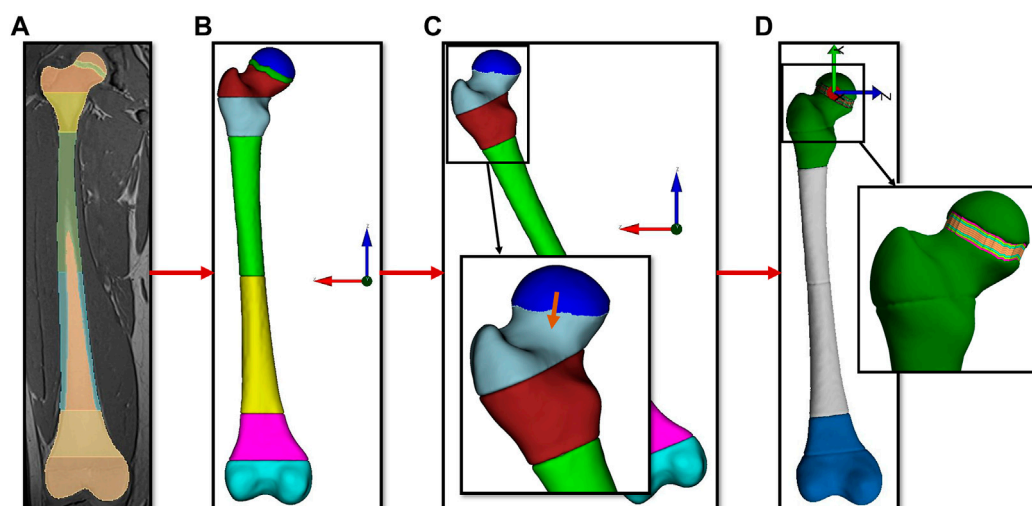


FIGURE 1

Visual description of the steps performed by the semi-automated toolbox with (A) the segmentation of the MRI data as input. Subfigure (B) shows the 3D geometry of the femur in the MRI reference system. In subfigure (C) the geometry was rotated to have the growth plate parallel to the XY plane, the growth plate was removed, the resulting gap closed by moving the proximal part of the femoral head and the edges smoothed. Sculpt tool of Coreform Cubit was used to create a hexahedral mesh of this geometry. Subfigure (D) shows the final mesh with ten layers of elements aligned with the growth plate.

to add perfectly aligned hexahedral elements in the growth plate later. Sculpt tool of Coreform Cubit (Coreform, Utah, United States) was used to create a hexahedral mesh with an element size of approximately 1.5 mm. A mesh convergence study was conducted based on three femurs to ensure that the results are not influenced by the number of elements in the mesh (see [Supplementary Material](#)). The part above the growth plate was moved to its original position and ten layers with equal height were added and presented the growth plate. Finally, the mesh was optimized to no longer include elements with negative Jacobians. This procedure was performed for each femur of all participants ($N = 50$) and resulted in meshes of approximately 150,000 nodes and 140,000 elements varying due to different femur sizes.

2.5 Finite element analysis

A FE model was created for each femur based on the subject-specific hexahedral mesh and the loading conditions obtained from the MSK simulations. All models were fixed at the femoral epicondyles and HCF and muscle forces were applied as nodal forces for the nine load instances.

For each load instance the HCF was distributed to the closest 100 surface nodes (approximately 2.25 cm²) in the direction of the HCF orientation. For each muscle a node was identified which was the closest node to the muscle attachment obtained from the OpenSim simulations ([van Arkel et al., 2013](#)). Due to discrepancies in the geometry, e.g., bending of the shaft, between OpenSim's femur and the participants' femur derived from MRI an algorithm was used to ensure that the defined muscle attachment was on the same side (anterior/posterior or medial/lateral) of the femur. Nodal forces were applied to this node in x/y/z directions according to the muscle directions obtained from the additional muscle analysis ([van Arkel et al., 2013](#)) in order that the

resulting force was equal to the muscle force estimated by the static optimization algorithm.

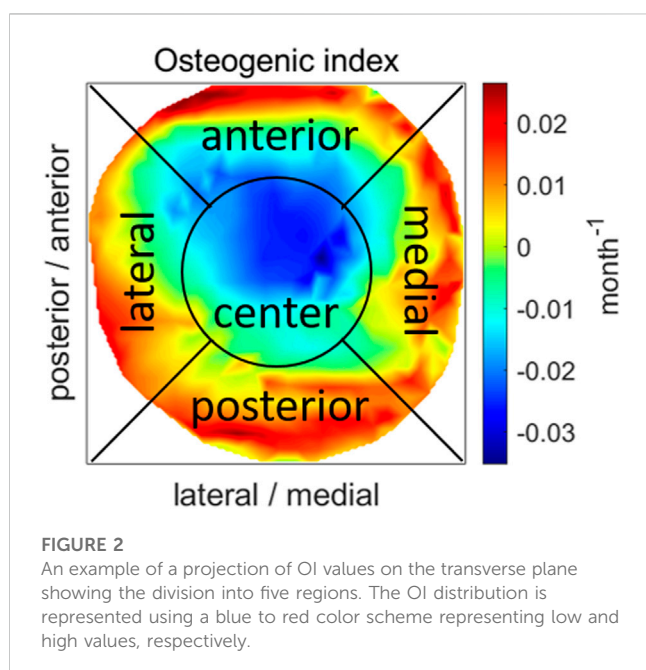
The FE model was duplicated and two different sets of linear elastic materials with Young's modulus and Poisson ratio described in [Table 1](#) were assigned to the different parts of the femur. The chosen values for material properties were based on literature and previously used values in mechanobiological growth studies ([Linde et al., 1985](#); [Rho et al., 1993](#); [Carriero et al., 2011](#); [Yadav et al., 2016](#); [Kainz et al., 2020](#)). A transition zone of three layers (out of the ten layers within the growth plate) between trabecular bone and the growth plate was modeled with linearly decreasing Young's modulus from the trabecular bone to the growth plate to represent the mineralizing bone tissue ([Kainz et al., 2020](#)). FEBio 3 ([Maas et al., 2012](#)) was used for FE simulations and to calculate principal stresses.

2.6 Osteogenic index calculation

The growth rate due to mechanical loading was estimated as the OI ([Stevens et al., 1999](#)). Considering that bone mineralizes on the diaphyseal side, the OI was determined for each element of the most distal layer within the growth plate (excluding transition zone). Similar to previous studies ([Shefelbine and Carter, 2004](#); [Carriero et al., 2011](#); [Yadav et al., 2016](#); [Yadav et al., 2017](#); [Kainz et al., 2020](#); [Kainz et al., 2021a](#); [Yadav et al., 2021](#)) the OI was estimated using the obtained principal stresses ($\sigma_1, \sigma_2, \sigma_3$) from the FE analysis (Eq. (2)). Hydrostatic stresses (σ_{H_i}) and octahedral shear stresses (σ_{S_i}) were calculated for each load instance ($i = 1 \dots 9$) (Equations (3) and (4) and constants a and b were chosen with values of 0.02 MPa⁻¹month⁻¹ and 0.01 MPa⁻¹month⁻¹, respectively, to have a ratio $b/a = 0.5$ similar to previous studies) ([Shefelbine and Carter, 2004](#); [Carriero et al., 2011](#); [Yadav et al., 2016](#); [Yadav et al., 2017](#); [Yadav et al., 2021](#)). The unit of the OI is therefore month⁻¹. Outliers identified as OI values that were more

TABLE 1 Sets of material properties used for the different sections of the femur.

Anatomical structure	“Youngs’ modulus”		“Poissons’ ratio”
	“hard”	“soft”	
growth plate	1000	100	0.49
prox. trabecular	10000	2000	0.3
dist. trabecular	10000	5000	0.3
cortical bone	20000	20000	0.3
bone marrow	1	1	0.3



than three scaled median absolute deviations away from the median (MATLAB's "isoutlier" function) were replaced by the corresponding minimum or maximum values. These identified outliers were located at the outer edges of the growth plate, which might be due to the lower quality of the hexahedral elements in this region compared to the rest of the growth plate. Therefore, this step was necessary to ensure smoother OI distribution for subsequent comparisons.

$$OI = a * \max(\sigma_{s_i}) + b * \min(\sigma_{H_i}) \quad (2)$$

$$\sigma_{s_i} = \frac{\sqrt{(\sigma_1 - \sigma_2)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2}}{3} \quad (3)$$

$$\sigma_{H_i} = \frac{\sigma_1 + \sigma_2 + \sigma_3}{3} \quad (4)$$

2.7 Quantification of the osteogenic index

To enable a comparison of OI between growth plates with different shapes, the OI values were projected on the transverse plane according to the elements' locations and interpolated to a squared grid. A blue to red color scheme was used to visualize OI

values representing minimum to maximum OI values, respectively. This resulted in heatmaps of equal size for all growth plates revealing the OI distribution (anterior/posterior and medial/lateral) based on the mechanical loading condition. Subsequently, the squared grid was divided into five regions representing the center, anterior, posterior, lateral and medial sections of the growth plate. The center was defined as a circle with a diameter of 50% of the growth plate's width and the other regions according to their corresponding anatomical sides of the growth plate separated by the square's diagonals (Figure 2). Consecutively, the region with the highest and lowest mean value was identified which indicates the area with maximally promoted and inhibited growth, respectively. Since these heatmaps were scaled to each analysis' minimum and maximum values the magnitude of the OI was neglected. Therefore, we additionally evaluated the range of the magnitude and the mean and median value of the OI.

2.8 Osteogenic index reference dataset

A representative reference OI distribution heatmap was created by calculating mean OI values across participants for the TD and the CP group. One can imagine this as stacking up all heatmaps. Due to the different shapes of the growth plates, on the outer edges only few OI values were available. To avoid incorrect values at these locations, mean values were only calculated for locations if data of more than half of the femurs, i.e. more than 12 and 13 for CP and TD, respectively, were available.

2.9 Intra-subject variability

Two main metrics were used to quantify the intra-subject variability of the OI for each participant. Firstly, the regions with the highest and lowest mean value were compared between each participant's left and right femur. Secondly, to quantify differences in shape and distribution of the OI (e.g. ring shape vs. linear-gradient), an image comparison between the heatmaps of the left and right femur was performed using OpenCV's template matching (Bradski, 2000). The "TM_CCOEFF_NORMED"-method was used which computes one resultant value between 0 and 1 that represents the probability that images are equal. For a more comprehensible metric, the result was subtracted from 1 so that high values indicate high variability. Additionally, to account for the magnitude of the

OI, the difference of the mean values and difference of the ranges between the left and right OIs were calculated. Subsequently, independent t-tests were performed to identify differences of the intra-subject variability between the CP and TD group.

2.10 Inter-subject variability

To assess the inter-subject variability between groups, we analyzed the mean occurring OI values in each region. Firstly, the mean value of each region was normalized to the range of the individual OI. Then, these normalized values for each region were compared between CP and TD group with independent t-tests to evaluate differences in general OI distribution. To identify statistically significant differences in the variability, the standard deviations of each region were compared between groups with a Levene's test.

Additionally, we compared each OI heatmap with all OI heatmaps of the same group, i.e. each OI of a TD child was compared to all other OIs of TD children, with the before mentioned image comparison method. Comparisons of equal heatmaps (e.g. "TD01 left side" vs. "TD01 left side") were neglected. Subsequently, the mean variability to other OIs of the group was calculated. This measure indicates the difference of shape and distribution of a single OI within its group. Next, the inter-subject variability within each group was compared between TD children and children with CP. Again, to account for the magnitude of the OI, the mean values and the ranges of the OIs were compared between groups with a two-sampled t-test.

2.11 Influence of MSK model and FE material properties

The sum of all muscle forces acting on the femur as well as the magnitude of the HCF at the first and the second peak were compared between the MSK simulations with generic-scaled and personalized models. Within each group (TD and CP), all parameters were tested for significant differences with two-sampled t-tests. Between groups, muscle forces and HCF of the personalized MSK model were compared with independent t-tests.

To answer our technical research questions on the influence of the MSK model and the material properties on the OI, we performed the same comparisons and statistical tests as described above for the simulation results obtained with altered loading conditions and altered material properties, separately. Subsequently, we identified differences in outcomes due to different loading conditions and material properties. Additionally, we evaluated changes of the regions with the highest mean value compared to the base analysis with "hard" material properties and personalized MSK models.

2.12 Geometrical analysis

To identify possible reasons for observed differences of the OI between the CP and the TD group, the shape, the location and the

orientation of the growth plates were analyzed. The shape was quantified by fitting a sphere through nodes in the middle of the growth plate. If the sphere's midpoint was distal of the growth plate the shape was convex, otherwise it was concave. The radii of these spheres were compared between groups. The location of the growth plate was determined by calculating the distance between the intersection point of the neck axis and the femur's proximal surface and the mean location of all nodes within the growth plate. The neck length was quantified as the femoral head radius plus the distance between the femoral head center and the point where neck and shaft axis have the minimal distance to each other. The location of the growth plate was normalized to the length of the femoral neck. To quantify the orientation of the growth plate the angles between the normal vector to the growth plate (obtained during mesh creation) and 1) the femur coordinate system and 2) the orientation of the mean and maximum HCF during stance phase in the anatomical planes were calculated. Additionally, angles between the neck axis and 1) the orientation of the mean and maximum HCF in the anatomical planes and 2) the normal vector to the growth plate were computed.

3 Results

3.1 Participant exclusion and FE analysis metrics

In total, 6 out of 50 (12%) FE analysis with "hard" material properties and the personalized MSK model did not converge and therefore four participants (all children with CP; in two participants, left and right side did not converge) had to be excluded from our study because intra-subject comparisons were impossible. Data of these participants was not used in any analysis. Therefore, all presented results include data of 8 children with CP and 13 TD children, i.e. 42 femurs in total. In the analysis sets with the generic-scaled MSK model and "soft" material properties 2 (4.75%) and 4 (9.5%) out of the remaining 42 FE analysis did not converge, respectively.

3.2 Osteogenic index reference dataset

The representative reference OI distribution heatmap generated from data of 26 TD children's femurs showed a ring shape with low values in the center region and high values at the border of the growth plate (Figure 3A). The descending order of the regions according to their highest mean was posterior, medial, lateral, anterior and center. The reference OI for TD children was distributed between $-0.024 \text{ months}^{-1}$ and $0.013 \text{ months}^{-1}$ with a mean value of $-0.003 \text{ months}^{-1}$.

The reference OI distribution generated from data of 16 femurs of children with CP had a different shape with highest values on the lateral side of the growth plate (Figure 3B). An indication of a ring shape distribution, similar to the TD children, was observed. The regions with highest mean values in descending order were lateral, posterior, anterior and medial followed by the center. The OI values ranged from $-0.011 \text{ months}^{-1}$ to $0.022 \text{ months}^{-1}$ with a mean of $0.003 \text{ months}^{-1}$.

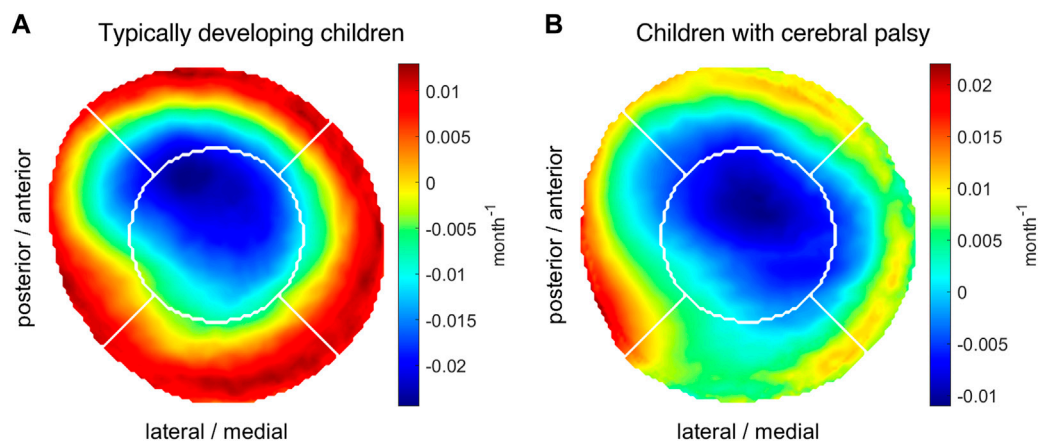


FIGURE 3 Average growth plate shape and OI distribution in TD children (A) and children with CP (B). The OI distribution is represented using a blue to red color scheme representing low to high values, respectively.

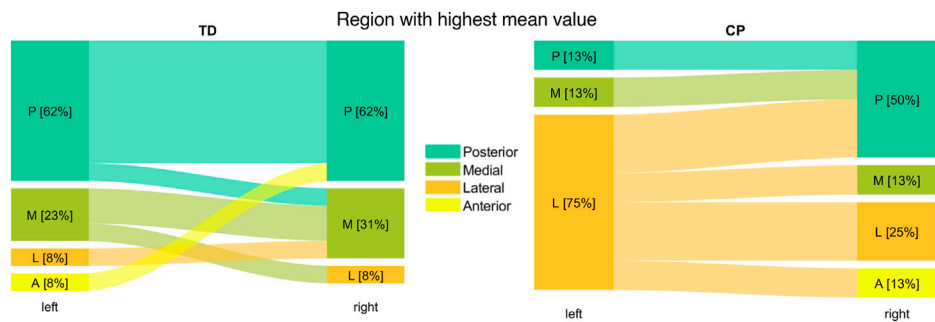


FIGURE 4 Intra-subject comparison of region with highest mean OI value between left and right growth plate for TD children (left) and children with CP (right).

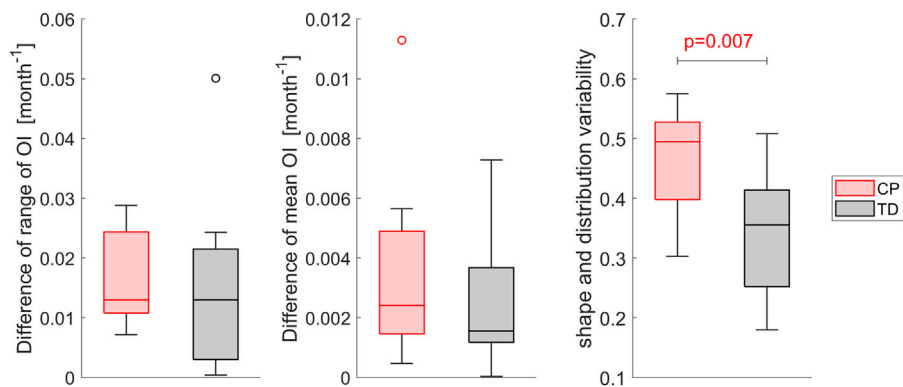


FIGURE 5 Comparison of the intra-subject variability of the magnitude of OI, i.e. mean value and range, and the variability assessed with template matching of the heatmaps of the left and right OI between children with CP and TD children. Higher variability values indicate a higher difference in shape and distribution, a value of 0 indicates equal OI shape and distribution. Significant differences were quantified with independent t-tests.

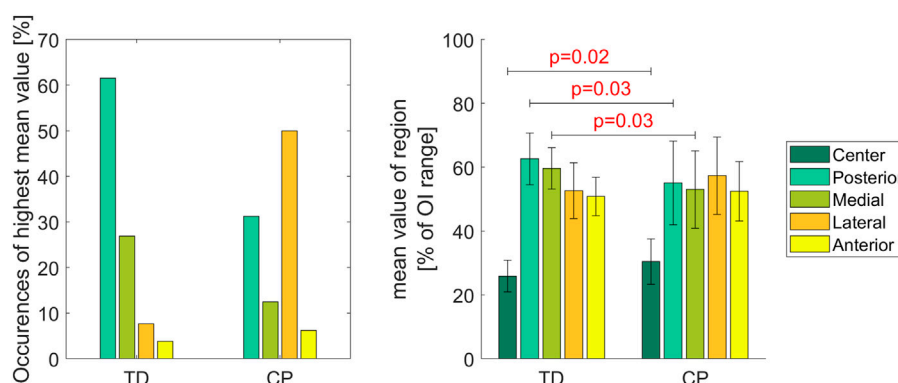


FIGURE 6

The left diagram shows how often the highest mean value was observed in a specific region. In the right diagram the colored bars represent the mean value of each region normalized to the range of the individual OI. Significant differences were quantified with independent t-tests. Vertical error bars indicate the standard deviation between participants within groups.

3.3 Intra-subject variability

When comparing the left with the right growth plate of each participant, the highest mean OI value occurred at different regions in 30.8% ($n = 4$) of TD children and in 62.5% ($n = 5$) of children with CP (Figure 4). The lowest mean OI value was observed at the center region in all TD children and most children with CP. In one child with CP the lowest mean OI value occurred in the medial region and in another child with CP in the posterior region.

The differences of the mean OI value as well as the range of OI values between the left and right side were not significantly different between both groups. The image comparison of the heatmaps to quantify the variability of the shape and OI distribution between left and right growth plate showed a significantly higher ($p < 0.01$) intra-subject variability in children with CP compared to TD children (Figure 5).

3.4 Inter-subject variability

In 61.5% ($n = 16$) of the femurs of the TD group the highest mean value of the OI was observed in the posterior region of the growth plate followed by the medial region (27%; $n = 7$). In children with CP the lateral (50%; $n = 8$) followed by the posterior (31%; $n = 5$) region were the areas with the most occurred highest mean OI values (Figure 6 left).

The mean values of the posterior and medial regions were significantly higher in TD children compared to children with CP whereas significantly lower values were observed in the center region for the TD children. Levene's test showed significant differences of the variances ($p < 0.05$) in the posterior and medial region between groups indicating that in children with CP the variability is higher compared to TD children (Figure 6 right).

The range of the OI as well as the mean OI differed significantly ($p < 0.01$) between the TD and CP group. In TD children, the range of the OI was higher and lower mean values were observed. Comparing each OI heatmap with all other OI heatmaps of its

group revealed significantly higher ($p < 0.001$) inter-subject variability in the CP compared to the TD group (Figure 7).

3.5 Geometrical analysis

The femurs of TD children were significantly ($p < 0.001$) larger compared to those of children with CP. No significant differences were observed for the neck length and the growth plate location between groups normalized to the femur's length and its neck, respectively. A wide range of AVA and NSA was present in the analyzed dataset but without any statistical differences between the CP and TD group. The shape of the growth plate did not differ between groups, all had a convex shape with radii between 10mm and 35 mm (Figure 8).

