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Towards Modelling Locomotion using EMG Informed 3D Models: Application to Cerebral Palsy

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Abstract

This position paper proposes a modeling pipeline to develop clinically relevant neuromusculoskeletal models to understand and treat complex neurological disorders. Although applicable to a variety of neurological conditions we provide direct pipeline applicative examples in the context of cerebral palsy (CP). This paper highlights technologies in; (i) Patient-specific segmental rigid body models developed from Magnetic Resonance Imaging for use in inverse kinematics and inverse dynamics pipelines; (ii) Efficient population based approaches to derive skeletal models and muscle origins/insertions that are useful for population statistics and consistent creation of continuum models; (iii) Continuum muscle descriptions to account for complex muscle architecture including spatially varying material properties with muscle wrapping; (iv) Muscle and tendon properties specific to CP; and (v) Neural based electromyography-informed methods for muscle force prediction. This represents a novel modeling pipeline that couples for the first time electromyography extracted features of disrupted neuromuscular behavior with advanced numerical methods for modelling CP-specific musculoskeletal morphology and function. The translation of such pipeline to the clinical level will provide a new class of biomarkers that objectively describe the neuro-musculo-skeletal determinants of pathological locomotion and complement current clinical assessment techniques, which often rely on subjective judgment.

1 Introduction

Cerebral palsy (CP) is an umbrella term for a group of motor impairment disorders caused by a non-progressive lesion in the developing child's brain during pregnancy or shortly after birth.¹ Following the central nervous system lesion the damage to the descending pathways causes (i) paresis, a reduction or failure of voluntary activation and (ii) muscle overactivity, which can be described as spasticity, spastic dystonia and spastic co-contraction². Spasticity, a velocity-dependent increase in muscle tone³, is the primary sign of spastic-type CP. Spasticity interferes with normal muscle growth⁴ resulting in the development of fixed contractures of the muscle-tendon unit leading to muscle weakness and loss of function⁵. While the brain lesion is static, secondary musculoskeletal problems such as reduced joint range of motion, increased joint stiffness, and muscle weakness can progress with age^{6, 7}. These impairments contribute to a gradual loss of functional capacity⁸, characterized by deterioration in gait and reduced muscular strength throughout adolescence and young adulthood in individuals with spastic-type CP⁹.

Orthopedic surgery is a key component in the clinical management of musculoskeletal pathologies in CP. Single- and multi-level surgeries, including muscle-tendon lengthening, tendon transfer and bone derotation osteotomies, are performed to avoid progressive worsening of musculoskeletal impairments, improve gait patterns, and thus, patients' quality of life¹⁰⁻¹². These treatments are commonly prescribed and performed with no objective understanding of the functional changes expected to occur at the neuro-musculo-skeletal levels post-surgery. Common methods to assess the degree of musculoskeletal pathologies and gait impairments prior to surgery include physical examination, observational analysis of walking and quantitative clinical gait analysis¹³. However, existing assessment techniques rely on subjective judgment¹⁴, do not account for complex muscle and tendon architecture nor do they account for the neural control of muscle during walking. As a consequence,

planning and evaluation of orthopedic surgery in children with CP has remained difficult. There is no agreement on the details of the structural changes that occur secondary to the neurological disorder¹⁵, and evidence for the efficacy of most orthopedic operations remains lacking^{10, 12}.

Patient-specific neuromusculoskeletal modeling pipelines can provide estimates of internal body variables that would be otherwise difficult to derive experimentally. These may include estimates of the mechanical force produced by muscles and series elastic tendons, their levels of stiffness, the mechanical loads exerted on articular joints, and the final impact on articular range of motion. This would enable objectively quantifying which muscles are too tight (i.e. preventing natural joint motion) or too weak (i.e. causing abnormal joint loads) pre surgery. Similarly, it would enable predicting how muscle and joint function would vary post-surgery (i.e. after muscle-tendon lengthening or tendon transfer), thus personalizing treatments to an individual patient and maximize the subsequent rehabilitation outcome.

Current modeling pipelines characterize either the neural^{16, 17} or the mechanical determinants¹⁸ of CP locomotion. This poses a major challenge to the treatment of motor impairment in CP, where disrupted mechanical function (i.e. abnormal joint loading and stiffness) must be understood in the context of its disrupted neural origin (i.e. abnormal neuromuscular function)¹⁹⁻²¹. As a result, despite the understanding of the neural and mechanical processes underlying CP movement, there currently is no relevant knowledge of the neuromechanical interplay and couplings *in vivo* in the intact individual²².

With this position paper we propose a clinically relevant neuromusculoskeletal modelling pipeline that accounts for both neuromuscular and musculoskeletal properties of an individual patient. Parts of the proposed pipeline can be applied to investigate a variety of neurological conditions (i.e. see Sections 6 and 7). However, with this paper we provide applicative examples in the context of CP and subsequent personalization of

neurorehabilitation interventions¹⁹. The past decade has seen critical advancement in the development of modeling formulations that characterize CP individuals' musculoskeletal morphologies and function, a central element driving this position paper focus towards CP^{16, 18, 23}.

This paper highlights technologies in; (i) Patient-specific segmental rigid body models developed from Magnetic Resonance Imaging (MRI) for use in inverse kinematics and inverse dynamics pipelines; (ii) Efficient population based approaches to derive skeletal models and muscle origins/insertions that are useful for population statistics and consistent creation of continuum models; (iii) Continuum muscle descriptions to derive muscle arc-lengths including spatially varying material properties with muscle wrapping; (iv) Muscle tendon properties specific to CP; and (v) Neural-based and electromyography (EMG) informed musculoskeletal modelling for simulating movement at the interacting neuro-mechanical levels.

2 Multibody clinical gait analysis for children with cerebral palsy

Children with CP are by far the largest patient population who undergo three dimensional (3D) movement analyses. In 2015 more than 60% of children seen by the Queensland Children's Motion Analysis Service were diagnosed with CP. There is no doubt that results from clinical motion analysis are useful in the clinical decision making process for children with CP^{24, 25}. However, approximately 23% of patients still experience negative outcomes even when the recommendations from 3D motion analysis are followed^{24, 26} potentially due to disparity in choice of surgical procedures performed across clinical facilities for a similar gait profile²⁷.

Traditional 3D clinical gait analysis methods provide information to estimate joint kinematics and joint kinetics, but do not provide direct objective information to assist with planning of these complex surgical procedures²⁸. In recent years, user friendly

musculoskeletal (MSK) modeling software (e.g. OpenSim²⁹ and AnyBody³⁰) has enabled calculation of muscle-tendon lengths³¹, moment arms³², forces³³ and joint contact forces calculations^{34, 35}. These data can be used to perform muscle-driven dynamic simulation to understand muscle contributions to joint and center of mass accelerations^{36, 37}. In this context, accurate estimates of muscle-tendon force can provide quantitative metrics for clinicians to guide assessment of abnormal motor function and devise targeted treatments in simulation before application to the actual patient.

MSK models are computational representations of a person's MSK anatomy. The models consist of multibody systems including rigid bodies (bones) connected by joints and actuated by muscle actuators producing force according to physiological behavior^{29, 38-41}. In these muscle actuators are represented as curvilinear pathways passing through via points or around warping surfaces. The MSK anatomy are generally derived from dissections of adult cadaveric specimens⁴²⁻⁴⁶ and used to implement generic models^{38, 39, 41}. In common applications, these models are linearly scaled to fit the anthropometry of individual subjects using information from 3D motion capture and/or anthropometric measurements. However, in the clinical setting it is arguable whether these additional information from MSK models can assist in surgical planning⁴⁷ or whether the kinematic, kinetic and muscle tendon results accurately and reliably reflect pathological locomotion^{48, 49}. Moreover, the generic nature of the MSK models employed mean they may not account for the muscle contracture, spasticity and bony deformities experienced by the children with CP. The conventional anatomical model used in clinical gait analysis^{50, 51} is based on joint center positions and axes estimated from the spatial trajectories of skin-mounted reflective markers and a limited number of anthropometric measurements. Inertial properties of the body segments are estimated using regression equations⁵².

2.1 Skeletal models

The anatomical parameters included in generic MSK models are representative of an adult (or elderly) musculoskeletal geometry, generally not pathological (dissections were generally performed on specimens with no reported musculoskeletal diseases) and do not provide an accurate representation of the skeleton in the pediatric population, let alone the deformed pediatric population^{53, 54}. This is important because outputs from dynamic simulations are sensitive to the geometry of the skeleton, joints definition and muscle attachments locations⁵⁵. For example, Bosmans et al.,⁵⁶ generated scaled generic and subject-specific musculoskeletal models to investigate the effect of aberrant proximal femoral bone geometry on hip joint contact forces and showed that scaled generic musculoskeletal models masked the real orientation of the hip joint contact force. Therefore, a first challenge for investigations on CP based on MSK models is the personalization of bone geometries, especially when alterations are evident compared to typically developing anatomy. The typical pediatric population has a large amount of variation in lower limb bone geometry, which continues to change throughout growth⁵⁷. Children with CP commonly develop a progressive internal femoral torsion deformity that reduces the mechanical advantage of muscles that cross the hip joint (i.e. hip abductors and glutei) leading to less efficient muscle contribution to locomotion^{50, 58}. Many children with CP also walk with excessive flexion at the hip, knee, and ankle (i.e. crouch gait) and develop an external tibial torsion deformity^{10, 59}. With advancement in medical imaging it is now feasible to incorporate accurate measures of femoral and tibial torsion in the clinical pathway⁶⁰⁻⁶².

