In Silico Biomarkers of Motor Function to Inform Musculoskeletal Rehabilitation and Orthopedic Treatment

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In this review, we elaborate on how musculoskeletal (MSK) modeling combined with dynamic movement simulation is gradually evolving from a research tool to a promising in silico tool to assist medical doctors and physical therapists in decision making by providing parameters relating to dynamic MSK function and loading. This review primarily focuses on our own and related work to illustrate the framework and the interpretation of MSK model-based parameters in patients with 3 different conditions, that is, degenerative joint disease, cerebral palsy, and adult spinal deformities. By selecting these 3 clinical applications, we also aim to demonstrate the differing levels of clinical readiness of the different simulation frameworks introducing in silico model-based biomarkers of motor function to inform MSK rehabilitation and treatment, with the application for adult spinal deformities being the most recent of the 3. Based on these applications, barriers to clinical integration and positioning of these in silico technologies within standard clinical practice are discussed in the light of specific challenges related to model assumptions, required level of complexity and personalization, and clinical implementation.

Keywords: modeling, simulation, osteoarthritis, cerebral palsy, adult spine deformities

Traditionally, clinical musculoskeletal (MSK) treatment pathways are based on static and often 2-dimensional medical imaging that merely evaluates geometrical features of bone, articular cartilage, and soft tissues. Rarely, functional imaging modalities are used in clinical practice—with the exception of standing radiographs to evaluate joint space narrowing in degenerative joint diseases (ie, osteoarthritis [OA]). Although dual-plane radiographs, dynamic computed tomography, and magnetic resonance imaging (MRI) have been explored in a research context, they have not yet been translated to routine care.

Integrated 3-dimensional (3D) motion analysis—combining camera-based systems, force plates, and surface electromyography—was first applied in research settings as a comprehensive means to understand the biomechanics of human locomotion in terms of joint angles (kinematics), joint moments (kinetics), and muscle activation.

Contrary to dynamic imaging, the use of 3D motion capture has made its way from the research lab into clinics in the early 1990s. In particular, for the study of cerebral palsy (CP), a neuromotor impairment following an oxygen deficit around birth, motion analysis has become well accepted for the clinical decision making and treatment planning of orthopedic interventions.1,2 Given the motor dysfunction complexity—with gait deviations occurring at different joints and different movement planes—the ability to provide objective information on gait kinematics and kinetics as well as muscle activation has helped clinicians to improve gait function in children with CP and decide on complex treatments—such as single-event multilevel surgery, that is, combining multiple soft-tissue and bone corrections in one surgical procedure.3-7 Furthermore, 3D motion capture provides an objective proof of treatment outcome and allows longitudinal follow-up in terms of gait function.6

Treatment goals for CP are often formulated not only in terms of normalizing gait kinematics but also in terms of normalizing MSK loading, muscle function, and even in terms of preventing the occurrence of secondary MSK disorders (ie, muscle contracture, bony deformities, or joint instability). It is, however, not a small incremental step to progress from observing lower leg movement and joint function, as described by 3D motion capture data, to the anticipated impact of therapeutic interventions on movement characteristics and consequent MSK loading, as is becoming increasingly possible with MSK modeling and predictive modeling approaches.

Ideally, such a clinical decision support system would offer a platform that accounts for patient-specific MSK deformity (informed by functional imaging), soft-tissue dysfunction, and muscle weakness (informed by functional tests) as well as central or peripheral neuromuscular impairments informed by electromyography. Furthermore, it would provide parameters that cannot be directly measured (herein referred to as MSK model-based parameters) linked to specific aspects of motor dysfunction, such as muscle force production, muscle–tendon excursion, or joint contact forces during functional activities. Finally, it would allow clinicians to explore the impact of specific impairments or interventions to the observed gait pattern—thereby exploring “what-if” scenarios.

In other populations requiring orthopedic interventions, for example, patients with OA or patients with complex spinal deformities, presurgical and postsurgical 3D motion capture is not integrated in the typical orthopedic care pathway. However, the use of an integrative framework combining information on clinical status, movement characteristics, skeletal deformities, and muscle weakness has already been integrated to different extents in a
research context. Such approaches have been used to evaluate the impact of (implantable) medical devices on motor function and MSK loading and are now already included by orthopedic companies as part of the (pre)clinical device testing.