The orientation of the growth plate was similar in relation to the femur's coordinate system between children with CP and TD children. The angles between the orientation of the maximum and mean occurring HCF during stance phase and the vector normal to the growth plate did not differ significantly between groups (Figure 9).

No significant difference was observed between the CP and TD group for the angle between the neck axis and the normal vector to the growth plate. The angle between the femoral neck axis and the orientation of the maximum ($p < 0.05$) and mean ($p < 0.001$) HCF was significantly different between CP and TD children in transverse plane. A statistically significant difference between CP and TD children was also observed in the frontal and sagittal plane for the angle between the neck axis and mean HCF during stance phase (Figure 10).

3.6 Influence of MSK model

The use of a generic-scaled instead of personalized MSK model changed the loading condition, i.e. HCF and muscle forces on the participants' femurs (Figure 11). At the first peak of the HCF, the magnitude of the HCF and the sum of all muscles acting on the femur were significantly lower in both groups when using a generic-

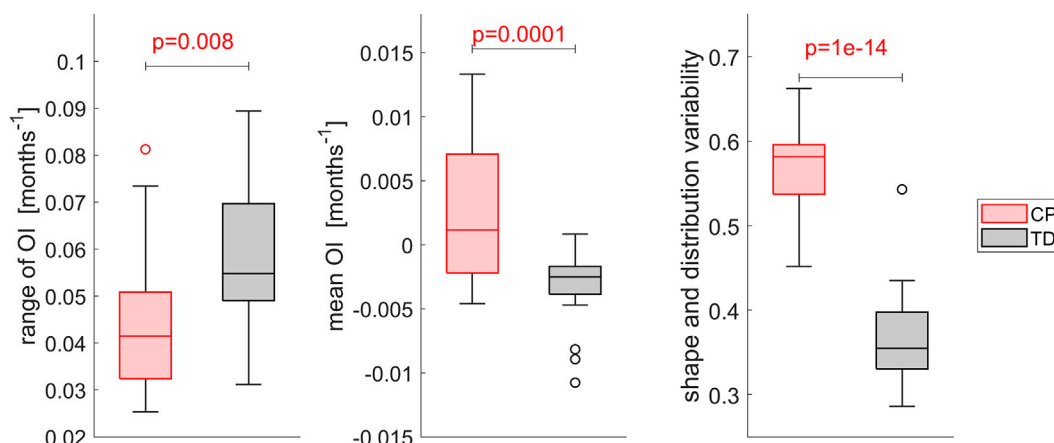


FIGURE 7

Comparison of the inter-subject variability of the magnitude of OI, i.e. mean value and range, and the variability assessed with template matching of the heatmaps. Each OI was matched with all other OIs of its group and the mean variability compared between groups. Higher variability values indicate a higher difference in shape and distribution, a value of 0 indicates equality. Significant differences were quantified with independent t-tests.

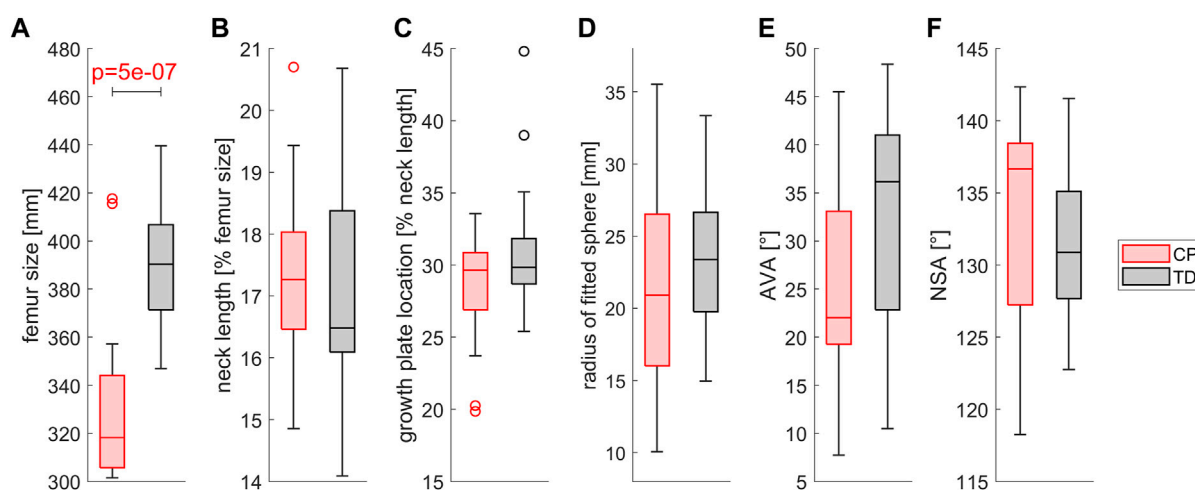


FIGURE 8

Comparison of (A) the femur size, (B) the neck length, (C) the growth plate location, (D) the shape of the growth plate, (E) the AVA and (F) the NSA between children with CP and TD children. Growth plate location was assessed as the distance between the intersection point of the neck axis and the proximal surface and the middle of the growth plate. The shape of the growth plate was assessed by fitting a sphere into the nodes of the middle layer of the growth plate. Significant differences were quantified with independent t-tests.

scaled model. In TD participants, the magnitude of the HCF and the muscle forces at the second peak of HCF were significantly lower with the generic-scaled compared to the personalized model. Independent t-tests showed significantly higher values of HCF peak as well as the sum of all muscle forces acting on the femur at both HCF peaks for TD compared to CP children. Two out of the 42 FE analysis did not converge when using the generic-scaled loading conditions. Against the general observation that HCF and muscle forces were lower when using a generic-scaled MSK model, in these two analyses the maximum HCF magnitude increased which led to non-convergence in the FE analysis.

The region with the highest mean OI value changed due to the MSK model that was used in 2 (14.3%) and 5 (19.2%) participants of the CP and TD group, respectively (Figure 12). The intra-subject comparison between left and right OI showed that in 30.8% ($n = 4$) of TD children and in 71.4% ($n = 5$ out of 7) of children with CP the highest mean OI value occurred in different regions of the growth plate. No statistically significant changes were observed for the differences of the mean OI, the range of the OI and the OI variability between the left and right side due to the MSK model that was used. The range of OI did not significantly differ between the CP and TD group when using the loads from the generic-scaled

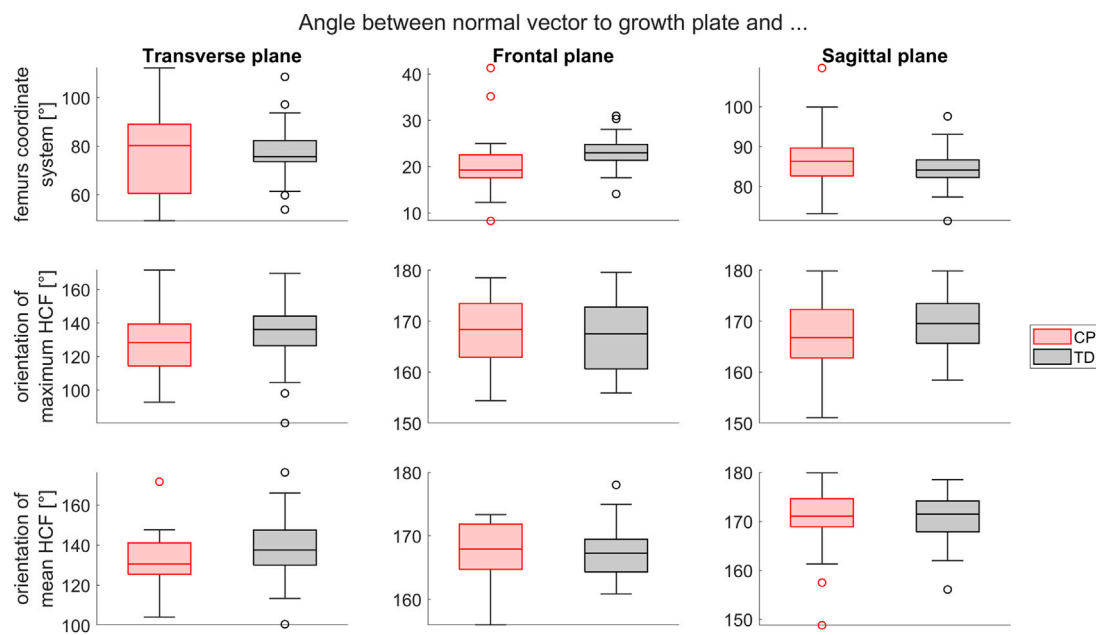


FIGURE 9

Comparison of the growth plate orientation (normal vector) between the CP and TD group in relation to the femur's coordinate system (top), the maximum HCF (middle) and the mean HCF during stance phase (bottom) in transverse, frontal and sagittal plane. Significant differences were quantified with independent t-tests.

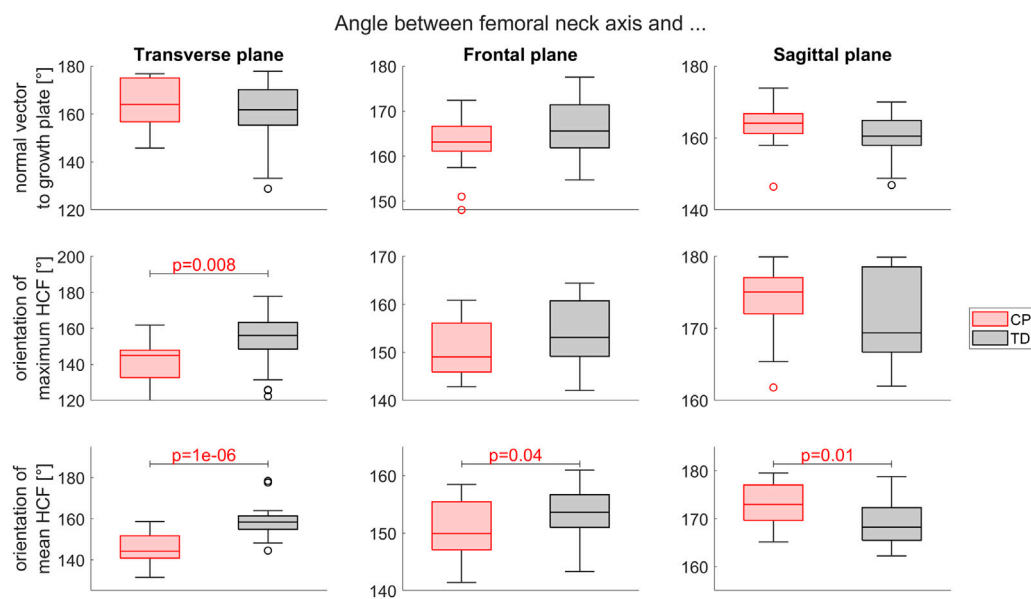


FIGURE 10

Comparison of the neck axis orientation between the CP and TD group in relation to the growth plates normal vector (top), the orientation of the maximum HCF (middle) and the mean HCF during stance phase (bottom) in transverse, frontal and sagittal plane. Significant differences were quantified with independent t-tests.

MSK models, whereas it was significantly different with personalized MSK models. Additional plots, similar to Figure 5; Figure 6 but based on the generic-scaled MSK model can be found in the [Supplementary Material](#).

3.7 Influence of FE material properties

For four children with CP the FE analysis did not converge with the “soft” material properties. This reduced the number of intra-

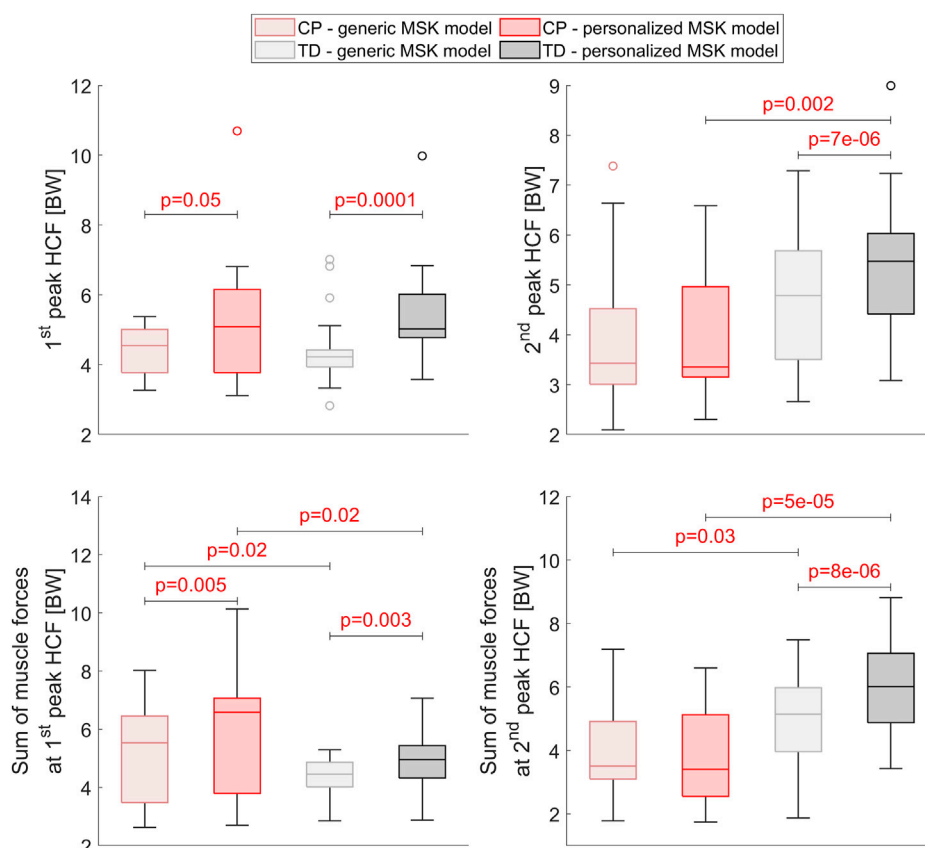


FIGURE 11

Comparison of the HCF and the muscle forces acting on the participants' femurs between the generic-scaled and the personalized MSK model within the CP and TD group as well as between groups for the personalized MSK model. Significant differences were quantified with dependent and independent t-tests within groups and between groups, respectively.

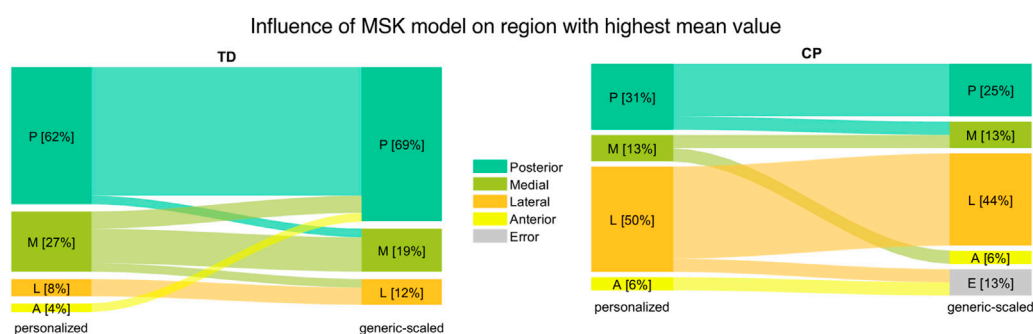
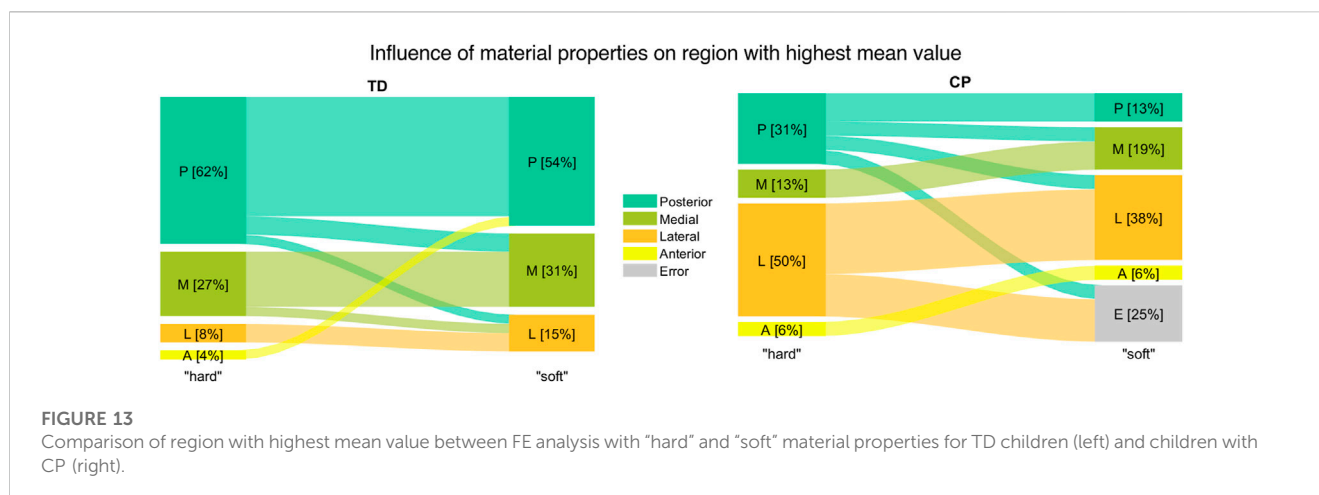


FIGURE 12

Comparison of region with highest mean value between the generic-scaled and personalized MSK model for TD children (left) and children with CP (right).

subject comparisons for CP children to 5 participants. The region with the highest mean OI value changed due to the material properties in 2 (16.7%) and 5 (19.2%) participants of the CP and TD group, respectively (Figure 13). The intra-subject comparison between left and right OI showed that in 38.5% ($n = 4$) of TD children and in 60% ($n = 3$ out of 5) of children with CP the highest

mean OI value occurs in different regions of the growth plate. With “soft” material properties, there was no significant difference of the intra-subject variability of the shape and distribution between the left and right side. Inter-subject comparison between the CP and TD group with “soft” material properties showed no significant differences in mean values for all regions. The mean OI was not



significantly different between groups whereas this was the case for “hard” material properties. Additional plots, similar to Figure 5; Figure 6 but based on the “soft” material can be found in the Supplementary Material.

4 Discussion

The aim of this study was to quantify and compare the OI in the proximal growth plate of the femur in a comparably large cohort of TD children and children with CP with subject-specific loading, femoral morphology as well as growth plate shape and orientation. The GP-Tool based on freely available software was developed, which enables one to create subject-specific FE models and perform the multi-scale simulations in a simple and comprehensive way. The GP-Tool has been shared with the community (<https://github.com/WilliKoller/GP-Tool>) to enable peers to conduct mechanobiological growth studies with larger sample sizes and enhance our understanding of femoral bone growth. In this study, the analyzed dataset included 26 femurs of TD children and 16 femurs of children with CP and empowered us to create a reference OI as well as to evaluate the intra- and inter-subject variability. The within-group variability in range of OI, mean OI, OI shape and distribution were significantly different between groups, suggesting different bone growth patterns may be present in CP and TD children.

The reference OI for TD children showed a clear ring shape with high values on the outside and low values in the center which indicates more growth on the outside compared to the inner part of the growth plate. This could support the finding that with time and under normal loading conditions, the growth plate changes its shape from a spherical to a flat disc (Kandzierski et al., 2012).

In children with CP the reference OI clearly differed from those of TD children with the maximum values occurring in the lateral region. Considering the high variability of femoral morphology and femoral loading patterns in children with CP, the presented reference OI does not reflect the whole population of children with CP and therefore should be interpreted with caution. Some children with CP had OIs that were similar to the reference OI of TD children while others were very different.

The inter-subject analyses showed that in most femurs of TD children, the region with the highest mean OI values were the posterior followed by the medial region. In both regions, we found significantly higher OI values within the TD compared to the CP group. Most previous studies based on loading conditions estimated from gait of TD children also found a ring-shaped OI distribution with the highest values on the posterior side of the growth plate (Yadav et al., 2017; Kainz et al., 2020). Carriero et al. (2011) reported a linear-gradient OI distribution with the highest values on the lateral side for a healthy child, which was contrary to the OI of our TD children but similar to the OI of our participants with CP. Carriero et al. (2011) however, conducted their simulations based on a model with a simplified growth plate, i.e. flat disc. The low participant number and simplified growth plate (Yadav et al., 2016) might explain the contrary results from Carriero et al. (2011) compared to the more recent investigations.

The analysis of the intra-subject variability showed that in most TD children the region with the highest mean value was equal between the left and right side while in the CP group this was only the case for approximately a third of the participants. The variability of the shape and distribution of the OI also revealed a significantly higher intra-subject variability in children with CP compared to TD children which could lead to asymmetric femoral growth.

In the analyzed dataset, the femurs of children with CP were significantly smaller compared to the TD group but the morphology in terms of neck length, AVA, NSA, growth plate location and growth plate shape was similar between groups. All morphological parameters were within the range of TD values reported in a study based on 508 participants (Szuper et al., 2015).

The use of generic-scaled instead of image-based MSK models significantly changed the femoral loading conditions, i.e. muscle forces and HCF, but the general findings remained similar. The only statistical differences between analysis based on the generic-scaled and personalized MSK model were observed for the range of the OI, whereas the generic-scaled MSK model led to fewer differences between the CP and TD group.

Four analyses did not converge when using material properties with the compliant material, i.e., low Young's modulus. In linear elastic materials, which were used in this study, lower stiffness leads to larger displacements. When elements are deformed resulting into

inverted elements, the FE solver cannot continue the analysis. In theory, the stress within a material only depends on the force and the cross-section of the geometry and therefore, stresses within the growth plate should not be influenced by the used material properties. However, in FE analysis the material properties are used to initially calculate the global stiffness matrix. Then, displacements are estimated and subsequently used to calculate the stresses (Bathe, 2006, 149ff). Hence, changes of material properties have an impact on observed stresses within the growth plate. However, observed changes in our analyses were minimal with the only statistical difference in the mean OI value reducing the difference between CP and TD group.