Several applications of MSK models to CP are available in the literature, although most have not considered bony geometrical alterations in their models^{33, 35}, but used linearly scaled generic models³⁹. In other studies, the generic model was personalized by including selected features of the patient geometry, such as femoral or tibial torsion^{53, 59}. More

comprehensive personalization has also been proposed by fully morphing a generic model, e.g. by Oberhofer et al.⁶³. In recent years, the possibility of acquiring medical images, especially MRI, has made available to clinicians and researchers a source of anatomical information *in vivo*. Manual or semiautomatic segmentation of muscles and soft tissues, combined with the use of specialized software such as NMSBuilder⁶⁴, allows the generation of patient specific (bone geometry and muscle paths) kinematic and kinetic models that can be used for patient assessment. The increasing complexity that can be captured by MSK models can be seen in Figure 1. Musculotendon actuators, briefly discussed below, can be included in the models as well, although their definition requires a considerable effort in pre-processing and model preparation.

Subject- or patient-specific segmental and skeletal models have recently been developed for clinical gait analyses⁶⁵. Using geometrical representations of the patient's bones, it is possible to identify joint parameters based on their shape. In lower limb models, the hip joint is represented as a ball and socket joint, whose center is located by fitting a sphere to the femoral head^{64, 66}. However, this choice may poorly represent a severe hip joint dysplasia and joint deformation resulting in risk of hip dislocation⁶⁷. The knee joint is often modeled as a hinge, by defining the epicondylar axis⁶⁸ or by fitting spheres to the condyles^{48, 65, 69}. The ankle joint is also modeled as a hinge, with the axis defined by a cylinder fitted to the trochlea surface of the talus^{70, 71} or by the line going through the centers of two spheres fitted to the medial and lateral aspects of the trochlea⁷². Both the knee and ankle joints can be implemented using more complex models, which include the constraining effect of the ligaments on the (passive) joint kinematics by considering them as inextensible⁷³ or minimally extensible⁷⁴. Examples of personalized joint models from medical imaging include the use of MRI^{66, 75}, low dose biplanar X-ray⁷⁶ and freehand 3D ultrasound⁷⁷.

It is worth noting that MSK modelling software generally uses inverse kinematics approaches to calculate joint angles from 3D experimental data⁷⁸⁻⁸⁰, while traditional gait analysis relies on direct kinematics⁵¹. These two techniques are conceptually different and a thorough comparison is necessary before being able to quantify the differences between generic and patient-specific models⁶⁵. The inclusion of markers visible in the MRI scans and collection of gait analysis data just after the medical images can lead to reduced error in placing virtual markers in the inverse kinematic procedure⁶⁵.

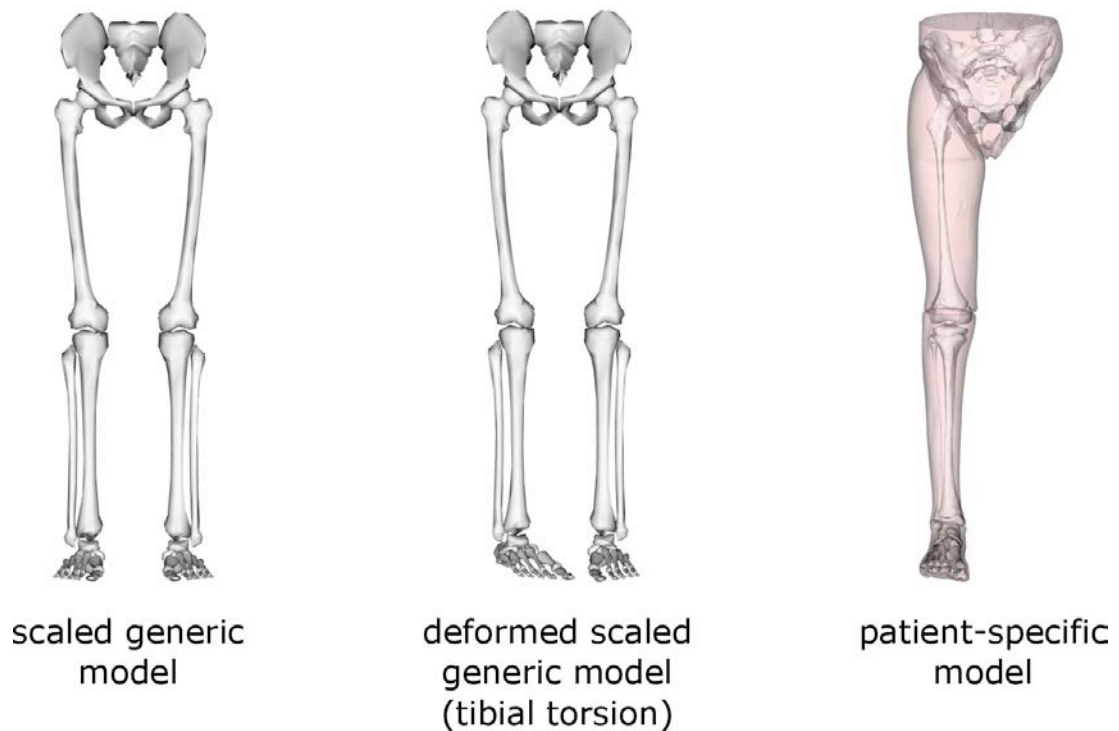


Figure 1 Varying amount of subject-specificity in relation to representing the skeletal system of children with cerebral palsy; a generic scaled model (left), a generic scaled model including some specific deformations, e.g. 30 degrees tibial torsion (centre), and a subject specific model obtained from medical images (right).

From the knowledge of joint kinematics and the external loads (i.e. ground reaction forces), and estimated inertial properties of the body segments^{81, 82}, net joint moments can be

determined using the inverse dynamics analysis⁸³. Using subject specific models derived from MRI (Figure 1, third model) it is possible to calculate subject specific inertial properties, assigning different densities for bone and soft tissues^{84, 85}. This is especially valuable when assessing individuals out of the ranges of the data used to generate the regression equations, e.g. obese patients and children with altered anthropometric proportions.

2.2 Case report of subject specific modeling of a child with cerebral palsy

The case report highlighted in Figure 2 suggests that, at least in the sagittal plane, the conventional models from gait analysis and the subject specific models can produce similar evaluation of the joint kinematics, kinetics and powers. In Figure 2, a subject specific model where all joints were modeled as ball and sockets is compared to results obtained using Vicon Plug-in-Gait. In these simulations the traditional and patient-specific models were driven using MRI-visible markers. The agreement between the two methodologies is important in at least two aspects: 1) it means that normal practice standard gait analysis is an appropriate tool for (this) patient assessment, and 2) it suggests that if patient-specific models were introduced in clinical practice, for instance coupled with further analyses such as musculotendon lengths or force estimation, they could add subject-specific information while maintaining consistency with a more traditional evaluation of the patient's neuromuscular function. This would also provide clinicians with biomarkers that directly relate to CP individuals' musculoskeletal function. This would facilitate objective quantification of patients' motor capacity throughout rehabilitation treatments and help control subjective judgment often associated with the use of clinical scales (i.e. Fugl-Meyer)¹⁴.

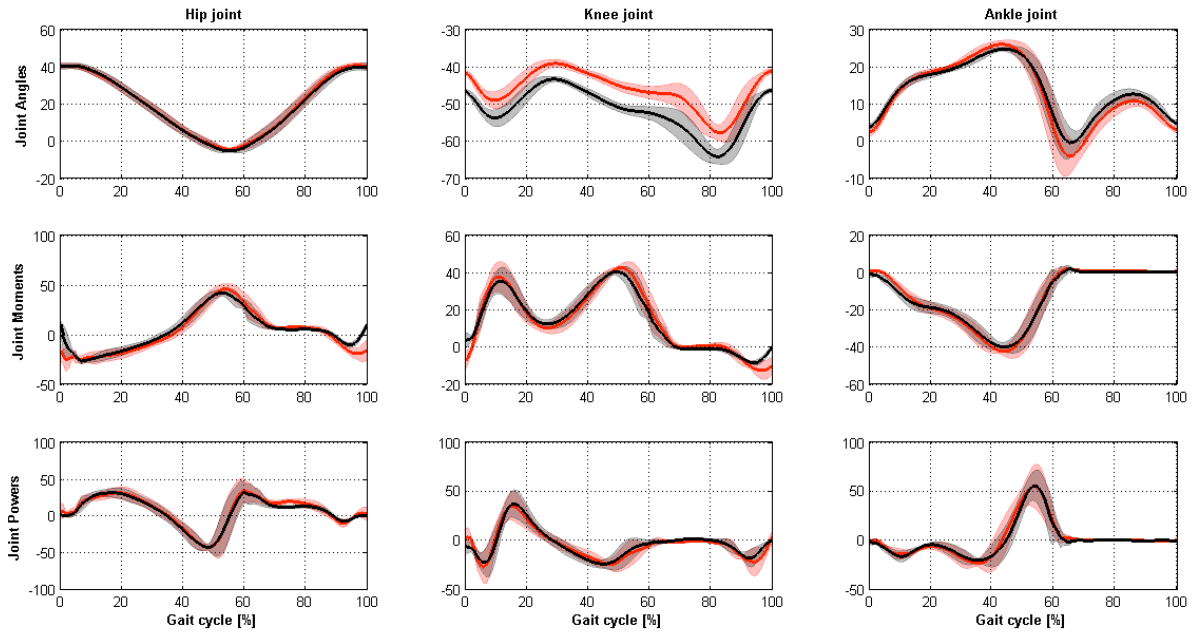


Figure 2 Example of joint angles, joint moments and joint powers obtained using the conventional model (Plug in Gait, in red) and a fully subject specific kinematic and kinetic model (in black). Results are presented only for the sagittal plane.