Despite differences between the clinical populations presented as examples earlier, they share common questions related to the behavior of the MSK system during dynamic movements in the context of optimizing treatment strategies. Specifically, what is the dynamic behavior of muscle–tendon structures in terms of length changes and force production? How does this relate to loading of the MSK system? To what extent do interventions targeting dynamic behavior of the MSK structures induce normalization of movement and MSK loading? Answering these questions requires access to variables related to dynamic MSK function that cannot be measured noninvasively.

MSK modeling workflows combine integrated 3D motion capture data with MSK models and dynamic simulations of motion, thereby using physics-based evaluation to estimate in silico model-based parameters related to MSK function and loading. MSK models describe bone and muscle geometry as well as the degrees of freedom (ie, permitted motions) of the joints. In the case of orthopedic deformities, medical images can be used to personalize the level of deformity in terms of both MSK geometry and/or alignment (eg, femoral anteverision or spinal deformities). Combining such personalized models with 3D motion capture data, inverse dynamic analysis, and muscle force distribution algorithms allows calculation of MSK loading in terms of the muscle forces and joint contact forces underlying the movement pattern. Furthermore, to analyze the impact of altered neural control strategies on movement dysfunction, or to predict altered movement characteristics after interventions (eg, muscle strengthening or muscle–tendon transfer), forward (ie, predictive) simulation workflows are now becoming more readily available for transfer into the clinical care pathways. (Figure 1).

In the remainder of this review, we will discuss how the framework of MSK modeling combined with dynamic movement simulation is gradually evolving from a research tool to a promising in silico tool to assist medical doctors and physical therapists in their decision making and ambition to improve MSK function (Figure 2). Note that when we refer to “MSK modeling combined with dynamic movement simulations,” we are referring to the ability of MSK modeling to estimate parameters that cannot be estimated using motion capture data alone. This review is by no means comprehensive, nor systematic, but primarily based on our own and related work to illustrate the framework and the interpretation of MSK model-based parameters in patients with degenerative joint disease (OA), CP, and adult spinal deformities (ASD) to the broader MSK modeling and simulation community. By selecting these 3 clinical applications, we also aim to demonstrate the differences in levels of clinical readiness of the different model-based simulation frameworks in introducing in silico (model-based) biomarkers of motor function to inform MSK rehabilitation and orthopedic treatment, with the application for ASD being the most recent of the 3 (Figure 2).

**Model-Based Analysis of Motor Dysfunction in Patients With Degenerative Joint Disease**

OA is a multifactorial condition affecting the entire joint, in particular inducing articular cartilage degeneration and leading to joint pain and reduced mobility. In individuals suffering from primary OA, that is, in the absence of previous trauma, alterations in articular contact loading (ie, magnitude and location of joint contact forces and pressures) are not well documented longitudinally. Nevertheless, altered mechanical loading is implicated as one of the contributing factors—with overloading typically being suggested as a key driver. MSK-based parameters, and in particular joint contact forces, attracted attention as model-based biomarkers as they are closely related to the mechanical joint environment. In the following paragraphs, we will demonstrate how these model-based parameters (ie, parameters that cannot be assessed without the use of MSK modeling) have been used to identify functional biomarkers for identifying risk factors for OA development and progression as well as for identifying effective surgical and physical therapy-based treatment strategies targeting joint loading modifications.