Four participants had to be excluded because in total, 6 out of 50 FE analysis did not converge with stiff material properties. The reasons for this were mainly tremendously high HCFs (~4000 N, above 10 times body weight) or very thin cortical bone. Thin cortical bone, i.e., only two or three element layers on the femoral shaft (bone marrow has low Young's modulus and can be neglected), is unlikely to support the full MSK loading. In future studies, attention has to be paid to the segmentation of the cortical bone. Unrealistic and insufficient cortical thickness and/or unrealistic high HCF might not converge and therefore make the estimation of the OI impossible.

We only estimated growth plate stresses and quantified the OI but did not simulate femoral growth. Femoral growth can be predicted with an additional FE analysis including a method to estimate the growth direction. To do this, different methods have been suggested to define the growth direction, i.e. femoral neck deflection direction or principal stress direction (Yadav et al., 2016). None of these methods have been validated based on longitudinal data and therefore we decided not to include the additional analysis in our study.

In children with CP muscle morphology and motor control are often altered compared to TD children, i.e. shorter muscle belly, muscle spasticity, decreased muscle volume and strength (Hanssen et al., 2021; Peeters et al., 2023). Assessment of individuals' muscle properties, e.g. maximum isometric muscle forces, with clinical tests is challenging in children with CP (Kainz et al., 2018). We accounted for the individuals' bony geometry which has been shown to have a larger impact on hip joint contact forces than the personalized motor control (Kainz et al., 2021b). Nevertheless, future studies could include ultrasound measurements to personalize muscle parameters (Schless et al., 2018), include a spasticity model (Falisse et al., 2018; Falisse et al., 2020) and account for the patient-specific motor control (Veerkamp et al., 2019) to further improve the accuracy of the MSK simulations.

Our study included the following limitations. First, bone is a highly complex structure with anisotropic material properties. In this study, the material of the bone was simplified to have linear elastic properties. Previous studies modelled the bone similarly (Shefelbine and Carter, 2004; Carriero et al., 2011; Yadav et al., 2016; Kainz et al., 2020; Yadav et al., 2021). FEBio supports complex materials, therefore, the developed GP-Tool can be modified to include more realistic materials for future studies. Second, during the automated meshing, a small number of elements with low quality metrics (at the very outer border) of the growth plate were removed. This was necessary to avoid inverted elements under load to ensure successful FE analysis. Third, the MSK models included only the personalized femoral morphology

whereas the geometry of the tibia was neglected. Changes of bony geometry alters moment arms of muscles and subsequently has an impact on the estimated muscle forces and HCF. However, tibial torsion only affects a limited number of muscles and therefore we assume the impact on HCF is negligible. Studies which investigate the impact of tibial torsion on HCF should be carried out to verify our assumption. Fourth, we used a static optimization algorithm to compute muscle activities. Approaches including electromyography (EMG) data might better represent the individuals' motor control (Pizzolato et al., 2015). Due to lack of EMG data in all our participants we could not perform EMG-informed analysis and therefore decided to use static optimization. Femoral geometry has a bigger impact on HCF than including EMG data in the optimization (Kainz et al., 2021b) and therefore we would expect to get similar OI with an EMG-informed approach.

The findings of this paper can help to identify possible pathological loading on the growth plate which might result in atypical femoral bone growth. If pathological loading is noticed at an early stage, subject-specific therapies like real-time biofeedback training could be used to alter joint loads (Comellas and Shefelbine, 2022; Uhlrich et al., 2022) and therefore change growth plate stresses. However, further studies have to be carried out to identify how different walking pattern and motor control strategies influence growth plate stresses.

To conclude, we developed the GP-Tool to create subject-specific FE models and estimate the OI in a semi-automatic way. The code of the GP-Tool has been made freely available to the research community as well as an executable file for users without a MATLAB license. On a standard notebook, the complete process of creating a subject-specific mesh from STL files, setting up and running the FE analysis takes around 30 min. We hope the GP-Tool encourages peers to conduct similar studies with large sample sizes to improve our general insights in femoral bone growth and to support clinical decision making in the near future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of the University of Vienna and Children's Health Queensland Human Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

WK, AB, and HK contributed to conception and design of the study. WK and HK collected and processed data. WK developed the GP-Tool which was used to perform OI analysis. HK, AB, and BG supported the development with ideas about implementation, testing and feedback. WK wrote the first draft of the manuscript.

All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fbioe.2023.1140527/full#supplementary-material>

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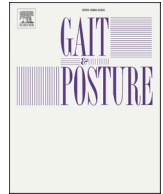
2.4. ESMAC Best Paper Award 2023: Increased knee flexion in participants with cerebral palsy results in altered stresses at the distal femoral growth plate compared to a typically developing cohort

Authors: Willi Koller, Elias Wallnöfer, Andreas Kranzl, Gabriel Mindler, Arnold Baca and Hans Kainz

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ESMAC Best Paper Award 2023: Increased knee flexion in participants with cerebral palsy results in altered stresses at the distal femoral growth plate compared to a typically developing cohort

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ABSTRACT

Introduction: Femoral deformities are highly prevalent in children with cerebral palsy (CP) and can have a severe impact on patients' gait abilities. While the mechanical stress regime within the distal femoral growth plate remains underexplored, understanding it is crucial given bone's adaptive response to mechanical stimuli. We quantified stresses at the distal femoral growth plate to deepen our understanding of the relationship between healthy and pathological gait patterns, internal loading, and femoral growth patterns.

Methods: This study included three-dimensional motion capture data and magnetic resonance images of 13 typically developing children and twelve participants with cerebral palsy. Employing a multi-scale mechanobiological approach, integrating musculoskeletal simulations and subject-specific finite element analysis, we investigated the orientation of the distal femoral growth plate and the stresses within it. Limbs of participants with CP were grouped depending on their knee flexion kinematics during stance phase as this potentially changes the stresses induced by knee and patellofemoral joint contact forces.

Results: Despite similar growth plate orientation across groups, significant differences were observed in the shape and distribution of growth values. Higher growth rates were noted in the anterior compartment in CP limbs with high knee flexion while CP limbs with normal knee flexion showed high similarity to the group of healthy participants.

Discussion: Results indicate that the knee flexion angle during the stance phase is of high relevance for typical bone growth at the distal femur. The evaluated growth rates reveal plausible results, as long-term promoted growth in the anterior compartment leads to anterior bending of the femur which was confirmed for the group with high knee flexion through analyses of the femoral geometry. The framework for these multi-scale simulations has been made accessible on GitHub, empowering peers to conduct similar mechanobiological studies. Advancing our understanding of femoral bone development could ultimately support clinical decision-making.

1. Introduction

Cerebral palsy (CP) is a neurological disorder where neuro-musculoskeletal abnormalities result in progressive disabilities in

activities of daily living. Gait impairments lead to decreased mobility depending on the severity of the disease. Pathological bone deformations of the femur are common problems in this patient cohort and are often treated with corrective de-rotation or re-alignment

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osteotomies performed during multi-level surgeries [1]. It has been shown that bone adapts its shape and strength in response to mechanical loading [2–7]. A better understanding of the relationship between gait patterns, loading on the bones and bone growth could help inform early-stage interventions to avoid the development of femoral deformities.

Cross-sectional studies have shown that the femoral neck-shaft angle (NSA) and anteversion angle (AVA) decrease during growth in typically developing (TD) children. Children with CP often have increased NSA and AVA [8–10]. Pathological bony geometries alter moment arms of muscles [11] which can affect muscle recruitment strategy [12] and therefore bone loads [13] and growth. The stresses within the proximal femoral neck growth plate determine the development of the femoral geometry in terms of NSA and AVA. Multi-scale studies based on musculoskeletal (MSK) and finite element (FE) simulations have been used to estimate muscle forces, joint contact forces and stresses within the proximal femoral neck growth plate [14–20]. Summarized, these studies conclude that stresses within the growth plate are sensitive to the overall femoral geometry [19], the geometry of the growth plate itself [16] and the loading conditions [14,15,17–19].

Data from the individual's bony geometry and walking pattern are required to estimate bone loads and perform mechanobiological simulations. Bony geometry can be obtained from medical images, e.g. computer tomography or magnetic resonance imaging. Furthermore, the walking pattern of a person can be objectively quantified with the use of instrumented three-dimensional gait analysis. The loading on the bones, i.e., joint contact forces and muscle forces, during activities of daily living cannot be measured in-vivo but estimated based on the gait analysis data, i.e. marker trajectories and ground reaction forces, using MSK simulations [21–23]. Subject-specific personalization of the bony geometries in the MSK model has been shown to improve the agreement between measured and estimated joint contact forces [24,25]. Individualized FE models with a hexahedral mesh aligned with the growth plate are required to calculate growth plate stresses for the mechanobiological growth simulations but are time-consuming to create. Therefore, previous studies mainly analyzed a small number of individuals (1–4 participants) [14–19,26], which did not allow a generalization of the results, or used generic FE models [15,27]. We recently developed a tool to create the FE models for the mechanobiological simulations in a semi-automated method, which enabled us to analyze growth plate stresses within the femoral neck growth plate of the femur in a comparably large dataset of 50 femurs [20]. We showed that the variability of the growth plate stresses within the CP group is significantly larger compared to the TD group indicating pathological growth patterns in some of the CP participants [20].

Mechanical lower limb axis malalignments, e.g. varus/valgus deformities, are common in adults and children with and without neurological disorders, e.g. CP [28,29]. Growth at the distal femoral epiphyseal plate influences the mechanical lower limb axis and is often guided by the use of temporary hemiepiphysiodesis [30–32]. Hucke et al. [26] recently showed that the stresses induced by an hemiepiphysiodesis reduced the growth rate at the implanted region in three patients. Furthermore, the authors highlighted that the subject-specific loading based on the person's gait pattern and the subject-specific shape of the growth plate are important factors influencing the growth plate stresses. The femoral AVA and NSA was not personalized in their models, which is known to influence hip and knee joint contact forces [33] and therefore growth plate stresses. To the best of the authors' knowledge, no studies have quantified the stresses within the distal femoral growth plate in healthy children. Knowing typical growth plate stresses in healthy children is a prerequisite to gain a deeper understanding of the relationship between healthy and pathological gait patterns, internal loading and femoral growth.

The aim of the present study was to comprehensively analyze the stresses within the distal femoral growth plate in TD children and participants with CP. To achieve this aim, we enhanced our previously

developed workflow and develop a tool to quantify subject-specific stresses at the distal femoral growth plate based on medical images and 3D motion capture data. Patients with CP have individual walking styles which can be classified into several patterns depending on the hip, knee and ankle kinematics [34]. Because knee kinematics influences knee joint contact forces [22] and stresses in the distal femoral growth plate, we divided the limbs of our CP participants in different groups depending on their knee kinematics. In addition to growth plate stresses, we compared the orientation of the growth plate between the CP groups and a group of TD participants. We hypothesized that 1) the orientation of the growth plates does not differ between TD children and participants with CP, 2) stresses at the distal growth plate differ between TD children and participants with CP due to different gait patterns, and 3) growth plate stresses differ between CP participants with different knee kinematics.

2. Materials and methods

The details regarding the materials and methods utilized in this study are briefly outlined in the main manuscript. For a more comprehensive understanding, a thorough methods section containing all details can be found in the supplementary material.

2.1. Data collection

Magnetic resonance images (MRI) and three-dimensional gait analysis data including marker trajectories and ground reaction forces of thirteen TD children (10 ± 2.2 years old, height: 144.5 ± 8.5 cm, mass: 36.8 ± 9.5 kg) and twelve participants diagnosed with CP (10.4 ± 3.8 years old, height: 133.6 ± 16.1 cm, mass: 30.1 ± 10.8 kg) with various walking patterns were analyzed for this study. Detailed information of participants with CP including Gross Motor Function Classification System (GMFCS), clinical diagnosis, age, sex, walking style and assigned group is presented in Table 1. All participants walked without walking aids and with a self-selected speed. Details of the data collection of the CP participants and three TD children are described by Kainz et al. [34]. The data of the remaining ten TD children was collected in the same manner, details are described in a previous publication [20].

2.2. MRI measurements, MSK and FE simulations

MRI scans were used to calculate femoral AVA and NSA [37]. The intercondylar distance, i.e. distance between the medial and lateral condyles of the femur, was quantified from the MRIs. MRI scans of the whole lower limbs were available in all CP and three TD participants, which enables us to additionally measure the tibial torsion [38] in these participants. These measurements were used to create subject-specific MSK models based on an OpenSim model [39], an alteration of the Rajagopal model [40] including the more complex knee joint of the Lerner model [24], which allows estimation of medial and lateral knees joint contact forces (KCF) as well as the patellofemoral joint contact force (PCF). To personalize the base model, the Torsion Tool [41] was used to modify the bony geometry to match each participant's NSA and AVA as well as tibial torsion, if MRI scans of the tibia were available. To fit the model to each participant's anthropometry, the pelvis, femur and tibia (if available) were scaled based on MRI measurements while the remaining body segments were scaled based on the location of surface markers [35]. Furthermore, the intercondylar distance was modified in the models to match each participant's value obtained from the MRI images [24]. Each participant's model and the corresponding gait analysis data were used to calculate joint angles, muscle forces and joint contact forces using inverse kinematics, static optimization by minimizing the sum of squared muscle activations and joint reaction load analyses with OpenSim 4.2, respectively [21,22].

Each femur was segmented using 3D Slicer [42] and divided into six parts representing different structural parts similar to previous studies

Table 1

Age, sex, clinical diagnoses, Gross Motor Function Classification Score (GMFCS), walking style based on visual inspection of marker data [36] and knee flexion classification of the participants with CP.

	Age	Sex	Diagnosis from clinicians	GMFCS	Walking style		Knee flexion group	
					Left	Right	Left	Right
CP01	12	f	left hemiplegic	1	crouch gait	normal	normal	normal
CP02	8	f	right hemiplegic	1	normal	equinus jump gait	high	high
CP03	13	f	right hemiplegic	1	normal	true equinus	normal	normal
CP04	12	m	spastic diplegia	2	crouch gait	crouch gait	high	high
CP05	20	m	spastic diplegia	2	apparent equinus	apparent equinus	normal	normal
CP06	5	f	spastic diplegia	2	equinus jump gait	equinus jump gait	high	high
CP07	11	m	diplegia	2	apparent equinus	apparent equinus	high	high
CP08	9	f	diplegia	2	crouch gait	crouch gait	high	high
CP09	10	m	right hemiplegic	2	normal	true equinus	normal	high
CP10	8	m	spastic diplegia	2	equinus jump gait	equinus jump gait	high	high
CP11	7	m	spastic diplegia	2	equinus jump gait	equinus jump gait	high	high
CP12	10	m	right hemiplegic	2	normal	true equinus	normal	low

[15,16,19,20]. The geometry was used to quantify the bending of the femoral shaft in sagittal and frontal plane. The previously developed and freely available GP-Tool (<https://github.com/WilliKoller/GP-Tool>) [20] was modified to create a hexahedral mesh with several layers of elements aligned with the proximal and distal growth plates based on the subject-specific femoral geometry. All operations were performed with software freely available for research purposes including Coreform Cubit, GIBBON [43] and MeshLab [44] and compiled MATLAB applications which can be run without a paying license. A subject-specific hexahedral mesh with an element size of approximately 1.5 mm was created for each femur ($n = 50$). For each participant, two representative steps (left and right) were chosen as loading condition. Similar to previous studies [16,19,20] nine load instances were selected based on the KCF peaks and the valley in-between during the stance phase. The medial and lateral KCF, PCF and muscle forces ($n = 26$) acting on the femur at these timepoints were used as loading conditions for FE analysis while nodes of the femoral head were constrained in all directions. Linear elastic materials were assigned to the different parts of the femur with varying Young's modulus and Poisson's ratio (Table S2). FEBio3 [45] was used for FE simulations and to calculate principal stresses in the distal growth plate.

2.3. Participant grouping

Limbs of participants with CP were grouped in three groups (CP_{normal}, CP_{low_knee_flexion}, CP_{high_knee_flexion}) depending on their knee flexion kinematics. Time-normalized knee flexion angles during the stance phase of each limb of CP participants was compared to the values obtained from the TD group. Knee flexion angle was considered as “low” or “high” if it was outside the mean ± 1.96 standard deviation range from the TD values for at least 5 % of the stance phase. If it was above and below the TD range at some time-points, the limb was included in the group where more time-points were outside the range.

2.4. Data analysis

Overall bone growth can be divided into the contribution of biological and mechanical factors [46]. Similar to previous studies, the growth rate due to mechanical loading was estimated as the osteogenic index (OI) [14–17,20,27,46]. The OI was calculated for each element in the growth plate using the obtained principal stresses from the FE analysis, details can be found in the [Supplementary material](#). Positive and negative OI values indicate regions where growth is likely to be promoted or inhibited, respectively. Considering that bone mineralizes on the diaphyseal side, the OI was determined within the most proximal layer of the distal growth plate.

To enable a comparison of OI between growth plates with different shapes, the OI values were projected on a plane parallel to the growth

plate and interpolated to a rectangle grid with a height to width ratio of 0.5. The rectangle was divided into four regions according to their corresponding anatomical sides of the growth plate separated by diagonals. A blue to red color scheme was used to visualize OI values revealing the OI distribution (anterior/posterior and medial/lateral) within each growth plate based on the mechanical loading condition (Fig. 1A). A representative OI distribution heatmap was created across limbs for each group.

Additionally, the region with the highest mean value was identified which indicates the area with maximally promoted growth. To assess the differences in OI between groups, we analyzed the mean occurring OI values in each region. The mean value of each region was normalized to the range of the individual OI and compared between groups. Furthermore, we evaluated the absolute range of the OI magnitude and the mean value of the OI. To quantify differences in shape and distribution, we compared each individuals OI heatmap with all OI heatmaps of TD participants with an image comparison method using OpenCV's template matching [47].

To identify possible reasons for observed differences of the OI between the TD and CP groups, the orientation between the distal growth plate and joint contact forces was evaluated. The angles between the normal vector of the growth plate identified with principal component analysis and the orientation of the medial and lateral KCF and PCF were calculated across the stance phase. Additionally, the orientation of the growth plate in the femoral coordinate system was evaluated (Fig. 1B).

2.5. Statistics

Significant differences between groups were quantified with ANOVAs. Statistical Parametric Mapping (SPM) [48] based on the SPM1D package (<http://www.spm1d.org/>) was used to compare time-dependent waveforms. In case of significance ($p < 0.05$), post-hoc tests with Bonferroni correction were used for pairwise comparisons.

3. Results

3.1. Participant groups and femoral bending

CP limbs were grouped depending on their knee flexion kinematics resulting in group sizes of 8, 1 and 15 for CP_{normal}, CP_{low_knee_flexion} and CP_{high_knee_flexion} respectively (Fig. 2A). SPM analysis revealed a significant different knee angle throughout the whole stance phase between TD and CP_{high_knee_flexion} groups. No significant differences were observed when the TD group was compared to the CP_{normal} group. Due to the fact, that only one limb was part of the CP_{low_knee_flexion} group, differences were not tested for significance and are not presented in the results of the main manuscript. All results and figures including this limb are available in the [Supplementary material](#). Walking speed normalized

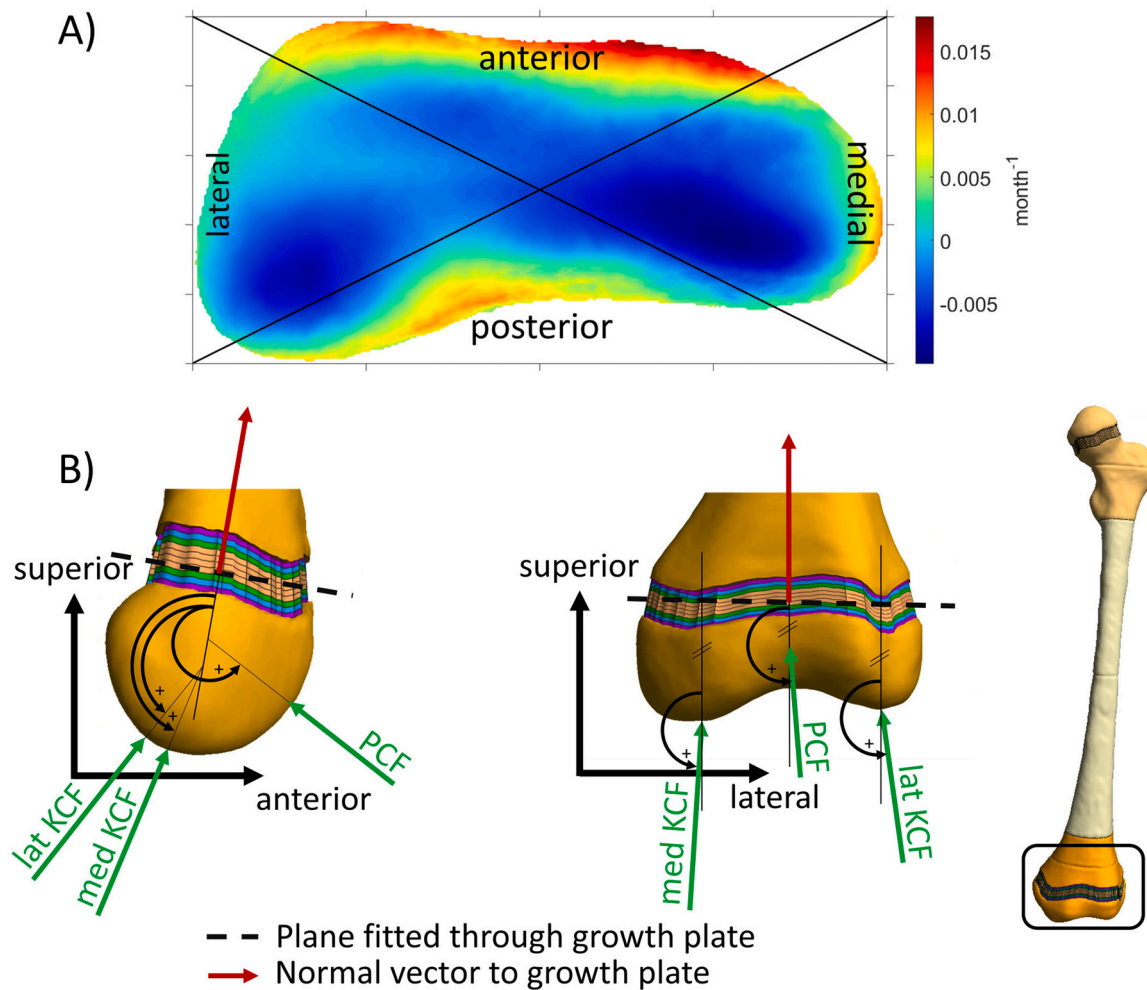


Fig. 1. A) An example of a projection of osteogenic index (OI) values on the plane parallel to the growth plate showing the division into four regions. The OI distribution is represented using a blue to red color scheme representing low and high values, respectively. B) Schematic illustration showing the orientation of the normal vector to the growth plate, medial and lateral knee joint contact force (KCF) and patellofemoral joint contact force (PCF) in sagittal and frontal plane and its corresponding angles.

to leg length [49] did not differ significantly between TD and CP_{high_knee_flexion} group (Fig. 2C). Lower body kinematics of the groups are reported in the [Supplementary material](#) (Fig. S1). The anterior bending of the femoral shaft was significantly different between all groups in sagittal plane showing that participants of the TD group had the straightest femurs, followed by limbs of the CP_{normal} and CP_{high_knee_flexion} group. In the frontal plane, limbs with high knee flexion had a higher lateral bending compared to the TD and CP_{normal} group (Fig. 2D).