3 From rigid-body to continuum models using statistical models

Modelling the biomechanical impact of CP at the tissue level requires applying the kinematic and force boundary conditions derived from rigid-body models to continuum models of tissue mechanics and response. Rigid-body models commonly use sparse or coarsely scaled bone and muscle geometry^{86, 87}, while continuum models, such as finite-element models, require accurate, patient-specific geometry often segmented from 3-D medical images⁸⁸. Segmentation of bones, and muscles, is time consuming, and prone to subjective errors. Statistical models can be used to predict 3-D anatomy from sparse data⁸⁹, thereby bridging the disconnect between rigid-body and continuum models and improving the clinical applicability of computational models in CP therapy.

3.1 Bone model generation

Cerebral palsy causes deformities in both the shape⁹⁰ and density⁹¹ of bones. These deformities impede normal function, such as walking or reaching tasks, and also lead to higher risks of osteoarthritis (OA), dislocation, and bone fracture⁹². Given the large spectrum of severity in CP deformities⁹³, continuum models of bone, combined with statistical models of bone morphology variation, can predict the efficacy of therapies in reducing the risks listed above for different variations of CP.

Statistical models of bone shape⁹⁴ and bone mineral density (BMD) distribution⁹⁵ efficiently capture the variations in 3-D bone morphology across a population. Such models are “trained” on a set of data (the training set) sampled from a population of interest. In the case of a shape model, this typically involves segmenting surfaces, re-parameterizing each surface in a correspondent manner (e.g. a common mesh topology), then registration to remove similarity transforms between the surfaces. A dimensionality reduction method such as principal component analysis can then be applied to the aligned surfaces to reveal significant modes of shape variation and/or clusters or shapes. In the case of a statistical model of BMD distribution, surface parameterization and registration are replaced by image registration. Such models, once trained, can be used to predict full 3-D morphology from sparse data⁸⁹, make classifications, and quantify the difference between specimens^{96, 97}.

We have demonstrated shape model based workflows for generating 3-D morphology from sparse data⁹⁸. These workflows combine data routinely collected in gait laboratories (motion capture marker coordinates, anthropometric measurements) and partial segmented surfaces (e.g. from the hip or knee) to generate 3-D surface meshes of the pelvis, femur, patella, tibia, and fibula. The meshes can be used as rigid-body shells for joint contact simulations⁹⁹ to study the development of osteoarthritis in CP, or volumetrically meshed for finite-element or multiscale models of the bone tissue¹⁰⁰. The use of statistical models in the

model generation process ensures anatomically feasible geometries and clinically feasible runtimes of minutes.

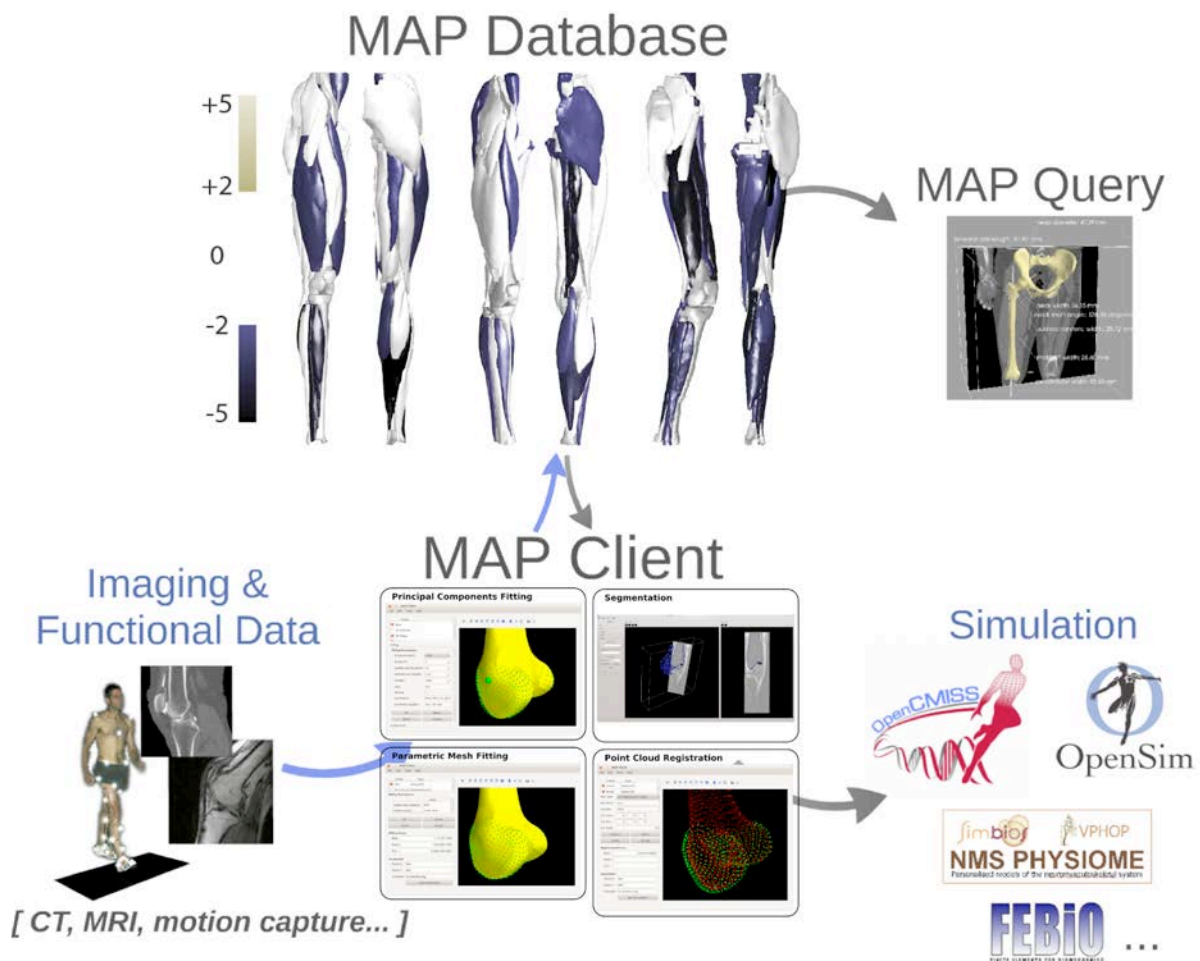


Figure 3: The Musculoskeletal Atlas Project provides workflows for generating musculoskeletal models from clinical data using statistical models. The MAP Client software manages plugins that perform steps such as model registration and mesh fitting. These steps can use data from the MAP Database for typically developed or cerebral palsy populations (CP limbs shown with significantly small muscles highlighted according to Z-score). The generated models bridge the gap between rigid-body and continuum models.

These workflows have been implemented in the open-source Musculoskeletal Atlas Project (MAP) Client software and are freely available to the community⁹⁸. The MAP (Figure 3) aims to consolidate into one common platform the many steps involved in musculoskeletal model generation (e.g. segmentation, registration, and mesh-fitting) as well as the statistical models on which they depend. Going forward, we see the MAP and MAP Client as useful

tools in the CP-oriented musculoskeletal modeling environment, as well as tools that can promote the use of computation modeling in a clinical setting.

3.2 Generative three-dimensional models of muscle

Cerebral palsy is associated with muscle weakness¹⁰¹, alterations in neural drive¹⁰², and altered mechanical properties of muscles¹⁰³. There may be significant shape variations in CP muscles as well. The use of statistical methods and data driven modeling is promising for processing, classifying, and analyzing 3-D datasets of muscle shape and size for CP. Thorough knowledge of CP-specific muscles will greatly aid CP modeling in rigid body models, but may also contribute to the use of continuum muscle models in rigid body frameworks, thus bridging the gap between these two modeling approaches.

As with bone and joints, subject-specific muscle shapes and sizes are often generated from manual or semi-automatic segmentation of medical images^{88, 104-107}, which is extremely time-consuming and often relies on subjective judgments by the user. In contrast to segmentation of bones where cortical or trabecular bone can be distinguished from neighboring tissues, muscle segmentation generally requires classifying neighboring and sometimes non-distinct regions of muscle tissue into specific distinct muscles. Statistical shape models of muscle are a promising tool that may improve automated muscle segmentation routines by providing statistically informed targets for muscle shape, size, and location that can constrain computer vision and image processing routines.