There is an unmet clinical need to identify patients with early knee OA that are at risk of accelerated disease progression. Particularly, given that disease-modifying drugs and targeted rehabilitation strategies are becoming available, it is of utmost importance to prepare for functional screening to identify early disease processes, even before radiographic evidence is present. Often suggested functional biomarkers, such as the knee adduction moment, have been shown to only be sensitive discriminators in end-stage knee OA, thereby missing the crucial window of opportunity in preventing progression from early to end-stage knee OA. Likewise, standard rigid-body MSK modeling (ie, without modeling cartilage-on-collagen contact mechanics) confirmed total resultant knee contact force to be only significantly different in end-stage OA subjects (Kellgren-Lawrence [KL] Classification of Osteoarthritis score 3–5), but not in early OA patients with limited radiographic structural changes (KL score max 1), suggesting mechanical knee overloading is only implicated following structural degenerative changes. However, complex MSK model-based parameters (ie, models accounting for cartilage-on-collagen contact mechanics and interaction and ligament balance) confirm an already increased medial compartment knee joint loading in early OA subjects, with a more lateral and posterior location. This evidence from cross-sectional data shows the potential gain in sensitivity offered by complex MSK model-based functional biomarkers in identifying early knee OA. To establish evidence that model-based functional biomarkers are also sensitive for accelerated medial knee OA progression, longitudinal studies are required. To this end, a recent post hoc analysis of a prospective cohort study followed patients with medial knee OA over a 2-year period and categorized them as progressing or nonprogressing, using KL scores to assess structural knee OA severity. Elevated medial and lateral knee joint contact pressure and a more posterior–lateral location of the loading area were observed in progressing compared with nonprogressing groups. Furthermore, similar evidence has been shown using rigid-body MSK models whereby resultant total joint contact forces were identified as discriminatory between progressing and nonprogressing (in terms of joint space narrowing) patient groups. Such MSK model-based functional biomarkers (derived from complex MSK models), thus, have clear potential to serve as a screening tool whereby patients could be identified not only as having early OA before structural progression (informed by emerging and previous cross-sectional studies) but also as being at risk of accelerated progression due to a further elevated knee joint loading magnitude and shifted loading location.

Interestingly, MSK model-based parameters suggest different OA pathomechanics in terms of joint loading for the hip and knee. In contrast to knee OA patients, subjects with end-stage hip OA
exhibit reduced external hip adduction and hip power generation during the stance phase of gait compared with controls. This results in reduced and more vertically inclined hip joint contact forces. These findings suggest that hip joint underloading contributes to hip OA disease progression rather than overloading, as seen in knee OA. Further discrepancies in the joint loading profile of end-stage hip OA compared with end-stage knee OA subjects become evident when evaluating joint loading during other activities of daily living. Indeed, movement adaptations induced overloading of the ipsilateral hip and contralateral hip and knee in patients with knee OA during stair ambulation. These changes in loading at nonprimary OA joints increase the risk of secondary OA, as illustrated by the aforementioned knee and hip OA functional biomarkers for OA onset and progression.

MSK model-based parameters also allow the exploration of assumed associations between aberrant joint loading and risk

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**Figure 1** — Identified biomarkers derived from MSK modeling and simulations for degenerative joint disease (osteoarthritis), CP, and ASD, the three conditions discussed in this article. The required input data and required level of model personalization for this model-based analysis are also illustrated. ASD indicates adult spinal deformity; CP, cerebral palsy; MSK, musculoskeletal; 3D, 3-dimensional.
factors for OA development and progression. The most important injury risk factor for knee OA development is an anterior cruciate ligament rupture as the rates of OA development exceed by far those in a typical cohort. In contrast to primary knee OA patients, anterior cruciate ligament rupture subjects typically show a reduced joint loading magnitude compared with a healthy cohort. This suggests that in the anterior cruciate ligament rupture cohort, the pathomechanics of OA development seem to be affected by unloading upon initial injury and associated inflammation. Altered joint alignment has also been identified as a risk factor for knee OA development, with dynamic varus malalignment predisposing more to increased knee joint loading magnitude than static frontal plane varus alignment. Indeed, knee frontal plane alignment is often considered for correction by high tibial osteotomy with the use of corrective physiotherapy and bracing. Additional work investigated muscle weakness as a risk factor contributing to OA progression using MSK-based parameters. By reducing the maximal force-producing capacity of numerous hip abductor muscles in MSK dynamic simulations, the effect of muscle weakness on both hip and knee loading was evaluated. Interestingly, dependent on the muscle weakness present, either an increased or decreased hip joint loading was observed. Conversely, weakening of any of the hip muscles always resulted in increased knee joint loading. Therefore, hip muscle strengthening exercise programs may have a role in preventing secondary increase in knee joint loading in knee OA patients. As such, through MSK modeling workflows, clinically identified risk factors for OA could be related to alterations in joint loading, and specific MSK model-based functional biomarkers were identified associated with an increased risk of OA and with a confirmed role in OA joint pathomechanics.