3.2. Joint contact force and growth plate orientation

There were no significant differences in joint contact forces acting on the distal femur, i.e. medial and lateral KCF as well as PCF between the TD and CP_{normal} group. The CP_{high_knee_flexion} group had significantly increased medial and lateral KCFs at the first peak and significantly higher PCF throughout the whole stance phase compared to the TD group (Fig. 3).

The orientation of the distal growth plate within the femur coordinate system showed no significant differences in the frontal and sagittal plane between all groups (Fig. 4A). In the frontal plane, medial and lateral KCF as well as PCF orientation showed no significant differences between groups (Fig. 4B–D) with values around 180° (approximately perpendicular to the growth plate). SPM revealed significant differences for the orientation of all three evaluated joint contact forces in the

sagittal plane between the TD and CP_{high_knee_flexion} group. More precisely, medial KCF was significantly different throughout 50 % of the stance phase, lateral KCF and PCF during the complete stance phase. The observed angles were lower, showing that the direction of the KCF points more anteriorly and the PCF points less posterior and more superior in respect to the growth plate orientation.

3.3. Osteogenic index reference dataset and differences between groups

The representative reference OI distribution heatmap generated from data of 26 TD limbs showed highest values in the posterior notch region and on the medial-anterior edge. The edges of the remaining growth plate have average values surrounding the middle where lowest OI values occurred. The OI distribution heatmap of eight limbs within the CP_{normal} group had its peak values in similar areas as the TD group but with additional peaks at the anterior-lateral edge. The OI distribution heatmap generated from data of 15 limbs of the CP_{high_knee_flexion} group showed a linear gradient from high to low values from anterior to posterior side (Fig. 5A).

The highest mean value was observed in the posterior region in 88.5 % (n = 23) and 37.5 % (n = 3) of the limbs within the TD and CP_{normal} groups, respectively. The anterior region was the area with the highest mean value in 100 % (n = 15), 50 % (n = 4) and 11.5 % (n = 3) of the limbs of the CP_{high_knee_flexion}, CP_{normal} and of the TD group. In one

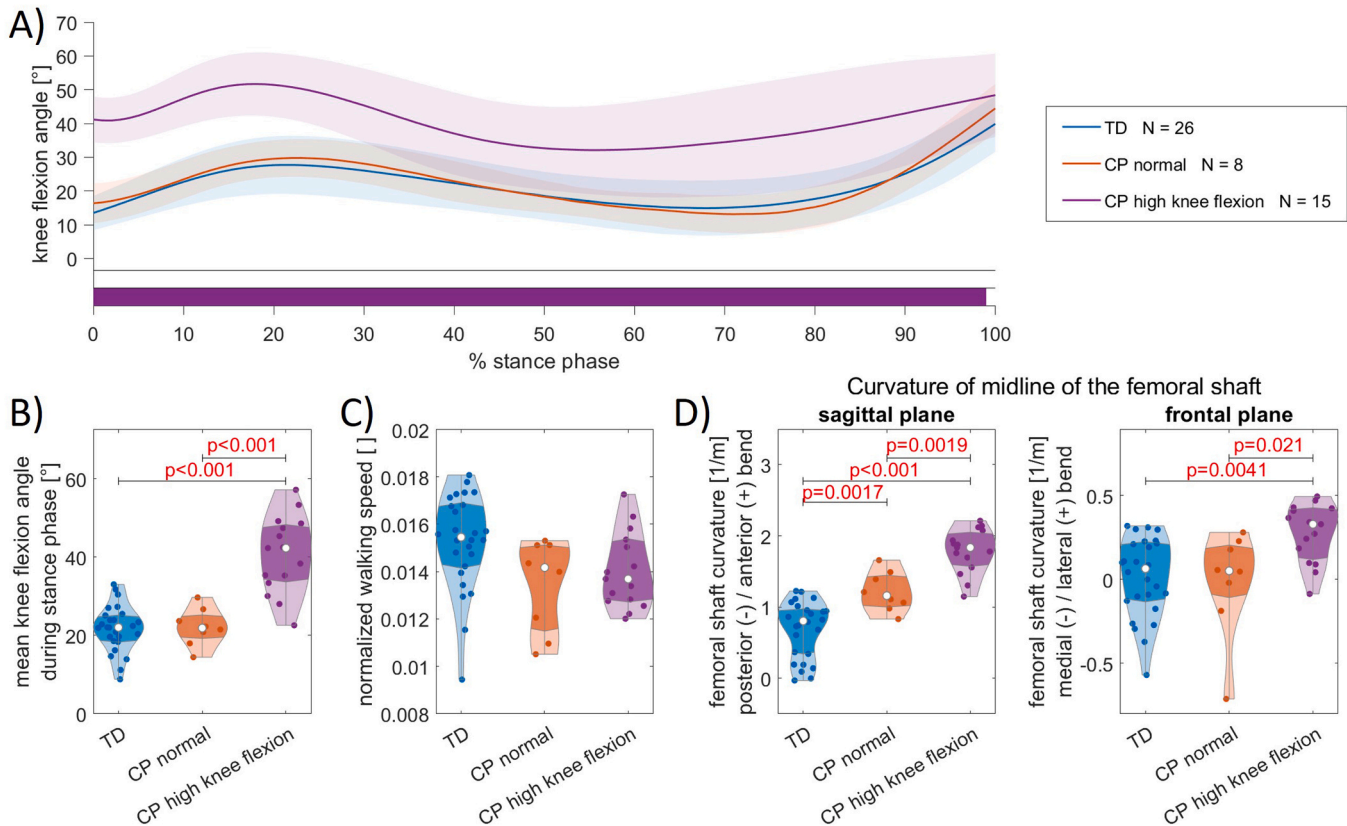


Fig. 2. A) Mean knee flexion angle and standard deviation (shaded) during the stance phase. Significant differences between TD and CP groups identified with SPM are visualized by corresponding colored bars (orange = "TD vs CP_{normal}"; violet = "TD vs CP_{high_knee_flexion}"). B) Violinplots show mean knee flexion angle during the stance phase. C) Violinplots show the non-dimensional walking speed normalized to leg length [49]. D) Curvature of the femoral shaft determined as the reciprocal radius of a circle fit to the midline of the femoral shaft [50].

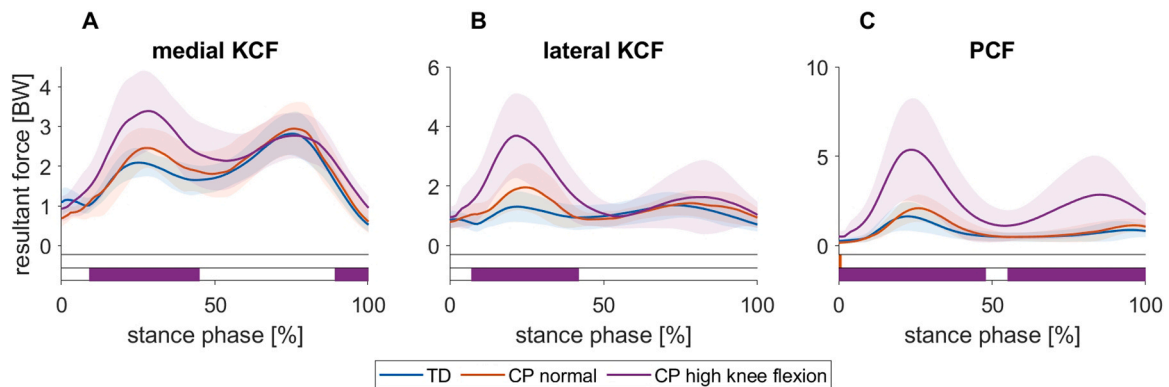


Fig. 3. Mean and standard deviation (shaded) of medial (A) and lateral KCF (B) and PCF (C) resulting magnitude during the stance phase. Significant differences between TD and CP groups identified with SPM are visualized by corresponding colored bars (orange = "TD vs CP_{normal}"; violet = "TD vs CP_{high_knee_flexion}") below each plot.

limb of the CP_{normal} group (12.5 %), the highest mean value was observed in the medial region (Fig. 5B left).

The mean values normalized to the range of the OI within medial and lateral regions showed no significant differences between the TD, CP_{normal} and CP_{high_knee_flexion} groups. The normalized mean values within the posterior and anterior regions showed significant differences between each pairwise group comparison. Specifically, the OI magnitude in the posterior region was decreased in CP_{normal} and even more in CP_{high_knee_flexion} groups whereas the mean values in the anterior region were increased in both groups compared to the TD group. (Fig. 5B right).

The range of the OI magnitude was significantly higher in the

CP_{high_knee_flexion} compared to the TD and CP_{normal} groups. CP_{normal} and CP_{high_knee_flexion} groups had significantly lower mean OI values than the TD group. The image comparison to quantify differences in shape and distribution of the OI heatmaps revealed significant differences for each group comparison (Fig. 6).

4. Discussion

We analyzed stresses within the distal growth plate of the femur in a comparably large cohort of TD children and participants with CP. In agreement with our hypotheses we showed that the orientation of the

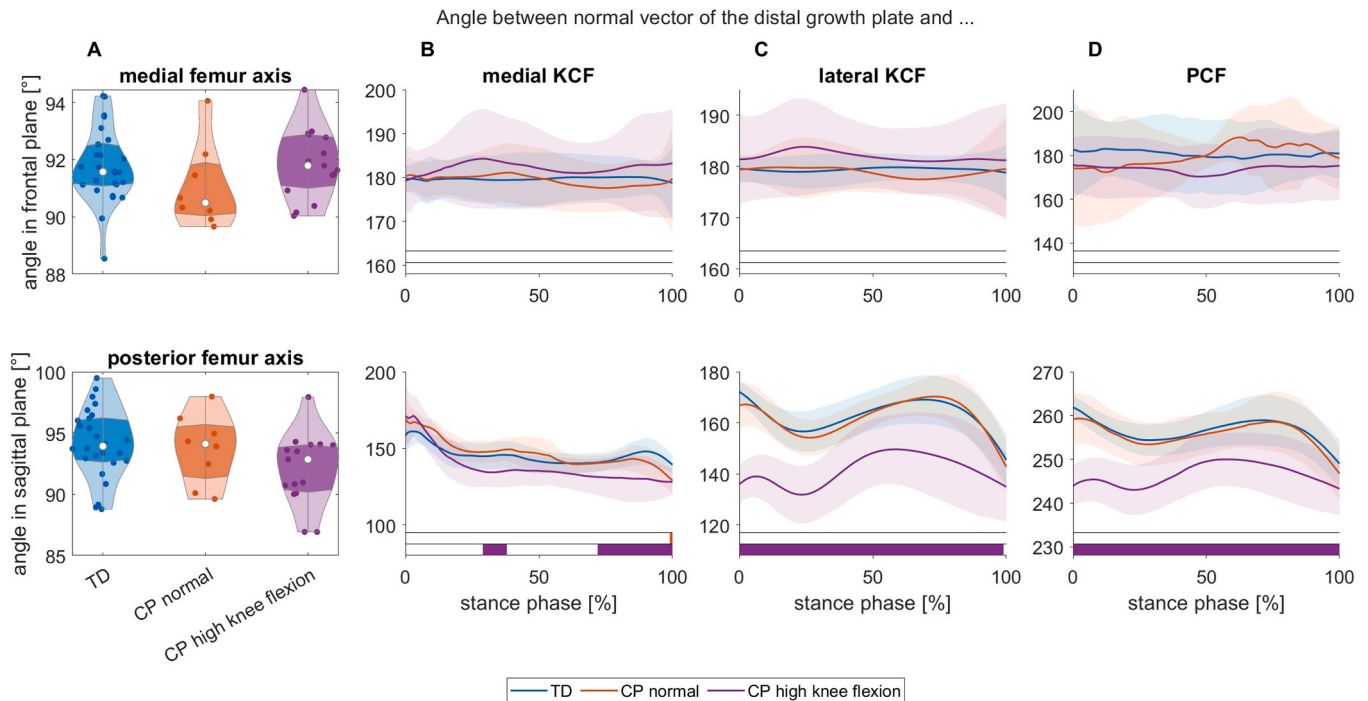


Fig. 4. A) Violinplots reveal the orientation of the distal growth plate in frontal and sagittal plane of the femur's coordinate system. B-D) Mean angle and standard deviation (shaded) between the normal vector of the distal growth plate and the medial (B) and lateral knee joint contact forces (KCF) (C) and patellofemoral joint contact force (PCF) (D) during the stance phase in the frontal and sagittal plane. Significant differences between TD and CP groups identified with SPM are visualized by corresponding colored bars (orange = "TD vs CP_{normal}"; violet = "TD vs CP_{high_knee_flexion}") below each plot. A schematic illustration on how the angles are expressed can be found in Fig. 1A.

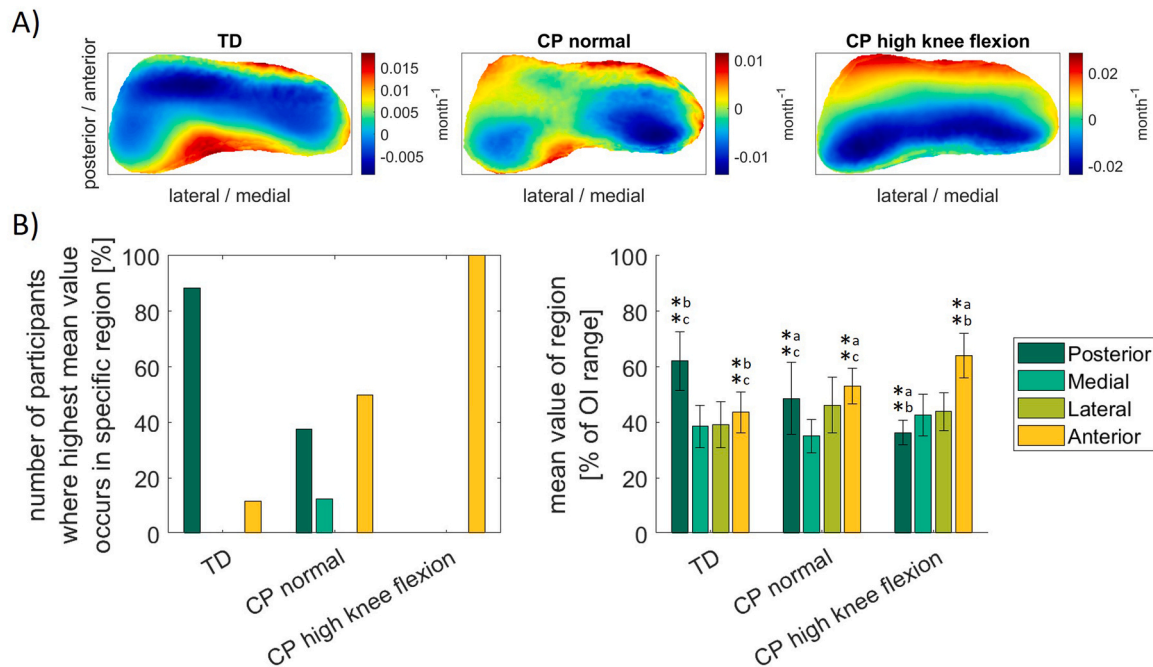


Fig. 5. A) Average distal growth plate shape and OI distribution in TD children, CP limbs with normal knee flexion and CP limbs with high knee flexion during stance phase. The OI distribution is represented using a blue to red color scheme representing low to high values, respectively. The unit is month⁻¹. B) The left plot shows how often the highest mean value was observed in a specific region. In the right plot the colored bars represent the mean value of each region normalized to the range of the individual OI. Vertical error bars indicate the standard deviation between limbs within groups. Significant differences were quantified with a two-way ANOVA with factors "region" and "group" where (*a) indicates significant differences to TD group, (*b) indicates significant differences to CP_{normal} group and (*c) indicates significant differences to the CP_{high_knee_flexion} group.

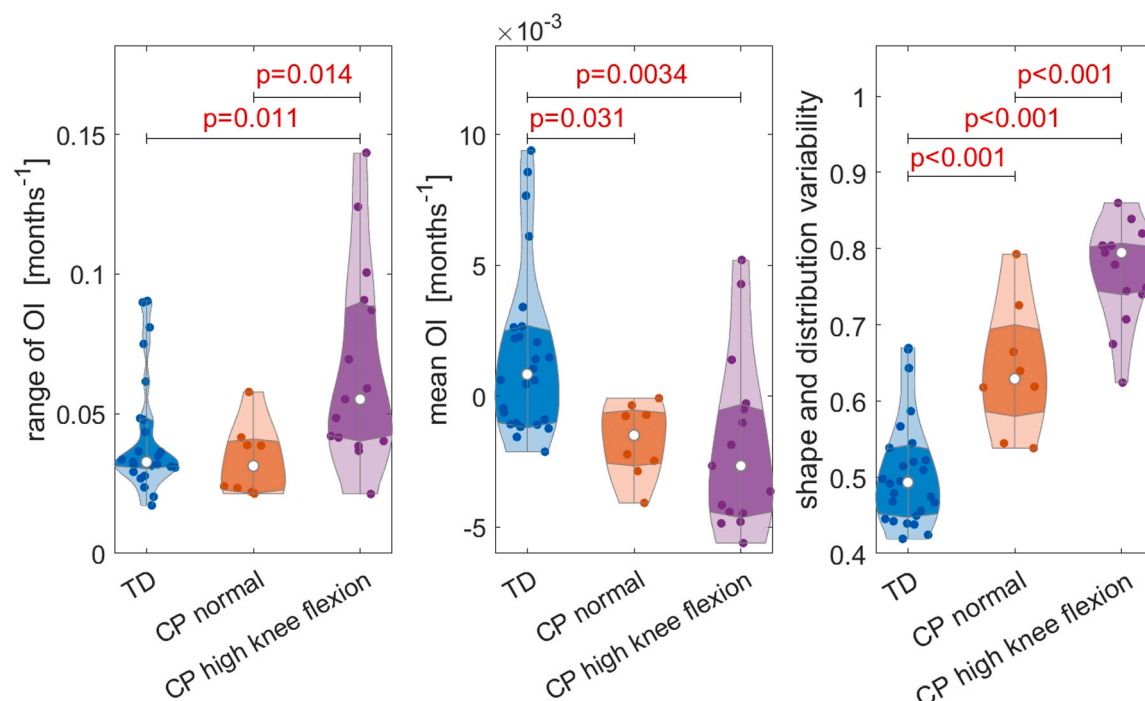


Fig. 6. Comparison of the variability of the magnitude of OI, i.e. range and mean value, and the variability assessed with template matching of the heatmaps. Each OI was compared to all OIs of the TD participants. Higher variability values indicate a higher difference in shape and distribution, a value of 0 indicates equality. Significant differences were quantified with ANOVAs with post-hoc Bonferroni correction for pairwise comparisons.

distal femoral growth plate is similar between TD and CP participants, but mechanical stress distribution differ between groups due to subject-specific gait patterns, muscle and joint contact forces.

As assumed, the growth plate orientation relative to the femoral coordinate system was similar in all groups. Additionally, or potentially consequently, the orientation of joint contact forces in respect to the growth plate was different in the CP_{high_knee_flexion} group compared to the other groups. The more anteriorly orientated medial and lateral KCF promoted shear stresses while the more superiorly orientated PCF promoted compressive stresses within the growth plate in this group. This in combination with higher magnitudes of joint contact forces caused a higher range of OI values in the CP_{high_knee_flexion} group, which could be interpreted as unevenly distributed growth.

CP limbs with typical knee flexion kinematics showed similar OIs within the distal growth plate as the TD group in terms of OI magnitude but a higher variability was revealed from image comparison of the OI heatmaps. These participants' kinematics showed a higher variability in frontal plane knee angle during the stance phase which could explain this finding. This means, CP participants with typical knee flexion kinematics during stance phase are likely to develop normal distal bone growth but the role of frontal plane knee kinematics should be further investigated as it might lead to different growth within medial and lateral regions of the distal growth plate. In this study, no significant differences regarding mean OI values in the medial and lateral regions, which could lead to potential varus/valgus malalignment, were found between groups.

Considering that high OI values indicate regions where bone growth and ossification is likely to occur, promoted growth in the anterior region compared to the posterior region would tilt the distal part of the femur posteriorly and, over a longer period, lead to higher anterior bending of the femoral shaft in the sagittal plane. This could potentially be a compensatory mechanism to normalize the angle between joint contact forces and the growth plate in the sagittal plane. In our participants, we found significantly higher femoral anterior bending in the sagittal plane in the CP_{high_knee_flexion} compared to other groups which could be a result of progressive promoted growth in the anterior

compartment. Patients with high anterior bend in the distal part of the femoral shaft, are not able to extend their leg completely as this would require a hyperextension at the knee. Hence, it cannot be said whether the knee flexion angle or the pre-existing high anterior bend is the cause, but our results indicate that both pathological patterns promote each other. To the best of the authors' knowledge, this is the first study to present OI values of the distal femoral growth plate, therefore, direct comparison to previous studies was not possible. Huckle et al. (2023) recently analyzed stresses within the distal femoral growth plate in three people with a pathological lower limb valgus alignment but did not use the OI for the presentation of their results. We provided the mean stress distribution of our groups in the same way as Huckle et al. [26] presented their results in the [Supplementary material \(Fig. S4\)](#). Differences in the estimated stresses in our study and Huckle et al. [26] are likely due to the different study cohort (healthy and CP participants versus children with pathological valgus alignment). We chose to analyze the OI since it is an established growth parameter, which has been used in several previous femoral growth studies and revealed physiological plausible results [17, 19,20]. OI distribution of the proximal growth plate of this cohort is presented in the [Supplementary material](#). Furthermore, our simulations are in agreement with the observed increased curvature of the femur in the CP_{high_knee_flexion} group compared to the other groups, as explained above.