Cerebral palsy is a heterogeneous diagnosis⁹³ and recent research has shown that muscle sizes in children with CP are heterogeneously distributed (Figure 3)¹⁰⁴. The breadth of manifestations of CP make statistical shape modeling a particular challenge; however, with sufficiently large training datasets and data-driven modeling approaches, muscle size and shape relationships and classifications may be achieved, allowing subsequent predictions

from sparse data. The accurate and fast determination of muscle size and shape information in subjects with CP will benefit rigid body modeling directly by providing more realistic inputs for relative muscle sizes in solving force optimizations^{86, 87}. In the future, it will also serve to introduce more sophisticated, continuum-level muscle models into a rigid body framework and enable greater use of models to answer clinical and surgical questions regarding CP^{87, 108, 109}.

4 Continuum descriptions of muscle

Muscle fiber orientations, moment arms and muscle contact interactions in CP are also likely to vary considerably from the general population. Continuum descriptions of muscles allow for spatially varying fiber orientations, muscle interaction including sliding and wrapping around the skeleton giving improved estimates of muscle moments arms and musculotendon lengths. Integration of continuum based muscles with free form deformation (FFD), a computer graphics morphing technique, can be used to efficiently morph underlying muscle geometries modeled with many degrees of freedom using a coarse enclosing mesh with only a few degrees of freedom. The coarse mesh is morphed so as to minimize the distance between strategically chosen control points (from MRI or motion capture) and this deformation is passed to the embedded muscle structures within. This idea was first demonstrated by Fernandez et al.¹¹⁰ using generic template muscle meshes developed from the popular Visible Human data set¹¹¹. The FFD method provides shape control over muscle curvature and length by using shape-based constraints called Sobelov smoothing¹¹². FFD can be performed at the individual muscle and bone level or be applied to the outer skin and whole muscle groups. Figure 4 shows FFD being used where the host is the skin with embedded muscles being internally deformed based on skin motion. Control points can be

located on the skin surface or within the limb and be used to control internal muscle deformation.

Muscle fiber information is a key component of muscle function, as it controls the direction of muscle contractile behavior and shape in 3D, and the pennation components of force in 1D Hill-type models. In 3D finite element muscle models, extracted fiber information from both cadaver dissections and MRI has been used to inform spatially varying fiber architecture¹¹³⁻¹¹⁵. Figure 4 shows a representative dissected cadaveric human rectus femoris muscle with visible fiber pennation angle. Discrete fiber angle measurements were made at different slices and mapped to a continuum fibre field, which becomes part of the generic muscle template.

In gait analysis, continuum muscles have been used to inform rigid body mechanics simulations with anatomically correct musculotendon arc-length paths and muscle moment arms. FFD requires high numbers of control markers, which is difficult to achieve in practice. This limitation has been partially addressed by introducing additional non-kinematic information including material behavior (constitutive laws), tissue interaction (contact mechanics) and volume conservation constraints¹¹⁶. Muscle arc-length centroids can be used to perform a virtual tendon excursion and evaluate moment arms. Figure 5 shows a hybrid finite element-FFD approach with wrapping surfaces, muscle sliding and bone interactions for the semimembranosus and semitendinosus muscles through 45° hip flexion. This extension to traditional FFD couples FE analysis allowing different material laws to be included accounting for stiffer tendon, spatially varying fiber fields, soft tissue sliding and volume conservation of muscle generating a more anatomically realistic shape with only a few control points needed.

This technique was further evaluated for the complete lower limb by Oberhofer et al.⁶³ by matching MR segmented geometries at 15° and 45° flexion with host-mesh predicted muscle shapes producing errors less than 3.7 mm RMS (Figure 5 lower). The FFD morphing method provides complex muscle scaling to patient data beyond the simple scaling currently offered in OpenSIM. The predicted deformations of five muscles were validated using MRI data of the same subject in two different lower limb positions. The walking model was considered the first of its kind, allowing the realistic deformation of several muscles throughout gait with reasonable computational costs.

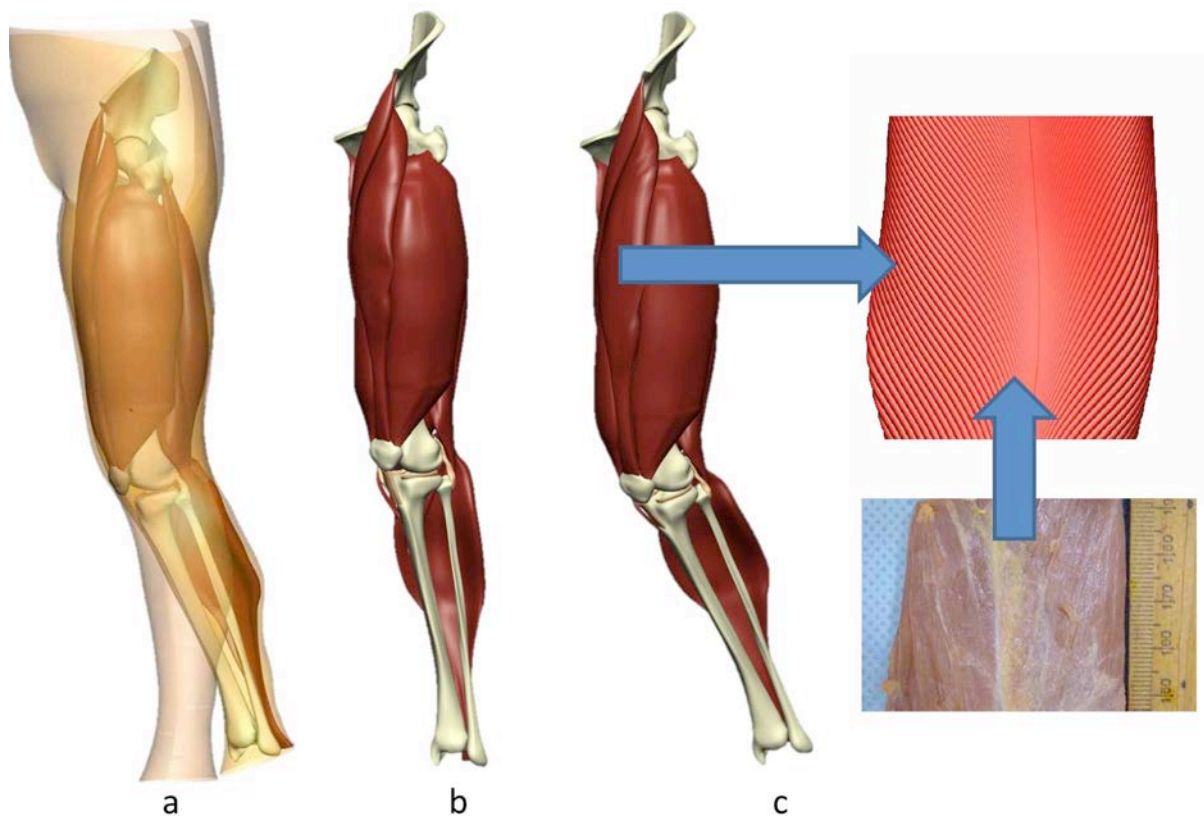


Figure 4: (a) Complete lower limb skin host-mesh with embedded muscles deformed using motion capture surface markers. (b) Initial embedded muscle pose and (c) resulting deformed muscle pose after 30 degrees flexion. Highlighted is the bipennate fiber field fitted for the rectus femoris muscle derived from cadaveric images.