MSK modeling workflows have been used to assess outcomes of numerous surgical techniques for patients with degenerative joint diseases. By modeling the effect of high tibial osteotomy, the effectiveness of high tibial osteotomy in reducing medial compartment knee joint loading, and, by extension, potential risk of knee joint OA development, was illustrated. Likewise, following total hip replacement, joint loading magnitude at the hip and knee during gait remained reduced compared with controls, even up to 12 months after hip replacement. Despite this underloading, the preoperative loading asymmetry between operated and unoperated sides normalized postsurgery, with loading symmetry recovering earlier at the hip than at the knee.

Finally, MSK model-based parameters can also assist in defining “in silico-informed” rehabilitation interventions to progressively load MSK structures. By comparing medial–lateral knee contact force distribution and muscle forces of the knee extensor muscles during regularly performed rehabilitation exercises, rehabilitation plans were defined to allow progressive loading of the extensor muscles but unloading of the medial knee compartment, thereby identifying squatting as a more suitable targeted exercise for medial OA patients versus stair negotiation for lateral knee OA patients. Furthermore, targets for gait retraining to gradually increase loading or to effectively unload the involved joint have been defined for subjects with knee and hip OA as well as gait strategies that may reduce edge loading of the prosthetic cup, which is considered a risk factor for prosthesis failure following hip replacement surgery.

Model-Based Analysis of Motor Dysfunction in Patients With CP

Treatment selection in CP is hard due to the complex interaction between MSK and motor control impairments. Dynamic simulations of gait based on personalized MSK models that account for a patient’s neuro-MSK constraints are a useful tool to understand how the complex impairments associated with CP affect MSK loading and movement patterns. CP results from a nonprogressive lesion in the immature brain impairing motor control. The resulting inability to selectively control muscles, spasticity or hyperreflexia, and muscle weakness limit the child’s ability to walk. Over time, due to the persisting alterations in gait pattern, secondary MSK impairments like bony deformities and muscle contractures develop, which further undermine the child’s mobility. Treatments aim at improving (gait) function and preventing or correcting secondary impairments. Botulinum toxin (BTX-A) is often administered to manage spasticity, whereas single-event multilevel surgery is common to treat MSK impairments. Yet, treatment outcomes are variable, possibly due to the large heterogeneity in impairments and the limited ability

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to determine the origins of observed movement deficits. In the remainder of this section, we will illustrate from our work how we use neuro-MSK modeling and simulation to gradually impact clinical decision making by enhancing our mechanistic understanding of movement impairments, assessing the effect of treatment on MSK function, and elucidating the relationship between neural and nonneural impairments and functional deficits, with the aim to finally predict treatment outcome.

We used neuro-MSK simulations to test a novel hypothesis about the mechanisms underlying joint hyperresistance, the most common symptom in CP (85% of the patients) and an important treatment target. Joint hyperresistance is attributed to both neural factors, that is, background muscle activity and stretch hyperreflexia, and nonneural factors, that is, passive tissue properties, but these cannot be differentiated experimentally in a clinical setting. Using neuro-MSK simulations, the contribution of neural and nonneural factors can be elucidated by modeling their impact on joint movement and muscle activity during clinical spasticity measurements, such as the pendulum test. Previous research that modeled reflex activity proportional to muscle fiber length and velocity, based on the textbook vision that muscle spindles sense fiber length and velocity, could not explain joint movement and muscle activity during clinical tests of spasticity.

Inspired by recent animal experiments, we proposed a novel model in which reflex activity is modeled proportional to muscle force and derivative of force, that is, yank rather than muscle length and velocity. Furthermore, by modeling movement history-dependent muscle force, that is, short-range stiffness, we captured the interaction between muscle activity—driven by muscle force through the muscle spindle—and background muscle activity. This novel neuro-MSK model was able to overcome the limitations of previous models and captured joint movement observed during clinical spasticity tests, in particular the pendulum test and muscle activity observed during passive joint rotations. Furthermore, our novel model also led to a novel testable hypothesis. If reflex hyperexcitability, indeed, interacts with background muscle activity through movement-dependent short-range stiffness in the muscle, prior joint movement should normalize the response to stretch; that is, indeed, what we found in a follow-up experimental study in children with CP. When we moved the lower leg up and down instead of keeping it still before dropping it from the horizontal position in a relaxed patient during the pendulum test, the pendulum movement of the lower leg was closer to healthy controls. This novel mechanistic insight is important to clarify the role of spasticity in functional movements, which is still poorly understood, and to distinguish different causes of joint hyperresistance, which is important for treatment selection.