It needs to be mentioned that, in addition to the high knee flexion angle during the stance phase, the CP_{high_knee_flexion} group showed less external hip rotation and significantly higher internal rotation of the subtalar joint (Fig. S1). However, the increased knee flexion angle significantly altered the magnitude and orientation of KCFs as well as PCFs and therefore is likely to have a much bigger impact on growth plate stresses than the differences in transverse plane kinematics.

Age and sex are key factors for growth plate thickness which is relatable to potential remaining growth. The aim of this study was to enhance our understanding of the relationship between gait pattern, loading, growth plate geometry and orientation, and induced stresses. As we did not predict the bone growth but evaluated the stresses at a single time point, the thickness of the growth plate is not of importance

in our simulations. Therefore, one participant with closed epiphyseal plates was included in the study cohort to increase our sample size. In all participants, the geometry and orientation of the growth plate was clearly visible in the MRIs, even in the participant where the epiphyseal plate was already closed.

Our study included some limitations common for MSK simulations, i.e. generic muscle properties and motor control [51,52], and FE simulations, i.e. number of components included and material properties. Furthermore, we personalized tibia torsion only in a subset of our participants [53]. Each of these limitations and its possible effect on the results of this study is addressed in detail in the [Supplementary material](#).

To conclude, this is the first study which evaluated stresses within the distal growth plate in a large cohort including different walking styles with subject-specific MSK models and bony geometry. Significant differences in OI were observed between TD participants and participants with CP. Our findings revealed that the knee flexion angle during the stance phase has a big impact on growth plate stresses at the distal femur. The simulation results of this study can serve as a reference dataset for future investigations. We would like to encourage peers to use the freely available GP-Tool (<https://github.com/WilliKoller/GP-Tool>) and conduct similar studies with large sample sizes to improve our general understanding of typical and pathological femoral bone growth with the ultimate goal to support and improve clinical decision making. If pathological femoral bone growth can be predicted at an early stage, subject-specific therapies like physiotherapy, orthosis or real-time biofeedback training could be used to alter joint loads [54–56] and therefore normalize growth plate stresses in the future.

Conflict of interest statement

The authors declare no conflict of interest.

Ethics approval was obtained from the local ethics committees (University of Vienna, reference no. 00578).

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CRedit authorship contribution statement

Arnold Baca: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Hans Kainz:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization. **Willi Koller:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jana Holder:** Writing – review & editing, Methodology. **Elias Wallnöfer:** Writing – review & editing, Visualization, Methodology. **Gabriel Mindler:** Writing – review & editing, Methodology. **Andreas Kranzl:** Writing – review & editing, Methodology, Data curation.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We, further, confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

Data Availability Statement

The code of the developed toolbox as well as an executable file is made freely available through a GitHub repository (<https://github.com/WilliKoller/GP-Tool>) including example data to perform the multi-scale workflow.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.gaitpost.2024.06.012](https://doi.org/10.1016/j.gaitpost.2024.06.012).

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2.5. Femoral bone growth predictions based on personalized multi-scale simulations: Validation and sensitivity analysis of a mechanobiological model

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Femoral bone growth predictions based on personalized multi-scale simulations: Validation and sensitivity analysis of a mechanobiological model

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Abstract

Musculoskeletal function is pivotal to long-term health. However, various patient groups develop torsional deformities, leading to clinical, functional problems. Understanding the interplay between movement pattern, bone loading and growth is crucial for improving the functional mobility of these patients and preserving long-term health.

Multi-scale simulations in combination with a mechanobiological bone growth model have been used to estimate bone loads and predict femoral growth trends based on cross-sectional data. The lack of longitudinal data in previous studies hindered refinements of the mechanobiological model and validation of subject-specific growth predictions, thereby limiting clinical applications.

This study aimed to validate the growth predictions using magnetic resonance images and motion capture data – collected longitudinally – from ten growing children. Additionally, a sensitivity analysis was conducted to refine model parameters.

A linear regression model based on physical activity information, anthropometric data, and predictions from the refined mechanobiological model explained 70% of femoral anteversion development. Notably, the direction of femoral development was accurately predicted in 18 out of 20 femurs, suggesting that growth predictions could help to revolutionize treatment strategies for torsional deformities.

Keywords: femoral bone growth, finite element analysis, mechanobiological model validation, musculoskeletal modelling, semi-automated growth predictions.

Statements and Declarations

The authors have no relevant financial or non-financial interests to disclose.

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1. Introduction

Bony deformities, particularly at the femur, are commonly observed in children with and without neurological disorders. Femoral deformities are often torsional, characterized by a misalignment of the femoral neck with the knee axis in the transverse plane. This torsion is quantified by the anteversion angle (AVA). In typically developing children, the AVA decreases during skeletal growth from approximately 40° to 20° ([Bobroff et al., 1999](#); [Fabry et al., 1973](#)). Therefore, normative values vary with age and the distinction between healthy and pathological development is challenging. An increased, but also a decreased AVA can lead to gait abnormalities (e.g., increased internal hip rotation, in-toeing foot progression angle) and subsequently altered joint loading, as well as further progressive problems such as pain and osteoarthritis ([Andriacchi et al., 2004](#); [Bruderer-Hofstetter et al., 2015](#); [Hudson, 2016](#); [Sharma, 2001](#); [Wheatley et al., 2023](#)). While the state-of-the-art clinical intervention to correct an

existing pathological AVA is a de-rotation osteotomy (Buly et al., 2018; Dreher et al., 2012), proactive non-invasive intervention strategies might be possible if pathological AVA development could be identified before its occurrence. This would allow the development of innovative intervention strategies such as gait-retraining (Kainz et al., 2024b; Uhlrich et al., 2022) to normalize bone loading in a non-invasive way and ensure typical bone growth.

With the introduction of Wolff's law in the 19th century, it has long been understood that bone growth is influenced by mechanical loads (Wolff, 1892). The Utah paradigm of bone physiology refined Wolff's law, recognizing that biological factors determine skeletal health and growth, but mechanical loads influence these factors and are crucial for bone growth (Frost, 2001). Shear and compressive stresses within biological tissues are key factors influencing the growth of tissues such as bone and cartilage (Carter and Beaupré, 2000; Carter and Wong, 1988; Pauwels, 1980). While many simulation studies investigating bone growth patterns focused on predicting trabecular remodelling at the micro-scale, few studies simulated bone growth on the macro-scale experienced during skeletal growth (Adachi et al., 2001; Buccino et al., 2022; Huiskes et al., 2000; Kainz et al., 2020; Yadav et al., 2021).

The shape of femur, in particular the AVA, affects the paths of muscles and therefore femoral loads (Kainz et al., 2023; Wheatley et al., 2023).

Furthermore, numerous studies have shown that the morphology of the lower limb bones can alter a person's walking pattern (Alexander et al., 2019; Bruderer-Hofstetter et al., 2015; Carriero et al., 2009; Hudson, 2016; Mindler et al., 2021). The walking pattern has a big impact on bone loads

(Carriero et al., 2014; Koller et al., 2023a), which in turn directs further bone development (Carter et al., 1996; Carter and Beaupré, 2000; Carter and Wong, 1988; Wolff, 1892). This illustrates the intricate interdependence between an individual's musculoskeletal morphology, gait pattern, mechanical loading on biological structures, and tissue growth (Figure 1).

Multi-scale simulations in combination with a mechanobiological bone growth model have been used to estimate bone loads and predict femoral growth trends based on cross-sectional data (Carriero et al., 2011; Kainz et al., 2020; Koller et al., 2024, 2023b; Shefelbine and Carter, 2004; Yadav et al., 2021, 2017, 2016). Within this workflow, the loadings on the participant's femur during walking are derived from musculoskeletal (MSK) simulations based on subject-specific models and 3D gait analysis data. Subsequently, the muscle and joint contact forces from the musculoskeletal simulations are applied to a finite element (FE) model of the femur created from magnetic resonance images (MRIs) to estimate the stresses within the growth plate. Based on these stresses, a growth rate and growth direction are calculated for each element within the growth plate. Finally, growth of the femur is simulated in a second FE analysis and the development of certain angles (e.g. change in AVA) can be quantified by comparing the final with the baseline geometry (Figure 2). Previous studies using this workflow to calculate growth plate stresses and predict femoral growth revealed plausible growth patterns for healthy and pathological populations (Carriero et al., 2011; Kainz et al., 2020; Koller et al., 2024, 2023b; Shefelbine and Carter, 2004; Yadav et al., 2021, 2017, 2016). However, this workflow includes many model parameters that are

based on assumptions. The lack of longitudinal data in previous studies

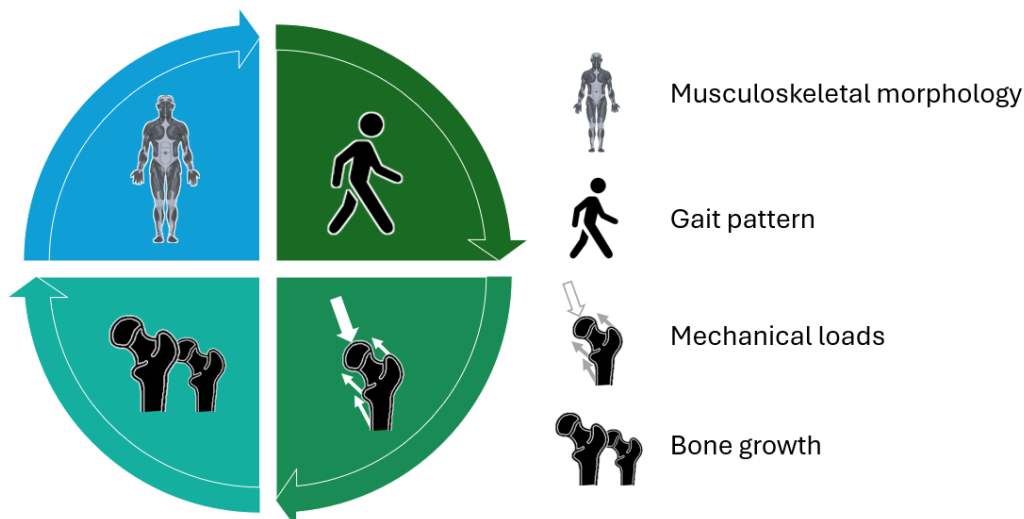


Figure 1: Schematic illustration of complex interplay between skeletal morphology, gait pattern, mechanical loading on bones and bone growth

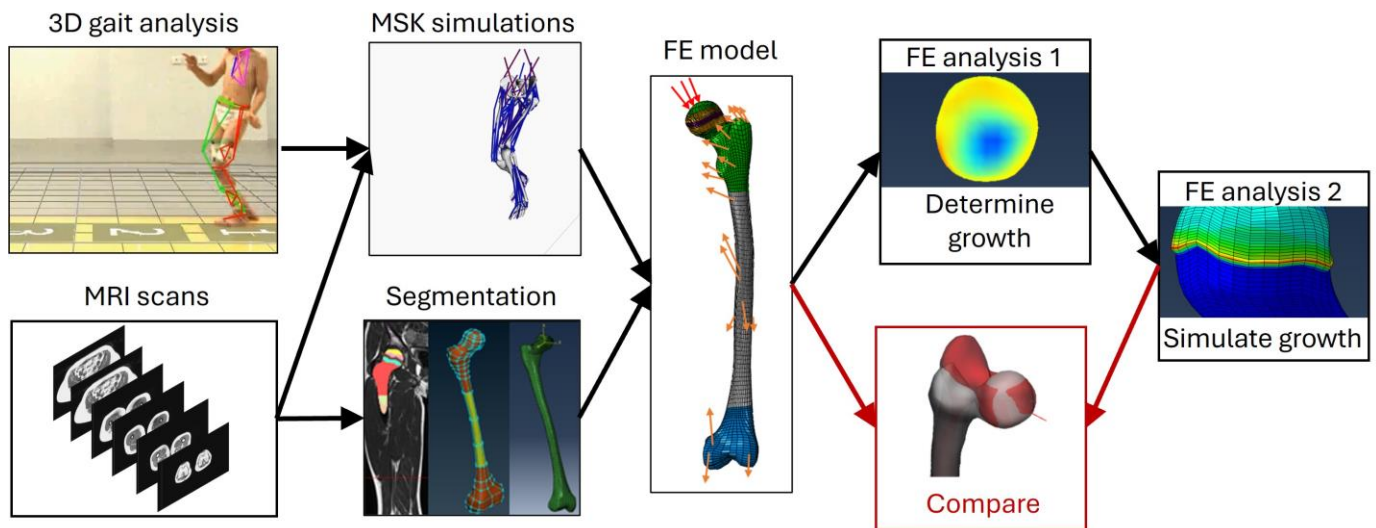


Figure 2: Schematic illustration of the mechanobiological multi-scale workflow to predict femoral bone growth. MSK = musculoskeletal, FE = finite element, MRI = magnetic resonance image.

hindered refinements of the mechanobiological model and validation of subject-specific growth predictions, thereby limiting clinical applications. The aim of this study was to close this research gap by collecting a unique longitudinal dataset, comprising 3D gait analysis data and MRIs at two time points, to experimentally investigate the subject-specific growth predictions. Furthermore, a sensitivity analysis was conducted to refine the model parameters. Multi-scale simulations were performed with two approaches to solve the muscle redundancy problem when estimating muscle forces, various parameter combinations to calculate the growth rate based on the stresses within the growth plate, and three different methods to model the growth direction. Our results demonstrate the feasibility of the refined mechanobiological model to predict femoral growth trends and show that it outperforms predictions based solely on anthropometric and physical activity data.

2. Methods

2.1. Data collection

Three-dimensional gait analysis data including marker trajectories, ground reaction forces and electromyography (EMG) of selected lower limb muscles as well as MRIs of the femurs of ten healthy children were collected on two occasions approximately two years apart (Table 1). Marker trajectories were collected with 200 Hz using a 12-camera motion capture system (Vicon Motion

Systems, Oxford, UK). The used marker set was based on the Plug-in Gait marker set (Kadaba et al., 1990) with additional clusters of three markers on each thigh and shank segment and an additional marker at the 5th metatarsal head of each foot. Ground reaction forces were simultaneously recorded with 2000 Hz with multiple force plates (Kistler, Winterthur, Switzerland). At the same time, EMG was collected with 2000 Hz of 7 lower limb muscles on each leg (tibialis anterior, gastrocnemius medialis, soleus, peroneus longus, vastus lateralis, biceps femoris, gluteus medius) with wireless surface electrodes (Cometa srl, Milan, Italy). Participants were asked to walk with a self-selected walking speed and several gait trials were recorded.

MRIs of each femur were collected using a 3T magnetic resonance scanner (MAGNETOM Vida, Siemens, Berlin/Munich, Germany) with a T1 viba sequence with voxel sizes between 0.8x0.8x0.7mm and 1.1x1.1x1.1mm.

Between both sessions, participants were asked to carry an activity monitoring device (Realalt 3DTrisport, London, UK) during a period of seven consecutive days to estimate their daily step count. At the second data collection session (S2), participants were requested to fill out a questionnaire about their sport and spare time activities to gain further information about their activity level. Ethics approval was obtained from the corresponding local ethics committee (University of Vienna, reference number 00578).

Table 1: Participant characteristics at first and second data collection session and the changes between session given as mean $\pm$ standard deviation and the range in brackets. BMI=Body mass index, AVA=Anteversion angle, NSA=Neck-Shaft-Angle.

	First session	Second session	Δ between sessions
Age [years]	9.9 $\pm$ 0.9 (8.4 – 11.3)	11.9 $\pm$ 0.8 (10.3 – 13)	2.0 $\pm$ 0.1 (1.8 – 2.1)
Height [cm]	143.3 $\pm$ 7.3 (130 – 154)	156.8 $\pm$ 8.7 (142 – 168)	13.5 $\pm$ 3.3 (9 - 20)
Weight [cm]	35.1 $\pm$ 7.4 (29 – 50.4)	43.3 $\pm$ 9.1 (34.2 – 62.3)	8.2 $\pm$ 3.3 (4.9 – 13)
BMI	17 $\pm$ 2.7 (14 – 22.4)	17.6 $\pm$ 3.1 (14.8 – 23.2)	0.6 $\pm$ 0.9 (-0.8 – 2.1)
AVA [°]	34.7 $\pm$ 8.9 (16.4 – 49.3)	33.4 $\pm$ 9.5 (14.8 – 48)	-1.3 $\pm$ 5.8 (-13.1 – 11.8)
NSA [°]	127 $\pm$ 4.2 (120.5 – 134.6)	130.3 $\pm$ 3.5 (125.8 – 138)	3.3 $\pm$ 3.4 (-5.1 – 8.9)

2.2. MRI measurements and segmentation of femurs

The femoral AVA in the plane perpendicular to the shaft axis and the neck-shaft-angle (NSA) were calculated based on six anatomical points of each femur defining the neck, shaft and knee axis selected in an oblique slice passing the femoral neck and in transverse slices ([Sangeux et al., 2015](#)) for both sessions. Due to uncertainties in this very common measurement methods ([Kaiser et al., 2016](#); [Sangeux et al., 2015](#)) and to increase our confidence in the obtained AVA, the measurements were initially performed by one researcher with four years of experience in bone segmentation and anatomical feature quantification. The selected points were reviewed following the two-person verification principle by the initial researcher and a second researcher with one year of experience in bone segmentation and anatomical feature quantification. In case of disagreement, points were repositioned with consent of both researchers. The second measurement was used for further analysis and the maximum difference of the change of AVA between the two measurements was used as a measurement uncertainty (Supplementary material, Figure S1). A total of 100 imputations of the measured development of AVA were created by adding a random value within this measurement uncertainty range leading to an evenly spaced distribution. These imputations were used for subsequent analysis. Furthermore, the intercondylar distance, i.e. distance between the medial and lateral condyles of the femur, the location of the hip and knee joint centers were quantified and selected from the MRIs of the first data collection session (S1). These measurements were subsequently used to personalize

musculoskeletal models which were used to estimate the loading on the femurs.

Each femur was segmented using 3D Slicer 5.2.2 ([Fedorov et al., 2012](#)) and divided into six parts – the proximal and distal trabecular bone, the proximal and distal growth plate, the cortical bone of the shaft and the bone marrow – similar to previous studies ([Carriero et al., 2011](#); [Kainz et al., 2020](#); [Koller et al., 2023b, 2024](#); [Yadav et al., 2016](#)). The GP-Tool ([Koller et al., 2023b](#)) was used to identify bony landmarks ([Modenese and Renault, 2021](#)), transform the femur into the OpenSim coordinate system and create a hexahedral mesh with elements aligned with the growth plate in ten separate layers. Element size was set to 1.5 mm and 3 layers were defined as transition zones between trabecular bone and the growth plate. Linear elastic materials were assigned to the different parts of the femur with Young's modulus and Poisson's ratio equal to previous studies ([Koller et al., 2024, 2023b](#)).

2.3. Quantification of loading on bones

MSK simulations based on subject-specific MRI-informed models were performed with OpenSim ([Delp et al., 2007](#)). A modified Rajagopal model ([Rajagopal et al., 2016](#)) which included the more complex knee joint of the Lerner model ([Lerner et al., 2015](#)) was used as a base model ([Kaneda et al., 2023](#)). This model includes three rotational degrees of freedom at the hip and two rotational degrees of freedom at the knee and ankle joints. The metatarsophalangeal joint was locked. The TorsionTool ([Kainz et al., 2024b](#); [Veerkamp et al., 2021](#)) was used to modify the femoral geometry to match each child's NSA and AVA. These modifications alter attachment and via points of

muscles acting on or passing the femur and therefore also the lever arms of muscles across joints. To fit the models to the participants' anthropometry, the pelvis and femur segments were scaled using the hip and knee joint measurements obtained from the MRIs. Other segments of the model were scaled using the location of surface markers ([Kainz et al., 2017](#)).

Inverse kinematics were used to calculate joint angles of corresponding gait trials for each participant. Markers on the knee and ankle were neglected during inverse kinematics, instead clusters of three markers were used to track the motion of the thigh and shank segments. All markers were weighted equally. Maximum marker errors and root-mean-square errors were accepted if less than 4 cm and 2 cm, respectively, as suggested by OpenSim's best practice recommendations ([Hicks et al., 2015](#)).

Since altering muscle attachment and via points on the femur can cause irregularities in muscle moment arms, the moment arms of all muscles acting on and spanning the femur were checked for smoothness during the motions derived from inverse kinematics. Discontinuities were observed for the anterior compartment of the musculus gluteus maximus (glmax1) in some participants and were corrected by stepwise reduction of the diameter of corresponding WrapObjects and visual inspection to ensure valid muscle paths. Subsequently, the MuscleParamOptimizer ([Modenese et al., 2016](#)) was used to map the muscle characteristics from the generic model to the personalized models. Furthermore, an actuator with an optimal force of 100 N was used to represent ligaments that passively generate the knee adduction moment.

Two approaches were used to solve the muscle redundancy problem: 1) Static optimization (SO) which minimized the sum of squared muscle activations and 2) an EMG-informed approach which minimized effort and tracking errors between EMG signals and muscle excitation patterns with OpenSim Moco ([Dembia et al., 2020](#)) with weights of 1 and 5, respectively. Subsequently, contact forces acting on the hip and knee joints were estimated ([Steele et al., 2012](#)). Additional analyses were performed to identify muscle attachments on the femur and obtain the effective directions of muscle forces ([van Arkel et al., 2013](#)). For each femur, the mean waveform of the resultant hip joint contact force (HJCF) from all trials was calculated and the trial with the lowest

root mean square difference to the mean waveform was selected as a representative step and chosen for further analysis.