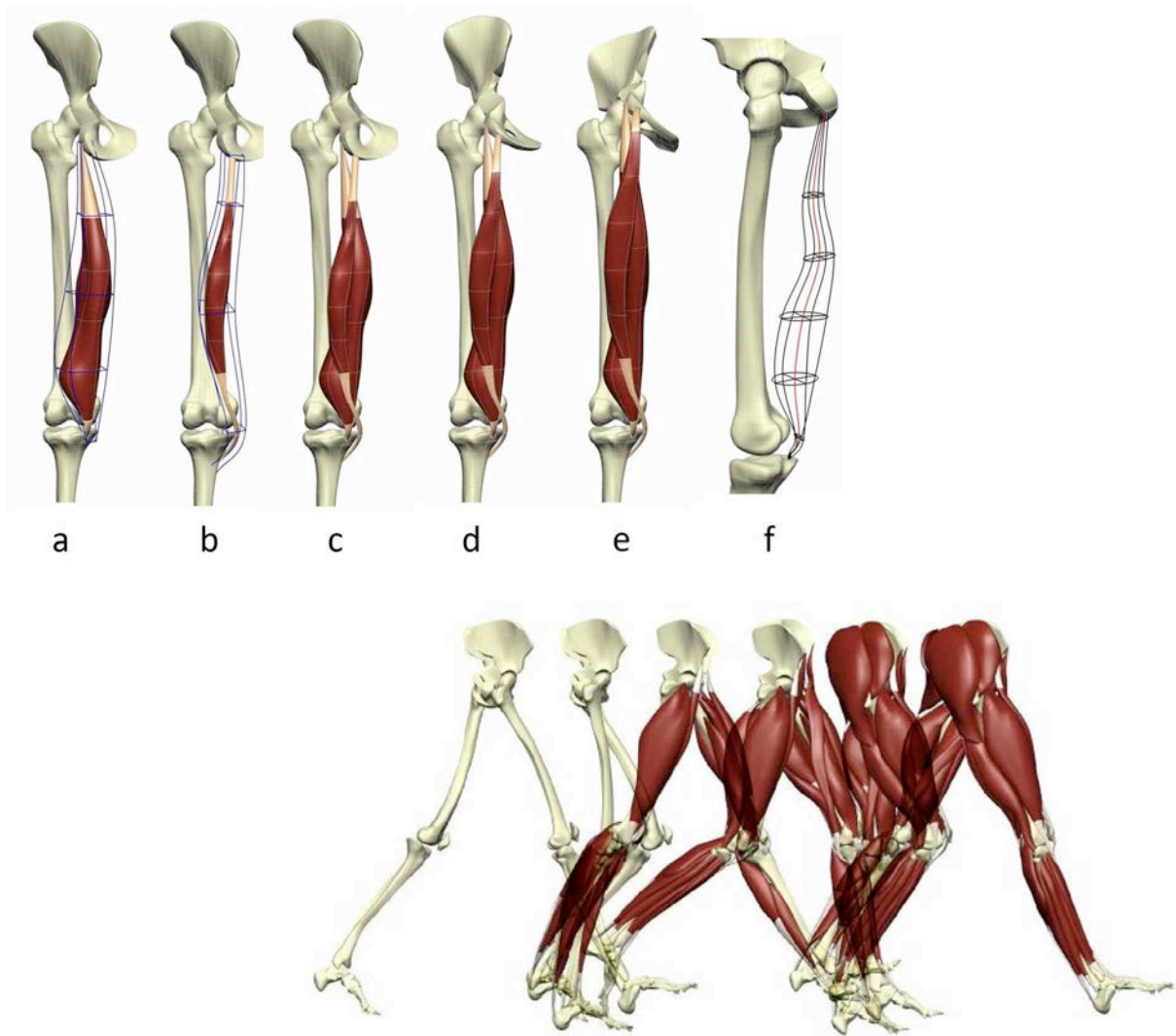


Figure 5: Top (a) Semimembranosus and (b) semitendinosus muscles embedded inside hybrid mechanics host volume meshes. (c-e) Finite elastic mechanics simulations of muscle deformation, sliding and wrapping through 45 degrees of hip flexion; and (f) muscle arc-length changes through muscle centroid (red). **Bottom** Soft-tissue muscle deformation during walking was derived from the deformation of a surrounding skin mesh based on inverse kinematics, i.e. segmental kinematics. The predicted deformations of five muscles were validated using MRI data of the same subject in two different lower limb positions.

5 Muscle adaptations in children with cerebral palsy

Whether using rigid multi-body or continuum model representations of muscle, muscular architecture is the primary determinant of muscle function¹¹⁷ and the specific musculotendinous adaptations in CP contribute to a loss of muscle strength⁷ and functional ability¹¹⁸. Individuals with spastic-type CP have reduced muscle volume, increased intramuscular fat, reduced or similar muscle fascicle lengths, increased muscle fascicle stiffness, and increased Achilles tendon length compared to their typically developing peers¹¹⁹⁻¹²³.

A review of gross muscle morphology and structure in the lower limb of children with spastic-type CP found consistent evidence for reduced muscle size with muscle volume reduced in the most impaired limb compared to the less impaired limb and muscles of children with typical development.¹⁰¹ The majority of studies investigating muscle volume focus on the calf (triceps surae) muscle. The calf is commonly impaired in children with spastic-type CP and it is frequently the target muscle for intramuscular Botulinum toxin type-A (BoNT-A) injections to reduce spasticity and correct equinus gait in addition to surgical and conservative treatments^{124, 125}. It is an important muscle because it provides vertical support and forward propulsion during walking.¹²⁶ In ambulant children with spastic-type CP the volume of the impaired calf muscle is reduced by 22-57%^{121, 123, 124, 127, 128} compared to children with typical development with differences in calf muscle volume already present by the age of 2-5 years,¹¹⁹ (Figure 6A). The decline in force-generating capacity of the muscle throughout the range of motion of the ankle has been directly attributed to reduced muscle volume,¹²⁰ (Figure 6B). In addition, a higher intramuscular fat content translates to a reduced proportion of contractile tissue within the muscle, which also contributes to weakness.¹²²

Increased passive joint stiffness (non-neurally mediated) in subjects with upper motor neuron lesions has been attributed to shorter muscles and muscles with shorter fascicles,^{129,}

¹³⁰ (Figure 6C). However, conflicting findings of studies comparing fascicle length on the paretic side in individuals with spastic-type CP and in typically developing individuals have been reported, with some studies reporting reductions in fascicle length,^{131, 132} while others report no differences.^{133, 134} These studies of in vivo muscle architectural properties in spastic-type CP have primarily been confined to measurements of resting fascicle length/angle. These measurements are typically made at the resting joint angle, where muscle tension is assumed to be negligible, and so do not reveal information about muscle stiffness. In the only study to date investigating passive mechanical properties at the fascicle level, the medial gastrocnemius fascicle has a shorter slack length (fascicle length when torque exceeded 0 Nm of plantar flexor torque) and undergoes 47% less strain in spastic-type CP compared to controls at approximately equivalent passive ankle torques, suggesting that muscle fascicles have a greater resistance to passive stretch in spastic-type CP,¹¹⁹ (Figure 6B).

The Achilles tendon interacts with the triceps surae muscles and plays an important role in force transmission and energy storage and return during functional activities. Importantly, the length and compliance of the Achilles tendon can uncouple the length changes of the fascicles from that of the muscle–tendon unit, and thereby influence the force-generating capacity of the muscle¹³⁵. Examination of the gross tendon structure and function in individuals with spastic-type CP reveal that the Achilles tendon is longer, thinner, and contributes more to passive muscle-tendon lengthening, compared to typically developed peers¹³⁶⁻¹⁴⁰.

Alterations to the musculotendinous unit and neural control have direct implications for functional performance in ambulant individuals with spastic type CP. Altered muscle-tendon unit function during walking^{141, 142} contribute to reduced power generation during gait¹⁴³, which in turn diminishes anaerobic performance¹⁴⁴ in children with CP. Strength is

moderately associated with walking speed¹⁴⁵ and activity limitations⁵ suggesting that muscle adaptations in children with spastic-type CP plays a key role in difficulties with functional mobility in children with CP.

From a clinical perspective, the ability to estimate pre-treatment levels of muscle stiffness or contracture in an individual patient would enable quantifying the major muscular determinants underlying CP motor function. This would be precious information for predicting changes in muscle function following interventions such as intramuscular Botulinum toxin injections and surgery.