2.4. Finite element simulations

The GP-Tool ([Koller et al., 2023b](#)) was used to create a subject-specific FE model based on the participant's femoral geometry (overall femoral shape, location and orientation of growth plate) and loading condition. Similar to previous studies ([Kainz et al., 2020](#); [Koller et al., 2023b](#); [Yadav et al., 2016](#)) nine load instances were selected based on the HJCF peaks and the valley in-between during the stance phase. The muscle and joint forces at these nine load instances were used as loading conditions for FE simulations. The HJCF was applied as nodal forces distributed to the closest 100 surface nodes (approximately 2.25 cm²) in the direction of the corresponding force orientation. Muscle forces were applied as nodal forces at the identified locations and directions. The nodes of the femoral epicondyles were constrained in all directions as boundary conditions. FEBio ([Maas et al., 2017, 2012](#)) was used to estimate stresses within the growth plate for these loading conditions.

Based on a weighted linear combination of shear and hydrostatic stresses, a value representing the growth rate due to mechanical stimuli named *osteogenic index (OI)* ([Stevens et al., 1999](#)) was calculated for each element within the proximal growth plate. Subsequently, a second FE analysis was conducted to simulate growth of elements taking the element's growth rate and the direction of growth into account using Abaqus' (Dassault Systèmes Simulia Corp, Rhode Island, USA) orthotropic thermal expansion ([Kainz et al., 2020](#); [Yadav et al., 2016](#)). Three different approaches to model growth directions have been proposed in the literature ([Carriero et al., 2011](#); [Hunziker, 1994](#); [Yadav et al., 2016](#)). A figure visualizing the three different growth direction methods is included in the supplementary material.

- a) Femoral Neck Deflection Direction (FNDD): A uniform growth direction was calculated based on the average neck deflection direction during loading. It was calculated as the mean vector between a node at the neck base and the femoral head center during the nine load instances. This growth direction was applied to all elements in the second FE analysis.

- b) Principal Stress Direction (PSD): For each element, the growth direction was defined as the direction of the highest principal stress. Therefore, each element had a unique growth direction vector.
- c) Normal to growth plate orientation (NORM): A uniform growth direction was calculated as the normal vector to the main orientation of the growth plate obtained using a principal component analysis. This growth direction was applied to all elements in the second FE analysis.

The AVA was identified by calculating the angle in transverse plane between the neck axis (i.e. vector between nodes representing the femoral neck base and the femoral head center) and the knee axis (i.e. vector between nodes representing the epicondyles). Doing so with the same nodes in the model before and after growth allows to quantify

the predicted development of AVA by the mechanobiological multi-scale workflow. A visual overview of both finite element analysis and the quantification of AVA is shown in Figure 3.

2.5. Sensitivity analysis

As the result of the mechanobiological simulation workflow depend on various parameters, a sensitivity analysis was performed to evaluate their influence. In total, 330 multi-scale simulations were performed for each femur and for each of those, the predicted development of AVA was evaluated.

Firstly, two loading conditions (SO and EMG-informed) were derived from MSK simulations for each femur and used to identify shear and hydrostatic stresses within the proximal femoral growth plate.

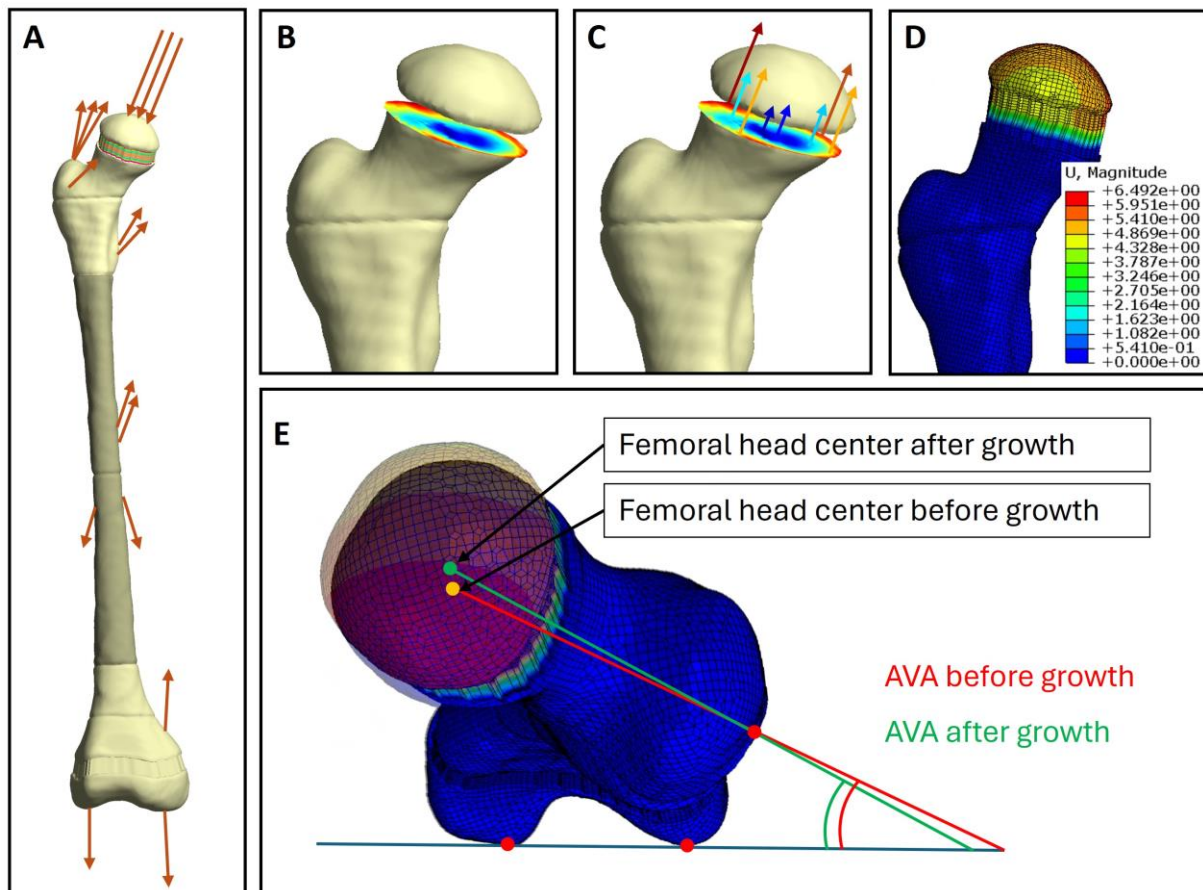


Figure 3: Visual description of the methodology to model growth and quantify the change of anteversion angle (AVA). Subfigure A shows the finite element analysis with muscle and hip joint contact forces applied to the femur. Subfigure B represents the calculation of the growth rate for each element within the growth plate based on the mechanical shear and compressive stresses and several influencing factors discussed in section 2.5. Subfigure C shows a simplified representation of the growth rate applied through orthotropic thermal expansion. The direction in which growth is modeled can vary depending on the chosen methodology (FNDD, PSD, NORM). In subfigure D the displacement due to modeled growth is visualized. Subfigure E shows the baseline and the grown model overlayed from a top view. The location of femoral head center is moved while other nodes stay at the same location. The change of AVA is calculated as the difference between the AVA before and after growth.

Secondly, with those stresses the growth rate was calculated for each element i within the growth plate using different parameter variations. In general, the growth rate includes a weighted linear combination of shear (σ_S) and hydrostatic (σ_H) stresses representing the OI (i.e. growth due to mechanical stimuli) (Equation 1) and a value representing the biological growth $growth_{bio}$ (Equation 2). The ratio of weighting factors a to b for shear and hydrostatic stresses was varied (0.02, 0.1, 1/7, 0.25, 0.5, 1, 2, 4, 7, 10, 50). Additionally, we introduced parameter sets where negative growth rates were avoided or where the growth rate was normalized to a specified range to account for differences in the magnitude of the OI. For each of the eleven ratios, the following growth simulations were performed:

- d) Including biological growth where the amount was twice the maximum mechanical growth as in previous studies, i.e. Equation 2 with $growth_{bio} = 2 * max(OI)$
- e) Neglecting biological growth, i.e. Equation 2 with $growth_{bio} = 0$
- f) Neglecting biological growth but avoiding negative growth, i.e. Equation 3
- g) Neglecting biological growth but normalizing growth rate, i.e. Equation 4
- h) Including biological growth and normalizing growth rate, i.e. a) and Equation 4

This resulted in 55 unique parameter combinations which led to different growth rates depending on the shear and hydrostatic stresses at the growth plate. Combining each of these 55 parameter variations with each of the loading conditions (SO and EMG-informed) resulted in 110 simulations.

$$growthrate_{mechanical}(OI_i) = a * \sigma_{S_i} + b * \sigma_{H_i} \quad \text{Equation 1}$$

$$growthrate_i = (growthrate_{mechanical} + growthrate_{bio}) \quad \text{Equation 2}$$

$$growthrate_{non_negative_i} = (growthrate_i + \min(growthrate_i)) \quad \text{Equation 3}$$

$$growthrate_{normalized_i} = \frac{growthrate_i + \min(growthrate_i)}{\max(growthrate_i) - \min(growthrate_i)} \quad \text{Equation 4}$$

Thirdly, three approaches how the growth direction can be modeled are proposed in literature. Therefore, we decided to run each of the so far 110 simulations with each growth direction method

(FNDD, PSD, NORM), which resulted in abovementioned 330 simulations for each femur.

2.6. Data analysis

HJCF magnitude and orientation as well as the sum of all muscle forces acting on the femur during the stance phase were compared between the SO and EMG-informed approach using paired t-tests with Statistical Parametric Mapping ([Pataky et al., 2013](#)).

To account for inaccuracies in AVA measurements, 100 imputations of the measured development of AVA were created by adding a random value within the measurement uncertainty range identified as the maximum difference between measurements, i.e. $\pm 3.58^\circ$. This resulted in an evenly spaced distribution. A stepwise multiple linear regression using a backward elimination procedure for statistically non-significant predictors ($p > 0.05$) was performed using AVA and NSA from S1, age (at S1 & change between S1 and S2), weight (at S1 & change between S1 and S2), height (at S1 & change between S1 and S2), steps per day and hours of sport per week as predictors and the measured development of AVA as independent variable. All predictors were normalized to their z-scores. The linear regression model was calculated for all 100 imputations (same predictors, randomly imputed independent variable) and the mean of all adjusted R^2 values was used for further evaluations. The regression model without the multi-scale predictions of AVA development was used as a baseline measure (i.e. *baseline model*).

Furthermore, for each of the 330 growth simulations, the same stepwise multiple linear regression was performed with the multi-scale prediction of the development of AVA as an additional predictor to identify the models' power to explain the development of AVA (i.e. *explaining model*). Again, these regression models were calculated for all 100 imputations. Subsequently, linear regression models which did not include the multi-scale prediction as a predictor or where this predictor was associated with a negative slope were excluded for further analysis. The linear regression models were ranked depending on their adjusted R^2 across imputations and the best performing models were analyzed in more detail regarding their similarities and differences within the various parameters of the workflow.

Additionally, the same procedure was performed to identify the models' power to predict the

development of AVA (i.e. *predicting model*), solely by the data from S1, steps per day, hours of sport per week and the multi-scale prediction of the mechanobiological model as this would be data that could be used for clinical decision-making.

2.7. Qualitative analysis of best explaining linear regression model and selected femurs

For the single best explaining model, the growth rates for each element in the growth plate were projected on the transverse plane according to the elements' locations and interpolated to a squared grid. A blue to red color scheme was used to visualize growth rates representing minimum to maximum values, respectively. This resulted in heatmaps of equal size for all growth plates revealing distribution of the growth rate and allowing to qualitatively identify differences between femurs experiencing different growth trends (i.e. decrease or increase of AVA). Additionally, the center of growth was calculated, similarly as one would calculate the center of mass of a disc where the growth rate represents the weight at a location.

3. Results

The ten children included in this study, aged 9.9 ± 0.9 years at the first data collection session, grew 13.5 ± 3.3 cm and gained 8.2 ± 3.3 kg of body mass during the two years. Participants' AVA was $34.7 \pm 8.9^\circ$ at the initial assessment and changed between -13.1° and $+11.8^\circ$ between data collection sessions (Table 1). The average daily step count was 9592 (range: 5671 – 15212) and participants reported to perform sports between 5 and 29 hours per week (mean 13.6 ± 7.8 hours).

3.1. Muscle and joint contact forces estimated with different approaches

The EMG-informed MSK simulations, where muscle activations of the model had to follow the shape of EMG-recorded muscle activations additionally to effort minimization, led to significant different ($p < 0.05$) muscle forces compared to the SO approach, which minimizes the sum of all muscle activations (Figure 4). The forces produced by musculus tensor fasciae latae, the hamstring muscles and the knee extensor muscles were significantly increased during the complete stance phase in the EMG-informed simulations

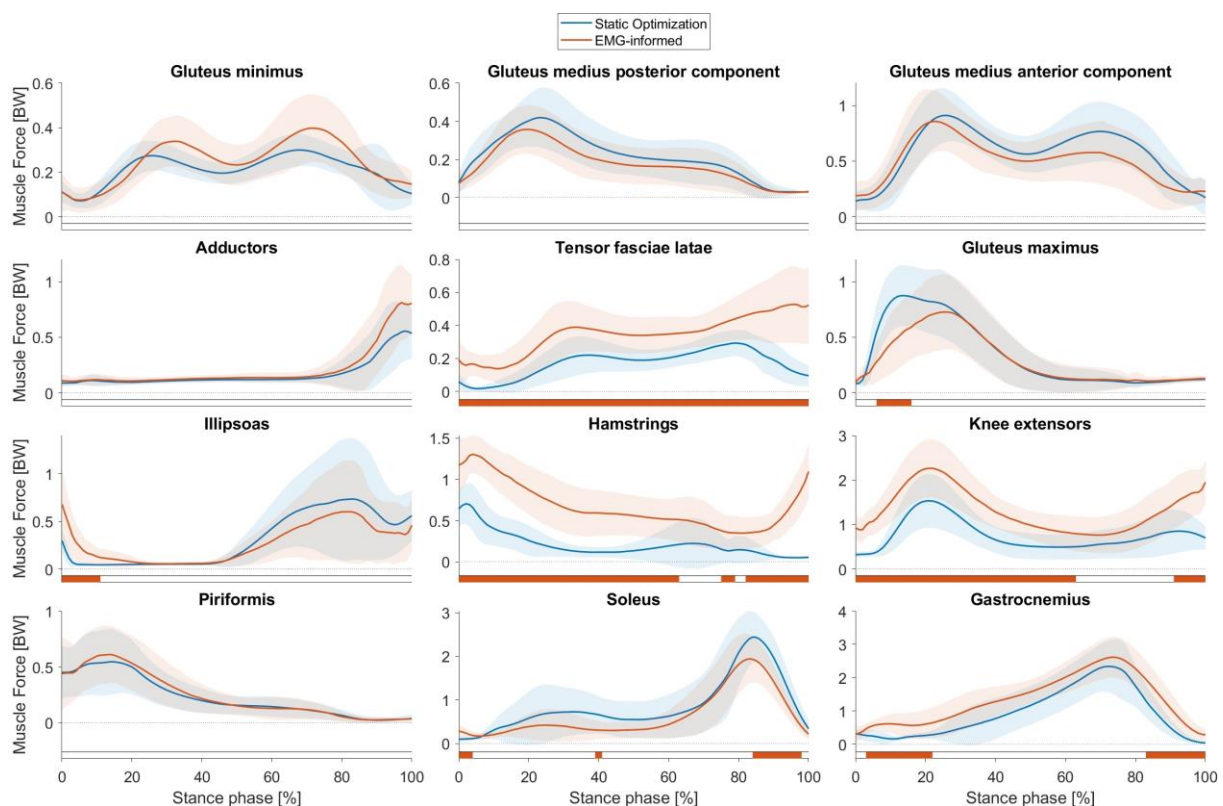


Figure 4: Muscle forces estimated by musculoskeletal simulations with two approaches to solve the muscle redundancy problem, i.e., static optimization (blue waveforms) and EMG-informed (red waveforms) approach. Significant differences ($p < 0.05$) between both approaches identified with Statistical Parametric Mapping are visualized by orange-colored bars beneath each subplot.

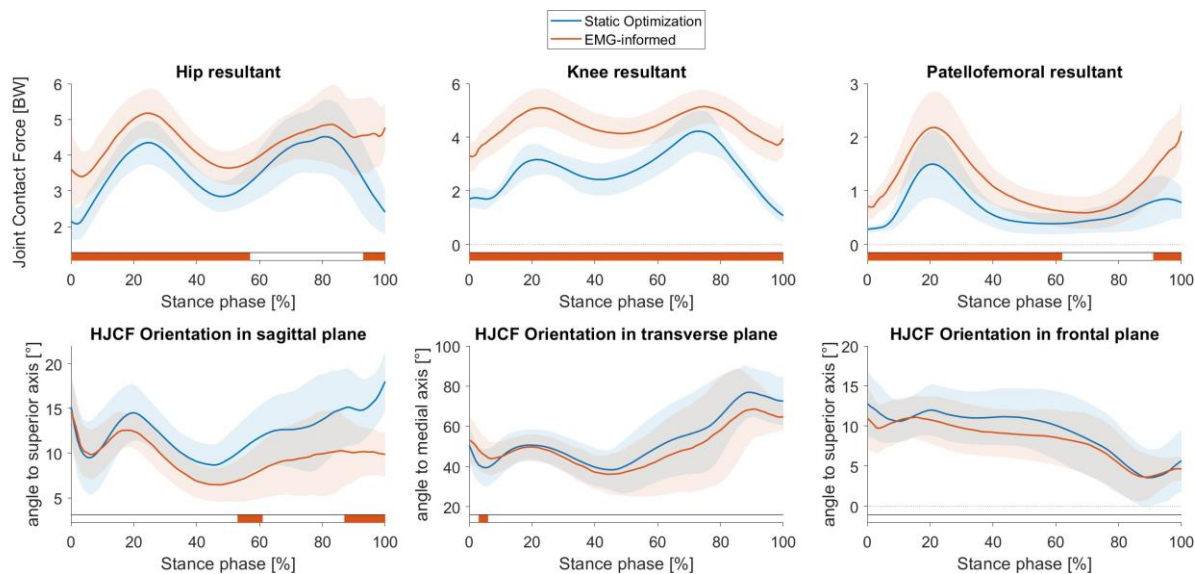


Figure 5: Joint contact forces and hip joint contact force (HJCF) orientation estimated by musculoskeletal simulations with two approaches to solve the muscle redundancy problem, i.e., static optimization (blue waveforms) and EMG-informed (red waveforms) approach. Significant differences ($p < 0.05$) between both approaches identified with Statistical Parametric Mapping are visualized by orange-colored bars beneath each subplot.

compared to SO simulations. The soleus produced significantly less force while the gastrocnemius forces were significantly increased in EMG-informed simulations compared to SO simulations. Unfortunately, the EMG data of one participant were not of sufficient quality and therefore all results involving EMG rely on data of 18 femurs. This participant's data was removed for performing statistical tests between SO and EMG-informed approaches.

The magnitude of hip, knee and patellofemoral joint contact forces were significantly higher in EMG-informed simulations compared to the simulations performed with SO (Figure 5). At the hip, mainly the vertical component was increased, whereas at the knee joint, all components are significantly higher. The orientation of the HJCF was only significantly different between both modelling approaches in small parts of the stance phase (Figure 5).

3.2. Sensitivity analysis with mechanobiological growth predictions

The *baseline* linear regression model, which did not include multi-scale predictions for AVA development, was highly significant ($p < 0.01$) and showed a moderate mean coefficient of determination ($R^2 = 0.46$) across the imputations. The AVA and the age at the first session, as well as change of weight between sessions were significant predictors with a negative slope. Average steps per

day and the change of height between sessions were significant predictors with a positive slope.