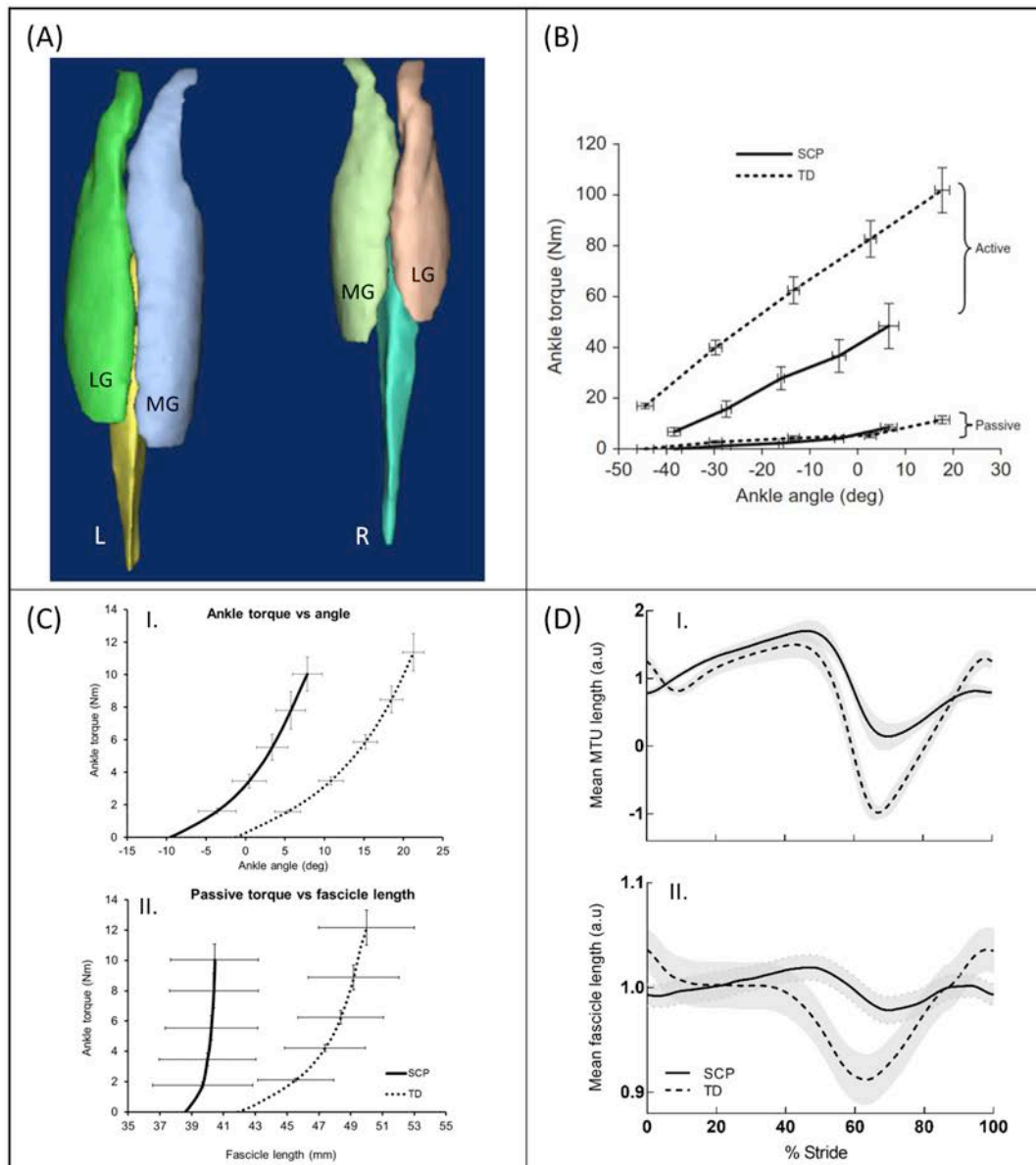


Figure 6. (A) MRI scan of both lower legs (L=left, R=right) of a child with spastic type cerebral palsy (SCP, right hemiplegia). Medial (MG) and lateral (LG) gastrocnemius muscles are segmented to measure muscle volume; (B) Active muscle properties, ankle torque versus angle, of individuals with SCP and typically developing (TD) peers (mean±SEM); (C) Passive muscle properties [I] ankle torque versus angle, [II] ankle torque versus MG fascicle length of individuals with SCP and TD peers (mean±SEM); (D) LG Muscle-tendon unit and fascicle functional during one stride of walking gait in individuals with CP and TD peers, 0% stride = initial foot contact

6B Reprinted from Journal of Biomechanics, 45(15): 2526-2530, Barber, L., Barrett, R., Lichtwark, G., Medial gastrocnemius muscle fascicle active torque-length and Achilles tendon properties in young adults with spastic cerebral palsy. Copyright (2012), with permission from Elsevier.

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6 Neural-based modeling control of locomotion

CP underlies disrupted function in the central nervous system. This needs to be first characterized and then incorporated in patient-specific MSK models to enable examining cause-effect relations with the resulting disrupted function at the musculoskeletal level.

Advances in neurophysiology are helping characterize the neural processing underlying human movement, i.e. the generation of synaptic inputs ultimately converging to pool of motor neurons and the transmission of the resulting neural drive to the innervated muscle fibers (Figure 7). The combination of a motor neuron and its innervated muscle fibers form a functional unit, called “the motor unit”, which operates for transducing neural inputs to mechanical muscle force^{146, 147}. Advances in electrophysiology are contributing to address the long-standing question of how the central nervous system handles the large number of movement degrees of freedom (DOFs). Increasing experimental evidence is demonstrating how specific motor unit action potentials are not the result of dedicated synaptic inputs sent to individual motor neurons, but the result of a common drive to a motor neuron pool to which individual innervated muscle fibers respond differently because of specific intrinsic properties¹⁴⁶. The concept of muscle synergies extrapolates to the macro-scale by supporting the existence of coordinative neural macrostructures, explicitly encoded in the central nervous system, that reduce the computational burden in the neural control of many fibers, from many muscles, during complex motor tasks¹⁴⁸ (Figure 7). Despite these advances, electro- and neuro-physiological analyses alone cannot explain the mechanical significance of the experimentally observed neuromuscular mechanisms¹⁴⁹.

Advances in gait analysis and MSK modeling are enabling understanding movement mechanics at the level of the underlying muscle forces, something central for investigating

how people solve for motor control in locomotion (Figure 7)¹⁵⁰. Current methods largely rely on optimization where muscles are recruited according to pre-defined criteria such as minimizing the sum of squared muscle activations, so that the emerging muscle-actuated movement tracks reference joint mechanics¹⁵¹, or shows agreement with joint mechanics normative values¹⁵², with additional control objectives such as minimal metabolic cost of transport¹⁵³. However, it is not possible to know *a priori* what the nervous system really optimizes. Therefore, the choice of one optimization criterion may substantially impact the computation of muscular and articular forces, thus biasing the final musculoskeletal analysis^{154, 155}. These approaches generate systematic and repeatable muscle force patterns that may be valid in specific conditions, but may not encompass an individual's neural repertoire, i.e. inability of synthesizing how neuromuscular patterns vary across subject-specific, context-dependent conditions including time, training, fatigue, pathology, motor tasks.

An alternative is that of building neural data-driven modeling formulations, i.e. formulations that use muscle electrophysiological recordings, rather than optimization, to solve for the muscle recruitment and force distribution problems (Figure 7)^{40, 147}. The idea is to use muscle electrophysiological recordings, such as electromyograms (EMG), in conjunction with advanced processing techniques to gain experimental access to neural information underlying an individual's motor function and pathology (Figure 8A). This enables deriving experimental estimates of subject-specific, context-dependent, and realistic neuromuscular strategies with no need to make *a-priori* assumptions on neuromuscular recruitment. This is especially valuable for estimating of pathology-dependent neuromuscular strategies with no need for creating complex numerical models of pathological neuromuscular function, which would be difficult to validate and therefore translate to the clinical level. Direct or indirect estimates of the neural drive to muscles will be termed as

“neural excitation”.

Following this rationale we have extracted neuromuscular features from surface EMG data including motor unit firing events^{19, 147} (Figure 8A), linear envelopes (Figure 9)^{147, 156} and muscle synergies (Figure 8B)¹⁵⁷. Linearly filtered envelopes enable demodulating the raw EMG and recover amplitude information proportionally to the neural drive received by individual muscles. However, the recovered amplitude may not necessarily be a direct reflection of motor unit spatial and temporal firing due to limitations that include electrode placement, detection volume, and motor unit action potential superposition¹⁴⁶. High-density EMG in conjunction with blind-source separation is now an established approach for discerning the interference EMG signal into the constituent motor unit activity and for resolving the inherent problem of motor unit action potential superposition (Figure 8A)¹⁴⁷. Synergies reflect low-dimensional, linear approximations of EMG statistical structure and distribution. They are derived using unsupervised machine learning methods such as non-negative matrix factorization¹⁵⁸ and enable capturing the elementary modules of multi-muscle co-excitation that are descriptive of a specific regime or motor condition, i.e. locomotion (Figure 8B).

EMG has been successfully used to derive excitations as a direct input to open-loop musculoskeletal models (Figure 7). These are predictive formulations where excitations directly drive muscle fibers and series elastic tendons, i.e. muscle-tendon units (MTUs). The forces produced by the EMG-driven MTUs are used to compute the resulting joint mechanical function blindly, i.e. with no tracking mechanism that accounts for prediction errors (Figure 7)^{40, 147, 156, 159}. This paradigm was applied to show for the first time that it is possible to achieve simultaneous, proportional, and accurate estimation of joint moments about six degrees of freedom in the human lower extremity as a direct function of EMG linear envelopes¹⁴⁷. The theory of muscle synergies¹⁴⁷ was then used to investigate to what

extent muscles are controlled individually or as part of a synergistic scheme, something central for understanding locomotion neural control. It was found that the excitations of 16 lower limb muscles recorded during four biomechanically different locomotion tasks could be well described by a shared lower-dimensional set of five excitation primitives (Figure 8B). Results showed, for the first time, that the five-dimensional primitive set not only reconstructed the experimental EMG data observed across all four motor tasks but also could be used to drive a large scale musculoskeletal model and reconstruct the resulting joint moments generated in six lower extremity DOFs with the same accuracy than when using 16 muscle EMG recordings. This provided further evidence that movement mechanical forces can be generated by neuromuscular strategies operating on a small number of excitation primitives^{157, 160}. More recently a robust basis of muscle primitives was derived and showed how this could be used to build predictive models of physiologically accurate muscle excitations across a large repertoire of unseen locomotion conditions¹⁶¹.

The open-loop formulation was then generalized into a closed-loop modeling formulation that accounts for excitation uncertainties that may contribute to bias the model-based joint dynamics estimates (Figure 9)¹⁵⁴. These include cross-talk, filtering artifacts and the inability of accessing deeply located muscles. For this purpose, the calibrated open-loop EMG-driven modeling formulation is coupled with a static optimization procedure. This allows extracting muscle excitations by balancing information from experimental EMG data and static optimization solutions. It was shown that a minimal adjustment of experimental EMG data (i.e. root mean squared error, RMSE < 5%), in conjunction with the static optimization solution for the hip flexing iliopsoas MTU, was sufficient to precisely track experimental multi-DOF joint moments during walking and running, with substantial improvement with respect to open-loop formulations¹⁵⁴.

6.1 Investigating movement neuro-mechanical interplay

The closed-loop formulation enabled the computation of muscle force solutions that reflect movement neural and mechanical levels precisely and simultaneously, i.e. muscle forces computed as a function of an individual's minimally adjusted EMGs, which concurrently satisfy experimental joint moments across all lower extremity DOFs (Figure 9)¹⁵⁴. This paradigm provides the basis to investigate the neuro-mechanical interplay in human locomotion, i.e. understanding the mechanical forces elicited by neuromuscular structures¹⁴⁹.

This opens up to the possibility of predicting a range of mechanical variables that are tightly dependent on neuromuscular mechanisms, difficult to synthesize, such as multi-muscle co-excitation¹⁶². Important co-excitation dependent mechanical variables include joint stiffness and joint contact force (Figure 7). Pure optimization-based methods alone can only reproduce some of the muscle co-excitation trends within selected locomotion conditions¹⁵⁴, thus limiting the subsequent ability of describing joint contact forces¹⁶³ and stiffness¹⁶⁴.

As a result, EMG-informed methods have consistently provided the best predictions of knee joint contact force across the majority of the Grand Knee Challenges past six editions^{165, 166}, the current gold standard for testing muscle force prediction methods. They recently, enabled characterizing the dynamics of complex joints such as the hip for which the major flexors (i.e. iliopsoas MTU) are deeply located and inaccessible via surface EMG with predictions validated at the level of *ex vivo* hip joint compressive loads¹⁶⁷. Importantly, EMG-informed modeling has just now enabled the derivation of dynamically consistent estimates of ankle and knee joint stiffness directly from the joint constituent muscle-tendon units as controlled by EMG-excitations¹⁶⁴.

6.2 Investigating disease processes

The proposed EMG-informed modeling approaches are especially advantageous when investigating neurological conditions like CP, where disrupted and altered neuromuscular function cannot be viably understood and synthesized into computational models. In this context, surface (or intramuscular) EMG has the advantage of providing a clinically viable solution for interfacing with the patient's nervous system *in vivo* and accessing neural information reflecting the specific neurological condition, as exemplified in Figure 8A. This is especially valuable for clinical interventions of limited duration, such as robot-aided rehabilitation¹⁹, where implanted nerve or cortical electrodes would be inapplicable^{168, 169}.

The ability of mixing excitations from EMGs and static optimization can account for patient-specific neuromuscular strategies and how they vary with time (Figure 9)¹⁵⁴. Current methods would have limited capacity in capturing non-physiological muscular behavior by means of an arbitrary objective function or basis of muscle synergies. Experimental EMGs could be recorded for target muscles that reflect the patient's non-physiological muscular behavior. These could be used to generate EMG-informed simulations that track patient-specific muscle recruitment strategies and joint dynamics, with patient-specific EMG-to-force relationships.

The ability to translate an individual's EMG activity into joint contact forces and stiffness is central to understand the neuro-mechanics of individuals affected by CP, where muscle contractures and crouched gait would result in both abnormal joint stiffness and contact forces¹⁷⁰. The ability of understanding cause-effect relationships between altered neuromuscular function (Figure 8A) and altered mechanical function (Figure 9) is central for delivering personalized rehabilitation treatments that restore physiological properties.

In this context, realistic, patient-specific estimates of co-activation dependent variables such as net joint stiffness and compressive loads are important biomarkers for quantifying CP neuro-mechanical determinants, in addition to those discussed in Sections 2 and 5. This would enable direct tracking of joint stiffness and joint loads discrepancies with respect to normative values observed from healthy individuals and would provide a reference for planning treatments such as muscle-tendon lengthening, tendon transfers or osteotomies.

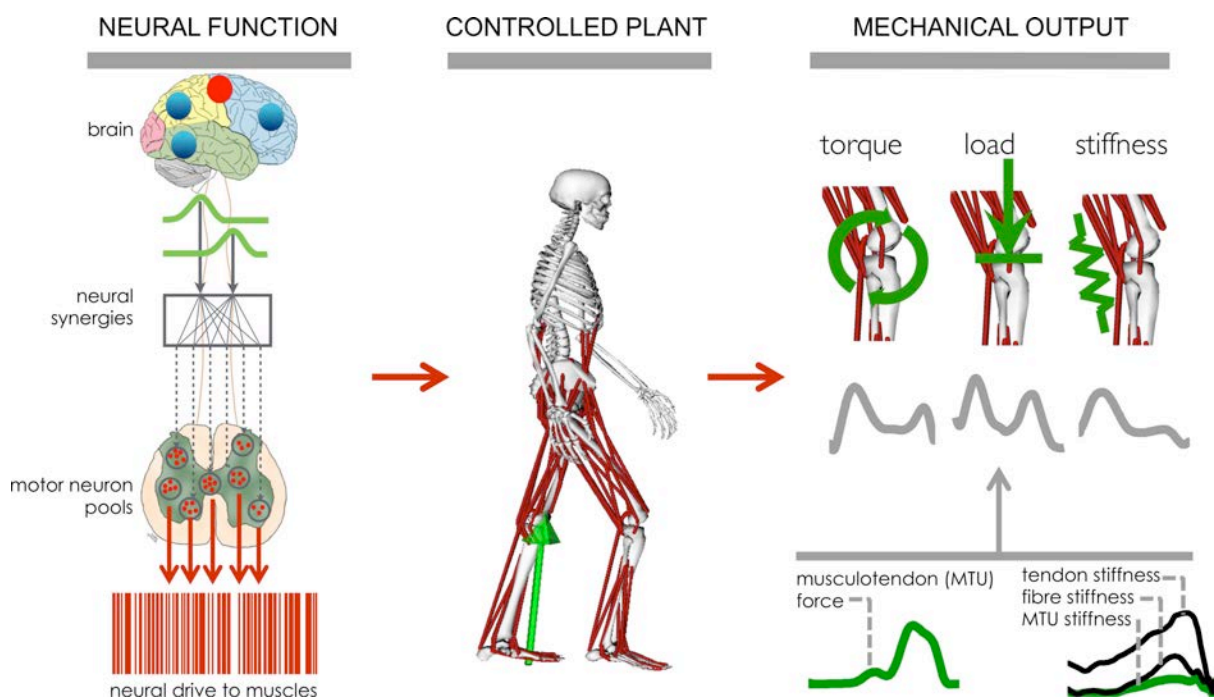


Figure 7: In the execution of a motor task, synaptic inputs are produced as a result of neural microstructures (i.e. neurons) as well as macrostructures reflecting the coordinated interaction between populations of motor, sensory and inter-neurons in the generation of rhythmic motor programs in the spinal cord (i.e. neural synergies). Synaptic inputs ultimately converge to pools of motor neurons, which integrate neural information and transform it into output spike trains (i.e. neural drive) sent to innervated muscles. Neurally controlled muscle-tendon units translate the neural drive into mechanical visco-elastic forces, thus causing articular and segmental body accelerations, multi-joint coordination and compliant body interaction with the environment.

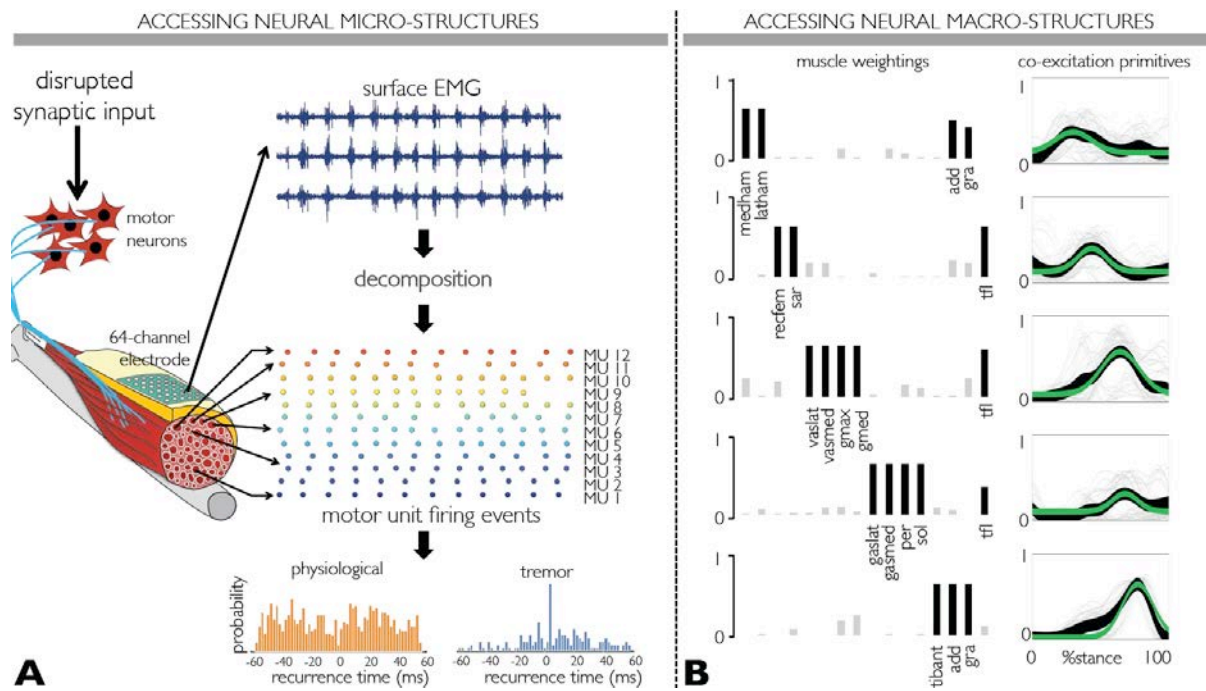


Figure 8: (A) High-density electromyograms (EMGs) are recorded from a tremor patient extensor carpi radialis during a resting task. EMG decomposition discerns the underlying motor unit firings, which corresponds to those produced by spinal motor neurons. In the tremor condition, motor units fire with an abnormally high level of synchronization i.e., see right-hand histogram depicting high probability for any two given motor units of firing within negligible time delays. (B) Five-dimensional synergy structure extracted from 16 lower limb muscles EMGs across four different locomotion tasks. The rhythmicity of the extracted primitives may reflect the dynamics of spinal pattern generators active during cyclic tasks. (A and B) Advanced recording and processing techniques give access to the function of neural microstructures (i.e. motor neurons) and macrostructures (i.e. muscle synergies) *in vivo* in the intact moving human.