In 140 linear regression models, the predicted development of AVA from the mechanobiological multi-scale workflow was excluded as a significant predictor during the stepwise backward elimination procedure, therefore these models were equal to the *baseline* model. One linear regression model included the multi-scale prediction with a negative slope, meaning that the predicted and measured change of AVA was inversely correlated, and was therefore excluded from further analysis. This model's adjusted R^2 across imputations was 0.65, therefore, not within the 10 best explaining models. 189 analyses remained for further examination. The 10 best performing models, i.e. models with the highest adjusted R^2 across imputations ($R^2 > 0.685$), used muscle forces and HJCF estimated with SO as loading condition to calculate stresses within the growth plate. In all of those models, negative values as growth rate were allowed. Furthermore, seven of the 10 best performing models did not account for biological growth and in six, the growth rate was normalized to a specific range. Regarding the ratio of weighting factors a to b for shear and hydrostatic stresses, respectively, no clear trend was observed. In eight of the 10 best performing models, the NORM growth direction method, in which the direction of growth is modelled normal to the orientation of the growth plate, was used (Figure 6). A figure visualizing the distribution of the

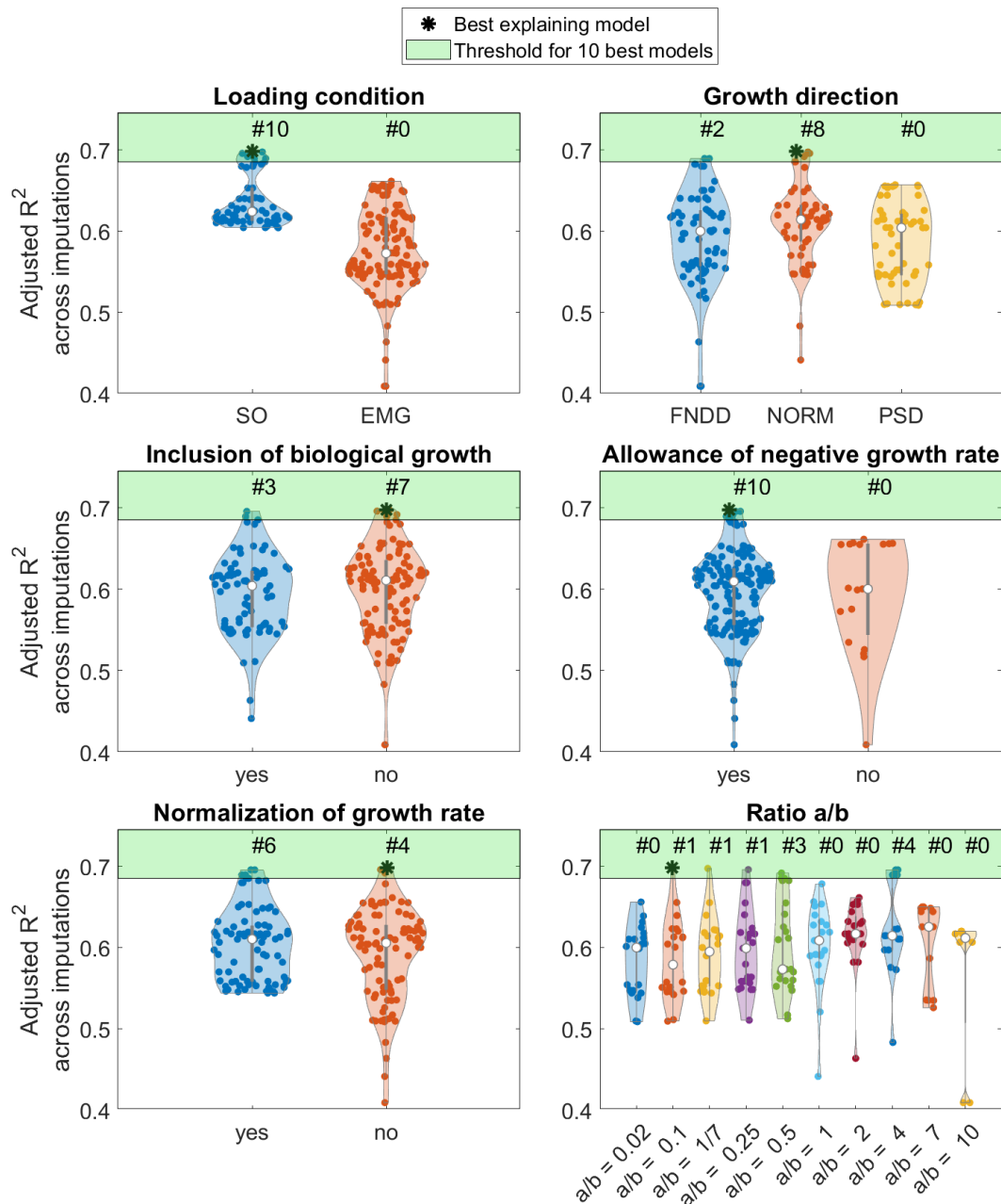


Figure 6: Adjusted R^2 of the linear regression models and parameters used for mechanobiological multi-scale simulations. The light green patch highlights the area above the threshold for the 10 best explaining models.

predicted AVA development from all 330 parameter sets is included the supplementary material.

3.3. Analysis of best explaining and predicting model

The model with best explanation power was a refinement of the *baseline* model with the multi-scale prediction and the NSA at the initial assessment as additional significant predictors with positive and negative slopes, respectively. The loading obtained from MSK simulations with SO were used as input to estimate the stresses within

the growth plate. Biological growth was not included, values were not normalized to a specified range and the growth rate values were allowed to be negative. The ratio of weighting factors a to b was 0.1. The multiple linear regression model was highly significant ($p < 0.001$) and showed a high coefficient of determination across imputations ($R^2 = 0.7$). In 18 femurs, the development of AVA was explained successfully in terms of direction. In the remaining two femurs, the measured development was low with values of -2.1° and $+1.7^\circ$ (Figure 7 left).

The best performing predicting model (i.e. based solely on data from the initial data collection and

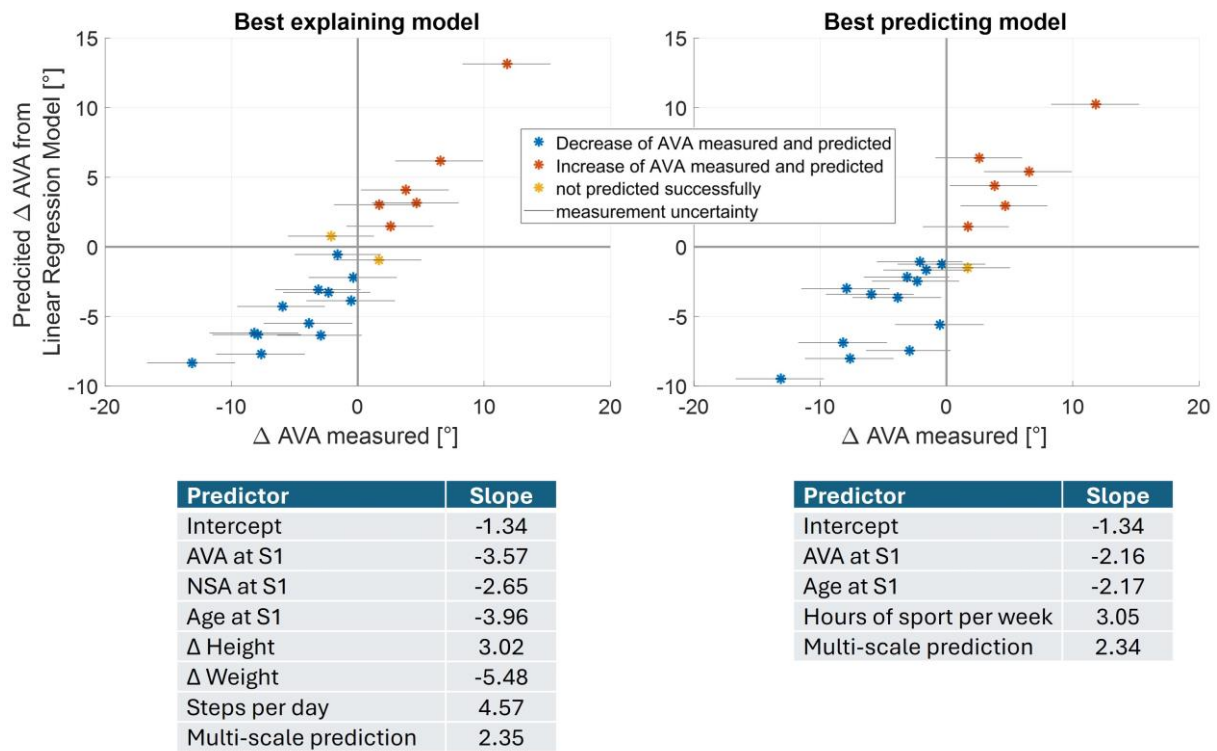


Figure 7: Scatter plot based on the measured anteversion angle (AVA) and predicted development of AVA for best explaining (left) and best predicting (right) model. The stars indicate the measured change of AVA assessed under the two-person verification principle and the horizontal lines passing the colored markups indicate measurement uncertainties. The tables below include the significant z-normalized predictors and their slopes of the corresponding model. S1 = first data collection session.

multi-scale predictions) was highly significant ($p < 0.001$) with almost as high coefficient of determination ($R^2 = 0.66$) across imputations as the best explaining model (Figure 7 right). It included only the age and the AVA from the initial assessment as significant predictors with negative slopes, as well as the hours of sport per week and the multi-scale predictions as significant predictors with a positive slope. The parameters of the multi-scale workflow were similar to those of the best explaining model except for the ratio of weighting factors a to b , which was 0.02.

3.4. Qualitative analysis of best explaining model

Heatmaps visualizing the growth rates of all femurs showed no clear trend and indication whether an increase or decrease was predicted by the multi-scale simulations (Figure 8). A significant correlation ($p < 0.05$) was found between center of growth in the medial/lateral direction and the predicted development of AVA with a low coefficient of determination ($R^2 = 0.25$). No significant correlation was found between the

prediction and the center of growth rate in anterior/posterior direction.

4. Discussion

We experimentally investigate a mechanobiological model to predict the development of femoral AVA with the use of MRIs captured at two occasions approximately two years apart. The sensitivity analysis identified best parameter combinations for the mechanobiological model. Linear regression models were able to explain ($R^2 = 0.7$) and predict ($R^2 = 0.66$) the development of the AVA based on the mechanobiological simulations with high coefficient of determinations.

The inclusion of the mechanobiological multi-scale predictions increased the explanatory power of the linear regression model compared to the *baseline* model. 70% of the development of AVA were explained by the best model including physical activity and anthropometric data of the first session and the changes between sessions as well as the multi-scale predictions. A model including only

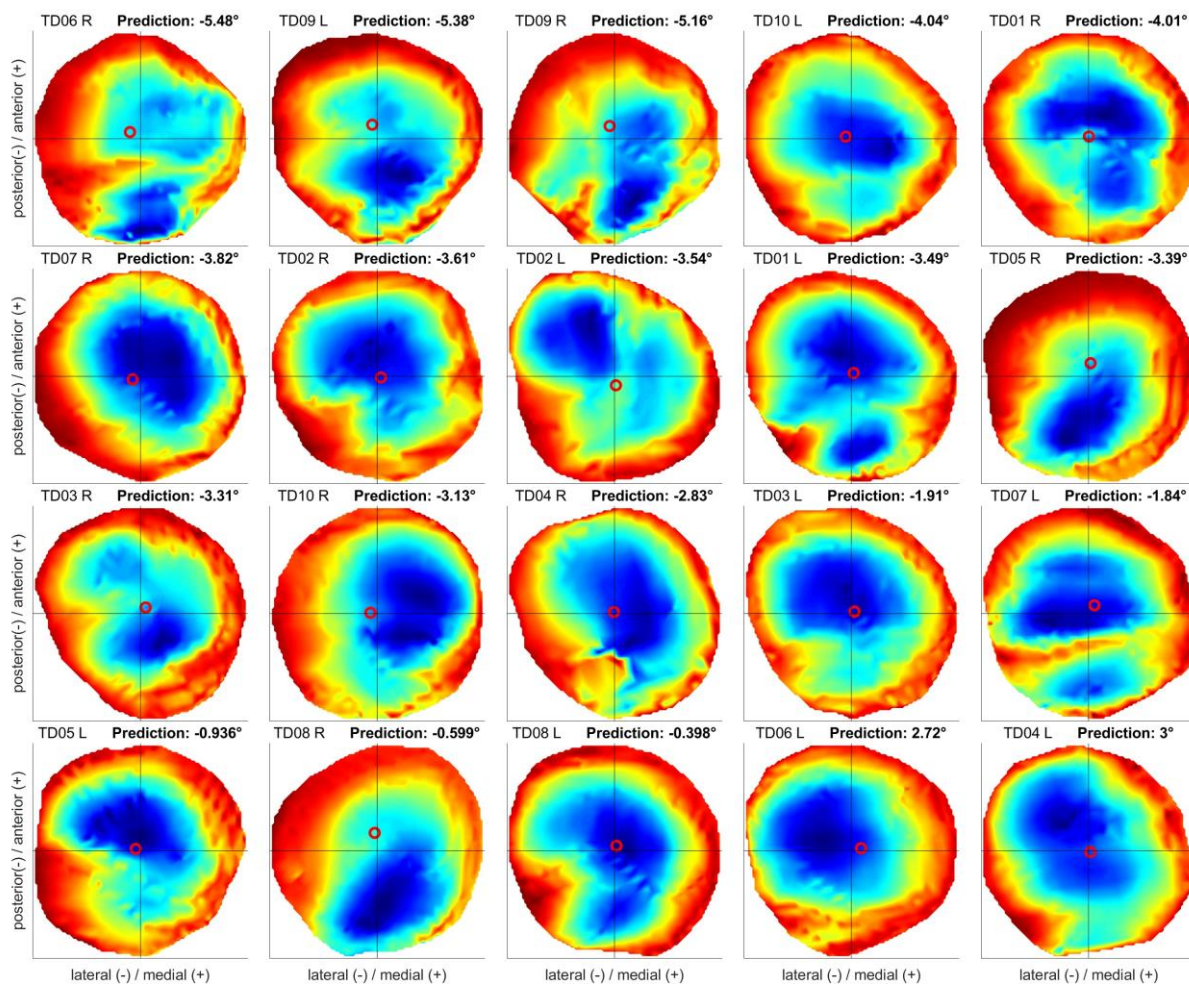


Figure 8: Growth rates of the best explaining model within the proximal femoral growth plate visualized using a blue to red color scheme representing low and high values, respectively. The red circle is indicating the center of growth rate. The order of the diagrams is based on the predicted development of AVA by the multi-scale simulation (left to right, line by line). A figure with a unique color scheme across all heatmaps is included in the supplementary material.

data of the first session and the multi-scale predictions had only 4% lower explanatory power than the best explaining model. Considering that bone growth is guided by mechanical loading (Carter et al., 1996; Carter and Beaupré, 2000; Wolff, 1892), but keeping in mind that there are other factors like nutrition or genetics which influence biological tissue responses (Stevens et al., 1999), the observed coefficient of determinations can be considered as high.

The shape and magnitude of muscle forces obtained with personalized musculoskeletal models and SO as approach to solve the muscle redundancy problem, were in agreement with previous studies (Lin et al., 2012; Trinler et al., 2019). The two approaches (SO and EMG-informed) to solve the muscle redundancy problem in musculoskeletal simulations estimated significantly different muscle and joint contact forces. The use of EMG data to inform simulations increased mainly muscle forces of the tensor fasciae latae, hamstring and knee extensor muscles.

This has also been observed in other studies and is possibly due to a higher co-contraction in some participants (Hoang et al., 2019). As a consequence of higher muscle forces spanning the hip and knee joints in the EMG-informed simulations, the magnitude of hip, knee and patellofemoral joint contact forces were significantly higher in EMG-informed simulations compared to those obtained with the SO approach. Furthermore, the orientation of the HJCF in the sagittal plane differed between both modelling approaches. As a consequence, different nodes of the femoral head are loaded which in turn modifies the stress distribution.

The sensitivity analysis revealed that multi-scale predictions based on the mechanical loading estimated with SO show higher coefficients of determination than those that used muscle and joint contact forces obtained with an EMG-informed approach. This is in contrast to our expectations because studies have shown that EMG-informed simulations increase the agreement between simulated and in-vivo measured joint loadings due

to the consideration of subject-specific motor control ([Bennett et al., 2022](#); [Hoang et al., 2019](#); [Manal and Buchanan, 2013](#)). However, in our study we analyzed healthy children with typical walking patterns. Walking in humans is a very efficient task and therefore low co-contraction can be assumed ([Anderson and Pandy, 2001](#); [Waters et al., 1988](#)). Comparing muscle activation patterns obtained with SO with experimentally measured EMG signals showed good agreement in our participants. Therefore, the results obtained using SO serve as a valid estimation for the investigated cohort. It might be that EMG-informed simulations better estimate the loadings in pathological populations, e.g. in participants with neurological disorders like cerebral palsy ([Wesseling et al., 2020](#)).

Growth simulated in the NORM direction led to the most accurate predictions. In most models with high explanatory power, the growth was simulated in NORM followed by the FNDD direction. As the growth direction of the FNDD method is highly influenced by mechanical properties of the FE model, we would encourage peers to use the NORM method for future studies because it demonstrates superior performance with reduced uncertainty compared to the other growth direction methods. Furthermore, it seems that the orientation of the growth plate has a big impact on the growth direction of the proximal femur. Nevertheless, it needs to be investigated if the NORM method also performs best in pathological cases in future studies.

The mechanobiological model includes many parameter combinations, which were analyzed with our sensitivity analysis simulations. The best explanatory and predicting models had a ratio of weighting factors a to b of 0.1 and 0.02, respectively, indicating that the factor b for the hydrostatic stress should be higher than a to ensure best predictions. While this is in contrast to the ratios used in previous cross-sectional studies using the multi-scale mechanobiological workflow ([Carriero et al., 2011](#); [Kainz et al., 2020](#); [Koller et al., 2024, 2023b](#); [Shelfelbine and Carter, 2004](#); [Yadav et al., 2021, 2017, 2016](#)) the visualization of the growth rates as heatmaps showed similar patterns compared to the previous investigations, i.e. ring-shaped with high values on the outside and low values at the center, and therefore might not impact the conclusions of previous studies. The inclusion of a generic value accounting for the biological growth, the normalization of growth

rates to a specified range as well as the restriction to positive growth rate values did not increase the accuracy of the predictions.

The visualized growth rates of the best explaining model did not reveal a clear distinction in terms of shape or distribution between individuals experiencing an increase or a decrease of AVA (Figure 8). The center of growth rate in these heatmaps could indicate to which direction the femoral head will tilt in the growth simulations. However, a significant but only low correlation was found between the weighted center of growth rate in medial/lateral direction and the predicted development of AVA. In detail, a more medially pronounced growth rate distribution correlated with an increase of AVA.

During skeletal growth, the AVA typically decreases from 40° to approximately 20° ([Bobroff et al., 1999](#); [Fabry et al., 1973](#)). We analyzed longitudinal data of healthy children and found an increase of AVA between sessions in some femurs, which is considered as unphysiological growth from a clinical point of view. The detailed analysis of femurs that experience pathological increase of AVA in terms of growth plate morphology and loading conditions did not reveal key factors that might explain the reason for this pathological development. This strengthens the need for the performed multi-scale simulations as it includes the subject-specific overall femoral geometry, the shape and orientation of the growth plate and the mechanical loading on the growth plate during walking to simulate the cells biological response to these stresses. Only accounting for all these aspects collectively led to the observed high coefficients of determination.

The used multi-scale mechanobiological model includes several simplifications and did not aim to mimic real femoral development, which includes surface bone re-modelling additionally to growth at the growth plates. In the used model, growth was only simulated at the proximal growth plate while all other elements were kept constant. Therefore, all geometrical changes result from a tilt and shift of the femoral head proximal to the growth plate, e.g. an increase of AVA would be represented by an anterior tilt of the femoral head. While this modelling choice did not include any surface bone re-modelling and adaptations, the model was sophisticated enough to fulfil its purpose to identify femoral AVA growth trends. Furthermore, previous studies showed that this model can distinguish between healthy and pathological

femoral development ([Carriero et al., 2011](#); [Kainz et al., 2021](#); [Koller et al., 2024, 2023b](#)). Due to the limitation of modelling growth only at the proximal growth plate, we decided to compare only the clinical important feature, i.e., AVA, between the measured and predicted values instead of comparing the entire shape of the bone. In the future, we plan to develop more realistic growth models that predict the full development of the femoral geometry. Methods such as Generalized Procrustes Analyses ([Bastir et al., 2024](#)) can then be used to compare the predicted with the actual femoral geometry.

Negative growth and ignoring biological growth is certainly not physiological plausible. Negative growth rates are theoretically possible because hydrostatic compressive stress is negative. Hence, if the negative term $b * \sigma_{H_i}$ is absolutely speaking larger than the term $a * \sigma_{S_i}$, the resulting growth rate for this element is negative. The model is based on experimental observation which showed that growth plate cartilage ‘likes’ compressive stress and therefore does not lead to ossifications, whereas the cartilage does not ‘like’ shear stress and therefore leads to ossification ([Stevens et al., 1999](#)). Therefore, negative growth rates indicate that growth is not promoted due to mechanical stimuli at these elements. However, if biological growth would be considered, the total growth would still be positive. Similar to previous studies, biological growth was modeled as a simple constant value. Surprisingly, ignoring the biological growth rate and allowing negative growth rates led to the best results, indicating that modelling the biological aspect with a simple constant value does not work very well and leads to worse predictions. Hence, future work is needed to come up with better and potentially subject-specific ways to include the biological growth amount.

This study included several limitations. Firstly, only data of TD children were included in this study. Collecting longitudinal data of participants with bony pathologies (e.g., cerebral palsy, skeletal dysplasia, rickets, etc.) is challenging because these patients typically undergo diverse clinical interventions, including de-rotation osteotomies, within such a long period of time. Nevertheless, a wide range of AVA changes were observed within the investigated cohort, which included typical but also pathological AVA developments. Secondly, the investigated cohort was relatively old considering that changes of AVA are higher in

early childhood. Nevertheless, several participants experienced a growth spurt accompanied with substantial development of AVA within the time period between data collection sessions. However, the identified best parameters might differ for other age groups. Thirdly, similar to previous studies ([Kainz et al., 2020](#); [Koller et al., 2024, 2023b](#); [Yadav et al., 2021, 2017, 2016](#)) generic linear-elastic material properties were used for all parts of the femur in the FE model. Fourthly, the model did not include all anatomical details, e.g., the Ring of Lacroix around the growth plate was not included. Previous studies, however, showed that the Ring of Lacroix has only a minor impact on the stress distribution ([Hucke et al., 2023](#); [Piszczałowski, 2012](#)). Hence, we kept the model similar to previous investigations, which already revealed plausible simulation results ([Kainz et al., 2020](#); [Koller et al., 2024, 2023b](#); [Yadav et al., 2021, 2017, 2016](#)). Fifthly, we used boundary conditions similar to previous studies ([Kainz et al., 2020](#); [Koller et al., 2024, 2023b](#); [Yadav et al., 2021, 2017, 2016](#)). However, a recent study investigated different boundary conditions in FE analysis of the femur and proposed a new method to represent the biomechanical loading situation more accurately ([Bavil et al., 2024](#)). Unfortunately, this new boundary condition restricts movement of selected nodes close to the proximal growth plate and therefore induces artificial stresses within the growth plate. Therefore, it was not suitable for this study’s modelling purposes. Importantly, the GP-Tool, which we developed and used in this study to create the FE models is open source and different boundary conditions can be implemented easily and used in future studies.

In conclusion, the findings of this study showed that multi-scale simulations combined with a mechanobiological model enables an accurate prediction of femoral AVA growth trends in children. No key factors were identified that could differentiate between healthy and pathological growth patterns, thereby reinforcing the necessity for the multi-scale workflow, which considers multiple factors collectively. The application of mechanobiological model-based predictions may facilitate a paradigm shift in the clinical management of femoral torsional deformities. In contrast to current reactive, invasive procedures such as de-rotation osteotomy, the prospective identification of abnormal loads (which lead to bony deformities) at an early stage could facilitate the implementation of proactive, non-invasive

interventions. In the event of pathological bone predictions, the loadings on the bones could be modified through non-invasive interventions, such as gait retraining ([Kainz et al., 2024b](#); [Uhlrich et al., 2022](#)), to ensure that the bone loads and growth are within normal range ([Kainz et al., 2024a](#)). However, to achieve accurate subject-specific predictions in the future, it is essential to investigate how certain model parameters influence simulation results. This study is the first step towards this goal but further studies including larger sample sizes and pathological cohorts are required to overcome several hurdles before this approach can be adopted in clinical practice. It is essential to identify the range of loading conditions that promote normal bone growth and to determine how participants can achieve these conditions.

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3. Discussion

3.1. Summary

MSK simulation results, i.e., muscle and joint contact forces, are used as input for the multi-scale mechanobiological growth predictions. Hence, within the first presented study, we analyzed the impact of scaling errors on MSK simulation results. We found that the simulation results were affected similarly between pathological and healthy gait patterns and errors occur at all muscles and joints due to the global optimization approach in MSK simulations (Koller et al., 2021). While mainly the magnitude of joint contact forces was influenced by scaling errors, the orientation of the joint contact force remained mostly unaffected. A previous study based on multi-scale mechanobiological simulation highlighted that the orientation of the hip joint contact force in the sagittal plane is a crucial factor for differentiating between healthy and pathological AVA development (Kainz et al., 2021a). Since we found very little differences in the orientation of the hip joint contact force, the impact of scaling errors within this multi-scale mechanobiological simulation workflow can be considered as negligible. However, scaling the MSK model to the participant's anthropometry is important and was therefore carried out with special care for subsequent studies and based on measures from MRI scans. Recently, tools to perform the scaling step automatically with a bi-level optimization approach have been published (Di Pietro et al., 2024; Werling et al., 2023). Nevertheless, it has to be evaluated how these tools perform on data of children in general and in people with pathologies.

It has been shown that the hip joint contact force is an important biomarker that determines femoral development (Carriero et al., 2011; Kainz et al., 2020; Yadav et al., 2021). Therefore, asymmetric hip loading might lead to asymmetric and pathological femoral bone growth. In children with CP, so-called single event multi-level surgeries including de-rotation osteotomies and muscle-tendon-lengthening, are often performed to correct femoral deformities, enhance the child's gait pattern and prevent further pathological development (Boyer et al., 2016; Carty et al., 2014; Gage et al., 2001). In the second study, utilizing what-if simulations, we investigated the contribution of the asymmetric femoral morphology and the asymmetry in the gait pattern on the asymmetry of hip joint contact force (Koller et al., 2023a). The results of this study indicated that the gait pattern has a significantly higher contribution to the asymmetric loading than the femoral morphology. Normalizing the gait pattern should therefore be of high priority in clinical interventions and might be even more important than correcting the bony deformities itself. Still, as a de-rotation osteotomy changes the moment arms of muscles, a correction of the bony morphology might be necessary to enable a typical walking pattern.

The developed GP-Tool allowed us to perform the multi-scale mechanobiological workflow in a large dataset and analyze femoral growth patterns. In the third study, plausible growth patterns were observed at the proximal femoral growth plate in TD children and children with CP (Koller

et al., 2023b). In TD and many but not all CP children, growth due to mechanical stimuli during walking was promoted at the outer edges and inhibited in the central region of the growth plate. Longitudinally, this leads to a change of growth plate shape from a convex to a flatter disc as it was observed in medical images previously (Kandzierski et al., 2012). In the remaining CP children, a linear-gradient growth rate distribution with promoted growth in the lateral region and inhibited growth in the medial region was observed. This potentially leads to atypical femoral growth with time.

A similar picture was observed for growth patterns at the distal femoral growth plate in the fourth study of this thesis (Koller et al., 2024b). We found that children with CP that have a high knee flexion angle during the stance phase showed growth patterns with severe promoted growth in the anterior compartment. Longitudinally, promoted growth anteriorly and inhibited growth posteriorly leads to a higher anterior bending of the femoral shaft. Indeed, this was also observed by analysis of the femoral geometry obtained from medical images in these children. Due to the cross-sectional dataset, it couldn't be said whether the increased knee flexion angle or the pre-existing femoral geometry is the cause, but our findings showed that both promote each other.

Within the fifth study, we recorded a longitudinal dataset including 3D gait analysis and MRIs of ten TD children to experimentally investigate the multi-scale mechanobiological growth predictions (Koller et al., 2024a). A sensitivity analysis was conducted to identify the best parameter combination to obtain accurate results. A linear regression model solely based on the data from the first session (age, AVA, hours of sport per week) and the multi-scale predictions was able to explain 66% of the AVA changes. In 18 of 20 femurs within this study, the direction of the growth, i.e., whether AVA will increase or decrease, was predicted correctly. Given that bone growth is guided by mechanical loading (Carter et al., 1996; Carter and Beaupré, 2000; Wolff, 1892) but other factors like nutrition or genetics influence biological tissue responses (Stevens et al., 1999), the obtained predicting accuracy can be considered as high.

3.2. Limitations

The presented studies within this thesis include various types of input data and computational simulations based on various models, each including several assumptions and uncertainties. In the following subsections, several limitations are presented and possible improvements for further studies are discussed.

3.2.1. Study cohort and data collection

We collaborated with the gait laboratory of Orthopedic Hospital Speising in Vienna to recruit participants for the thesis' purpose which should have included TD children and children with CP. Unfortunately, the recruitment of children with CP turned out to be unfeasible for the purpose of this thesis, due to the fact that nearly all children with CP would undergo diverse orthopedic

interventions between data collection sessions. These could include de-rotation osteotomies, muscle tendon transfer, Botulinum toxin A injections or selective dorsal rhizotomy (Gage et al., 2001; Schwartz et al., 2004). All of these interventions would either modify the MSK morphology or influence the muscle coordination which would in turn change the gait pattern of the patient and therefore the loading on the bones. Consequently, we would not be able to use data of these patients to validate the mechanobiological model as the natural interaction between MSK morphology, gait pattern, loading on the bones and bone growth would have been disturbed. Consequently, due to high risk of dropouts paired with the substantial costs of data collection, we decided to exclude participants with CP and only focus on TD children. Future work could focus on leveraging retrospective data from clinical databases, specifically 3D gait analyses and medical imaging of patients who did not undergo any interventions between data collection sessions.

Recording of muscle activity using surface EMG is severely influenced by several factors like skin preparation, electrode placement or movement artefacts. We recorded the muscle activity of eight lower limb muscles per leg for every prospectively collected TD participant. In the children with CP, no EMG recordings were available. Therefore, we used EMG data to inform MSK simulations to estimate muscle activations only in the last study. Multiple approaches to implement EMG-informed simulations are available (De Groote et al., 2016; Dembia et al., 2020; Pizzolato et al., 2015). Despite, extensive preparation, controlling and accurate placement, in some participants, not all EMG recordings were of sufficient quality to be used to inform MSK simulations.

Furthermore, MRIs of all participants were collected with a T1-weighted sequence. However, various parameters as relaxation and echo time change the visualization of structures substantially. This led to different image quality between the previously and prospectively recorded datasets. Nevertheless, the different sections of the bones (cortical bone, trabecular bone, bone marrow, growth plate) were clearly visible in all MRIs and thus, not influence the studies' conclusions. The use of CT scans would additionally allow to estimate material properties of the femur (Helgason et al., 2008; Rho et al., 1995). However, CT scans utilize radiation and invasive imaging techniques should only be performed when clinically necessary. For future studies, machine learning based approaches could be used to create pseudo-CTs from MRIs to obtain subject-specific material properties (Florkow et al., 2024; Kapanen and Tenhunen, 2013).

3.2.2. Musculoskeletal simulations

MSK simulations in general have various limitations including simplification of the human MSK system, personalization of the model and the use of mathematical optimization approaches to solve the muscle redundancy problem (Delp et al., 2007; Hicks et al., 2015; Seth et al., 2018).

Despite these limitations, MSK simulations offer a reliable method to estimate muscle and joint contact forces during dynamic activities (Modenese et al., 2021; Steele et al., 2012).

In the presented studies different MSK reference models were used, and personalization was performed at various degrees. In papers 4 and 5, the overall femoral geometry was personalized by including the NSA and AVA (Veerkamp et al., 2021) and multiple measures from MRIs, i.e., pelvis dimensions, femur length, femoral inter-condylar distance, were used for scaling and individualization. Changes of bony geometry alters moment arms of muscles and subsequently has an impact on the estimated muscle and joint contact forces. However, the personalization was only performed for the femur while other bones of the lower limbs (e.g., tibial torsion) might also impact simulation results. However, tibial torsion only affects a limited number of muscles and therefore we assume the impact on joint contact and muscle forces acting on the femur is negligible. Studies which investigate the impact of tibial torsion on joint contact forces should be carried out to verify our assumption. Image based MSK models accounting for the whole lower limb MSK morphology might reveal best estimates but are time-consuming to create (Modenese and Renault, 2021). Streamlining the workflow to create MSK models from medical images might increase the use of highly personalized models. However, medical images of the whole lower limbs would be needed to create such models.

To solve the muscle redundancy problem, static optimization, which minimizes the sum of squared muscle activations, was used in all presented studies. Muscle activation is closely related to metabolic cost. Therefore, this optimization approach assumes that movement is performed with as little effort as possible. This is a common and valid approach in healthy participants. However, for children with neurological problems such as CP, different approaches accounting for the individual's motor control might reveal more accurate results as higher co-contraction and spasticity is commonly observed in these patients (Hoang et al., 2019; Pizzolato et al., 2015; Veerkamp et al., 2019). Due to the lack of EMG data in all participants with CP, we were not able to perform EMG-informed simulations. In the latest paper, we exclusively used prospectively collected data from TD children and applied a SO and EMG-informed optimization approach (Dembia et al., 2020)) to estimate femoral loading conditions. In contrast to our expectations, predicted AVA changes from multi-scale mechanobiological simulations using loadings estimated with SO showed better agreement with AVA development quantified with MRI scans than using loadings from an EMG-informed approach. Comparing muscle activation patterns obtained with SO with experimentally measured EMG signals showed good agreement in our participants. Therefore, the results obtained using SO serve as a valid estimation for the investigated cohort. In patients with neurological disorders, EMG-informed approaches might reveal better results.

We used MSK simulations to estimate the mechanical loading on the femur during walking. However, other activities of daily living, like running, stair climbing, sitting or rising from a chair, would lead to different muscle and joint contact forces (Bergmann et al., 2001, 1993), which was

neglected in our studies. A previous study evaluated the impact of the orientation of the hip joint contact force occurring in activities of daily living on femoral growth predictions (Yadav et al., 2021) and found that most activities lead to similar growth trends. Nevertheless, future studies could investigate the effect of other activities common in children with CP with more impairments, e.g., walking with crutches or sitting in a wheelchair, on femoral bone growth. MSK simulations of such activities can be performed and used in the developed GP-Tool as input to estimate the stresses occurring during these activities and subsequently predict the femoral development under these conditions.

3.2.3. Finite element simulations

We used the subject-specific femoral geometry including the individual's orientation and shape of the growth plate to perform FE simulations. In paper 3, we performed a mesh convergence analysis to ensure that the mesh size is fine enough to obtain accurate stresses within the growth plate and evaluated the impact of different material properties on the obtained results. However, FE simulations are also highly dependent on the boundary conditions which should reflect realistic scenarios. Similar to previous studies, we used a simplified approach by limiting translation and rotation at the distal epicondyles to evaluate the stresses in the proximal femoral neck growth plate (Kainz et al., 2020; Yadav et al., 2021, 2017, 2016). A recent study investigated different boundary conditions in FE analysis of the femur and proposed a new method to represent the biomechanical loading situation more accurately (Bavil et al., 2024). Unfortunately, this proposed boundary condition restricts movement of several nodes close to the growth plate and therefore, artificial stresses are induced in the investigated area which makes this approach unfeasible for the purpose of this thesis. Nevertheless, the GP-Tool offers the possibility to adjust the boundary conditions to better reflect the biomechanical situation for future studies.

Despite that we showed that the effect of material properties on the obtained stresses within the growth plate is limited (Koller et al., 2023b), FE simulations could be further improved by using more detailed, subject-specific material properties. The properties of cortical and trabecular bone can be quantified through bone density assessments using CT scans or pseudo-CTs derived from MRI (Florkow et al., 2024; Kapanen and Tenhunen, 2013). However, the growth plate is a heterogeneous cartilaginous tissue, and its material properties cannot be measured directly in vivo. Instead, MRI-based metrics, such as the collagen and water content, can be quantified using specific MRI protocols and subsequently used to inform FE models (Hesper et al., 2014). While we observed only minor differences in stress outcomes within the proximal growth plate when using two distinct sets of material properties (Koller et al., 2023b), material properties most likely have a significant impact on other mechanical outputs such as strain, strain energy density and displacements. Therefore, using personalized femoral material properties would allow a more accurate simulation of the femur's mechanical behavior under loading.

3.2.4. Mechanobiological model

In the presented studies, a relatively simple mechanobiological model was used to predict bone growth (Shefelbine and Carter, 2004; Stevens et al., 1999). The model estimates growth response directly from tissue stresses without any modeling at the cell level. However, previous studies using this mechanobiological model showed realistic and plausible growth patterns and our experimental validation revealed accurate growth predictions (Carriero et al., 2011; Kainz et al., 2021a; Shefelbine and Carter, 2004; Yadav et al., 2021). A model should meet the objectives by including all important components and features but at the same time avoid unnecessary complexity. While the used mechanobiological model included sufficient level of detail for our purposes, further adaptations (e.g., including appositional growth) can be made and tested to investigate if they improve the accuracy of the predictions.

Currently, growth due to mechanical stimuli is calculated as a linear combination of the shear and hydrostatic stresses acting at elements within the growth plate. Other mechanical factors, such as strains or strain energy density have been proposed to influence tissue growth and could be included in the mechanobiological model (Carter et al., 1987). However, the used material properties for these FE simulations will severely influence these results. Therefore, this might only be a valid improvement if the individual's material properties can be obtained from CTs, pseudo-CTs or MRI scans with specialized sequences.

In this thesis, femoral growth was only modeled at the growth plates. However, during skeletal growth, the femur expands in all directions. Hence, the femoral head, the greater trochanter, the shaft diameter, as well as the epicondyles increase in size. Future studies could investigate if the bony development of the whole femur can be modeled with a mechanobiological model.

3.3. Outlook

Computational mechanobiological models are used to predict biological response to mechanical stimuli. As described by Comellas and Shefelbine (2022) such models usually develop through four stages in which the models are used to 1) explore phenomena, 2) explain pathologies, 3) predict clinical outcomes and 4) design therapies (Figure 6).

The presented studies within this thesis are part of stage 2 and stage 3 of the development cycle, and underlines the capability of multi-scale simulations incorporating mechanobiological models to identify femoral bone growth trends. The absence of key factors distinguishing pathological from healthy femoral AVA development (see Chapter 2.5) highlights the importance of utilizing this multi-scale workflow as it considers confounding factors such as the participant's MSK morphology, subject-specific loading conditions and detailed femoral morphology collectively. However, clinical applicability is yet limited, due to the limited sample size in our longitudinal study and the absence of pathological participants.

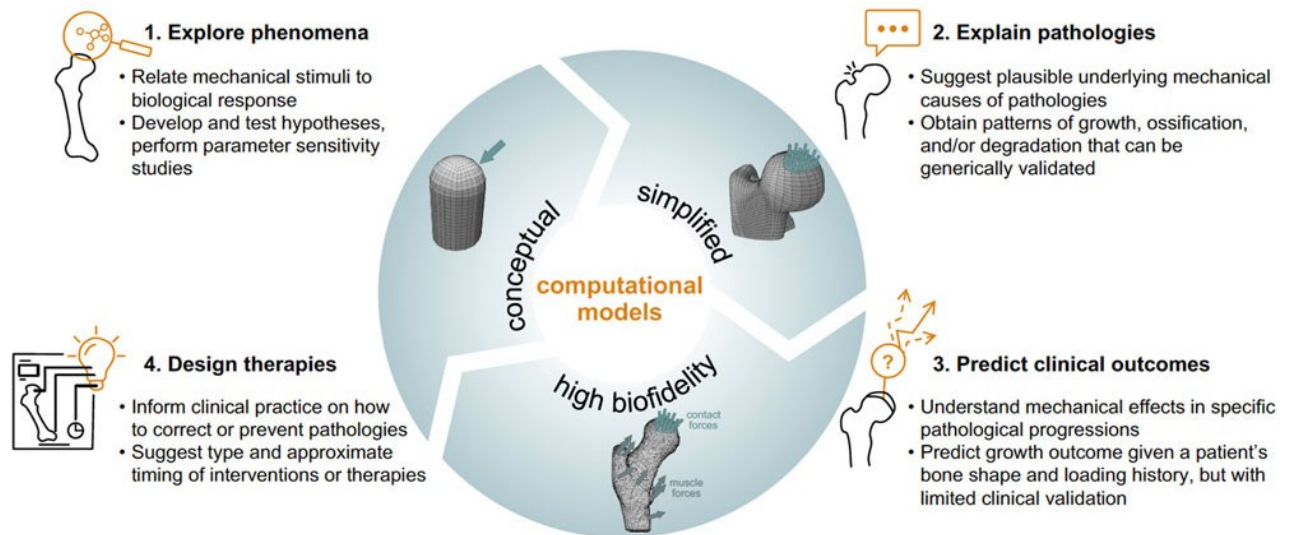


Figure 6: Description of the four stages of a computational mechanobiological model. Figure from Comellas and Shefelbine (2022)

Nevertheless, the road is paved to perform mechanobiological simulations on large samples and clinical populations in the near future. Recent developments of automated MSK simulation workflows allow to estimate subject-specific bone loads in short time without the necessity of expertise in MSK modeling (Werling et al., 2023). Several machine learning approaches facilitate fast and reliable segmentation of bone structures from CT scans, which are frequently collected for clinical purposes (Milara et al., 2024; Wasserthal et al., 2023). This data can be used as input data to the developed GP-Tool that allows to run the mechanobiological growth predictions semi-automatically and in short time. Given these recent developments, the multi-scale mechanobiological workflow could be performed in clinical settings without the need for additional data collection and tremendous expertise or computational time.

Furthermore, the multi-scale mechanobiological workflow can be used to address numerous clinical research questions in the future. The effects on the mechanical loading regime within the growth plates due to guided growth treatment strategies, such as hemiepiphysiodesis or transphyseal screwing, can be investigated in detail with such simulations (Gok et al., 2017; Hucke et al., 2023). As the code of the GP-Tool is open source, adaptations and improvements to the FE model to answer such research questions can be easily implemented.

Mechanobiological simulations may enable a shift in the clinical treatment strategy for femoral deformities. In contrast to current reactive, invasive procedures such as de-rotation osteotomy to correct deformities, the identification of abnormal bone loads at an early stage could facilitate the implementation of preventive, non-invasive interventions. In case of pathological growth predictions, the loadings on the bones could be altered by novel interventions like gait retraining (Kainz et al., 2024; Uhlich et al., 2022). However, the loading condition which promotes normal bone growth might be different in each individual and needs to be individually quantified for each

patient. Real-time biofeedback of growth plate stresses might be essential in these interventions to help the participant to reach the desired loading situation. FE simulations are computationally expensive and therefore not suitable for real-time applications. However, FE simulations based on subject-specific models could be performed beforehand for various muscle and joint contact force combinations. Machine learning methods can then be used to create a surrogate FE model (Pizzolato et al., 2020), enabling real-time estimation of growth plate stresses. Future studies need to investigate the applicability of these interventions in pathological populations, e.g., children with cerebral palsy.

To conclude, multi-scale mechanobiological simulations have the potential to identify pathological bone growth and assist in their treatment. However, future projects and studies are necessary to overcome several hurdles before these simulations can be used in clinical practice.

4. Abbreviations

AVA	Anteversion angle
NSA	Neck-Shaft angle
TD	Typically developing
CP	Cerebral palsy
MRI	Magnetic resonance images
CT	Computer tomography
EMG	Electromyography
MSK	Musculoskeletal
FE	Finite element
SO	Static optimization
GP-Tool	Growth-Prediction-Tool

5. Figures

Figure 1: Schematic illustration of the complex interplay between skeletal morphology, gait pattern, mechanical loading on bones and bone growth. 12

Figure 2: Schematic representation of the neck-shaft angle (NSA) and anteversion angle (AVA). NSA defined by the orientation of the neck (green line) and the shaft axis (blue line). The AVA is defined as the angle between the neck axis and a line passing the epicondyles in transverse plane (red line). 14

Figure 3: Finite element (FE) simulations at a macro scale can be used to estimate the mechanical loads at tissue level due to muscle and joint contact forces acting on the bone. Similarly, the consideration of a volume that incorporates detailed tissue enables estimations of stresses and strains on bone cells. According to the signals perceived, cells can update the bone tissue properties which in turn alters the bone structure at the macro scale. Figure adapted from García-Aznar (2021). 16

Figure 4: Schematic illustration of the mechanobiological multi-scale workflow to predict femoral bone growth. Data from three-dimensional (3D) gait analysis and magnetic resonance image (MRI) scans is used to perform personalized musculoskeletal (MSK) simulations to estimate muscle and joint contact forces acting on the femur. MRI scans are segmented to create a subject-specific mesh of the femur with hexahedral elements aligned with the growth plate. In finite element (FE) analysis 1, the stresses within the growth plate are assessed. In FE analysis 2, the biological response to these mechanical loads is simulated. Predicted growth changes can be quantified by comparing the grown with the baseline geometry. 19

Figure 5: Schematic illustration of longitudinal study design used in Chapter 2.5. Data of magnetic resonance image (MRI) scans and three-dimensional gait analysis was used to perform multi-scale simulations and model the mechanobiological response to predict femoral growth. MRI scans of the second data collection session were used to validate the predicted development. 21

Figure 6: Description of the four stages of a computational mechanobiological model. Figure from Comellas and Shefelbine (2022). 104

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7. Declaration of Authorship

I hereby certify that I have written this work independently and have not used any sources or aids other than those indicated. All direct or indirect sources used are acknowledged as references.

The work has not been submitted previously to qualify for any other academic degree. The content is the result of work since the official commencement date of the PhD program.

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