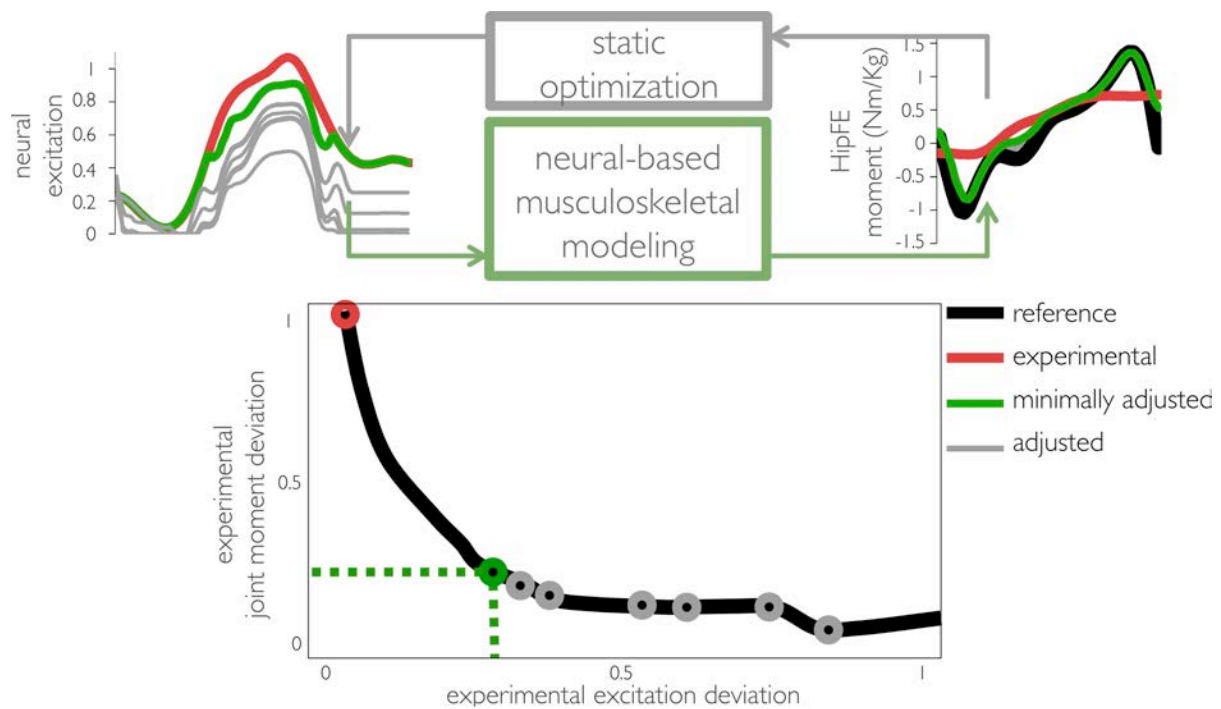


Figure 9: Closed-loop neural-based musculoskeletal modeling formulation. It comprises of two main components: the neural-based forward dynamics musculoskeletal model, and the static optimization component. Recording and modeling uncertainties typically limit forward dynamics prediction capacity. The static optimization component modulates the input excitations to account for forward dynamics prediction errors, i.e. see example gluteus maximus excitation and hip flexion-extension moment prediction error in this figure. In a subject-specific musculoskeletal model, the transfer function between the level of excitation adjustment and moment prediction error is L-shaped, i.e. all dynamically consistent neural solutions exist in a neighborhood of the experimental input data.

7 Challenges and future perspective

A current limitation of patient-specific models is that there is no standard methodology to produce muscle geometries. Mapping techniques from pre-existing atlases⁶⁴ and free form deformation methodologies^{63, 171} have been presented, but the lengthy processing times required currently makes them far from being clinically applicable. Definition of the muscles is also problematic with respect to musculotendon parameters, which are known to be altered for these clinical populations^{120, 172} and play a crucial role in the muscle force generating capacity. Methods relying both on anthropometric dimensions^{173, 174} and functional trials^{40, 175, 176} have been proposed to estimate the musculotendon parameters required to personalize

generic muscle models ¹⁷⁷, but currently none has been used and validated in applications with a CP clinical population.

First the bottlenecks of obtaining anatomical MSK structure from medical images and defining muscles' path and contraction parameters need to be solved. Once done, it will be possible to routinely apply consistent neuromusculoskeletal and finite element models, built from the same patient-specific bone and muscle geometries, to assess MSK tissue loading conditions calculated by the multi-body simulations and applied to equivalent continuous bone models ^{167, 178}. Biofidelic muscle lines of action ¹⁷⁹, joint reaction forces ^{35, 180} and external forces (inertia and gravity) will be included in the FE simulations, allowing one to investigate tissue loading over multiple tasks and loading conditions previously simulated using musculoskeletal models ^{178, 181, 182}.

While many statistical models have characterized the bones and muscles of healthy populations, building the initial training set is a major challenge for CP populations. Statistical models trained on healthy populations cannot adequately approximate CP-deformed anatomies for accurate model generation. The paucity of data is partly due to the typically young age of patients, which restricts the use of ionizing X-ray CT imaging, particularly around the hip joint; and patient discomfort that restricts time-consuming magnetic resonance imaging. Nevertheless, the collection of large datasets of CP musculoskeletal geometry is essential, and possible through data-sharing initiatives such as the MAP.

Beyond driving the model creation process, a major potential for statistical models is in the classification of CP. Dimension reduction on combined data of bone shape, muscle shape, muscle activation patterns, and functional metrics may identify clusters of CP phenotypes. Computational modelling can determine the optimal therapy for each cluster. A new patient can then be classified based on the cluster they fall within and treated

accordingly. An interesting question will be how well these clusters match current CP classification and treatment strategies. Given the number of anatomical and functional measurements possible and the great degree of variation, data-driven methods offer the best chance to make the best use of clinical data for diagnosis and treatment planning.

The presented MSK modeling methods, based on imaging techniques, population based approaches and continuum muscle descriptions, have the potential of providing high-fidelity patient-specific formulations describing pathological features of muscles and bone structures accurately. However, the associated large computational requirements and challenges in validating resulting predictions may represent additional factors limiting the effective translation to clinical setting. In this scenario, high-fidelity formulations could be synthesized into simpler, surrogate models that describe the complex musculoskeletal structures using computationally efficient structures such as multidimensional splines¹⁵⁹, regressive polynomials¹⁸³ or artificial neural networks¹⁸⁴. These could be coupled with neural based and EMG informed modeling and create fully personalized, clinically viable formulations, which capture neurophysiological, anatomical and morphological abnormalities altogether.

The development of patient-specific neuromusculoskeletal modeling pipelines is central for understanding how neurally controlled muscles elicit joint mechanical function (i.e. rotational, contact and visco-elastic forces) at any particular instant in time. This would fill the gap between current formulations modeling either the neural or the mechanical processes underlying pathological movement^{16, 17, 19} and would provide new means for explaining movement function, pathology and recovery. The translation of neuro-musculoskeletal modeling pipelines to the clinical level is a promising avenue for deriving a new class of biomarkers that directly correlate to a patient's impairment and subsequent recovery. This would complement current assessment techniques based on clinical scales (i.e. Fugl-

Meyer), which often rely on subjective judgment¹⁴ and on indirect estimates of neuromuscular function. Although EMG-informed modeling enables simulations reflecting both movement neural and mechanical levels, the thorough validation of complex pipelines such as the one introduced in this paper is a major challenge for wider adoption and impact in the health care sector. The challenge is to assure that modeling advancements are followed by direct experimental observations of the simulated mechanisms¹⁷⁰. With complex models being capable of predicting a wide range of musculoskeletal variable there is the need for increasingly more sophisticated experimental techniques for measuring validation data.

The integration of neuromusculoskeletal modeling pipelines in future rehabilitation processes will help objectively reveal how neurological patients can (re)learn and execute large repertoires of motor tasks with direct implications in the development of personalized neurorehabilitation treatments and technologies.

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