MSK modeling allows evaluating the effect of different treatment approaches on MSK loading. Only limited differences in calculated muscle forces before and after BTX-A were seen in children with diplegic CP. Indeed, compared with the limited effects of BTX-A, single-event multilevel surgery not only induced significant changes in both joint kinematics and kinetics but also improved muscle and joint contact forces. Likewise, selective dorsal rhizotomy, a neuurosurgical procedure to alleviate muscle hyperreflexia at spinal level, improved joint kinematics and kinetics as well as muscle forces in children with diplegic CP. To further, studied the potential impact of deviant gait kinematics and interventions on femoral growth in patients with CP with different gait patterns. To this aim, we combined MSK simulations to estimate hip contact forces with a finite element model of bone growth. Importantly, frontal plane pelvic and hip kinematics, suggestive of a trendelenburg gait with ipsilateral upward tilt of the pelvis and hip abduction, were found to be the main determinants initiating pathological femoral anteversion in the model. BTX-A only normalized joint loading and bone growth in the child with apparent equinus. To summarize, MSK modeling can provide insight into how treatment affects MSK loading, an important driver of MSK impairments.

An important benefit of MSK model-based simulations is that they allow study of the influence of isolated neuro-MSK features by adjusting the related model parameters. This allowed us to study the interaction between hip geometry and gait kinematics, both of which are altered in CP. In the presence of aberrant hip geometry, a healthy gait pattern leads to higher hip contact forces than the patient’s gait pattern. When walking in crouch, a common gait pattern in CP, increased femoral anteversion and neck-shaft angle increased the potential of the glutei to extend the hip by increasing the muscle’s lever arm in the sagittal plane. To study the effect of impairments on the movement pattern (rather than on loading), forward or predictive simulations that do not require measured movement patterns as input can be used. We performed a series of simulations to evaluate the differential effects of altered muscle properties, spasticity, and reduced selective control. We found that, in the presence of aberrant MSK anatomy, altered muscle–tendon properties rather than motor control impairment caused crouch gait in the patient under investigation. In agreement with our simulations, treating the MSK impairments improved the gait pattern of this child, and no additional neural interventions were needed.

Simulations have the potential to improve clinical decision making by allowing us to test the influence of different treatment scenarios on MSK loading or the gait pattern. We recently developed a computational tool to perform virtual surgeries on an MSK model. By combining this tool with predictive simulations, we can evaluate the effect of surgery in silico, allowing the surgeon to test “what-if” questions. Our initial evaluation in 2 case studies shows the potential of such an approach but also highlights the need for additional efforts to improve model personalization.

**Model-Based Analysis of Motor Dysfunction in Patients With Adult Spinal Dysfunction**

ASD is a degenerative disease of the spine that results in a wide range of 3D spinal malalignments. This progressive condition mostly affects older adults, with a reported prevalence of up to 36% in adults older than 60 years and further increasing due to the aging population. ASD is characterized by a heterogeneous clinical presentation, including symptoms such as axial back and/or leg pain, walking and balance impairments, and increased risk of falls, resulting in severely decreased participation in daily life activities. Multilevel spinal fusion surgical treatments involving spinal instrumentation to structurally realign the progressively deforming spine are increasingly used, with 44% of patients eventually being referred to surgery. Currently, surgical decision making to select the appropriate fusion levels and the choice of spinal instrumentation is predominantly based on radiographic 2-dimensional parameters of the global static spinal alignment in an upright position. This approach lacks standardized guidelines and is highly subjective and biased by personal
experience of surgeons, \textsuperscript{55} inevitably leading to high complication (69.8\%) \textsuperscript{66} and revision (9\%–35.6\%) rates. \textsuperscript{67,68} In addition, postoperative patient-reported outcomes for ASD patients are often poor, primarily due to a lack of improvement, or even worsening, in functional impairments 6 months after multilevel spinal fusion, measured by a reliable and validated clinical scale (the Function Assessment Scale for Spinal Deformity). \textsuperscript{69} To date, there is international consensus that a shift from only measuring 2-dimensional static spinal alignment toward more 3D dynamic functional assessments is needed, requiring the introduction of 3D motion analysis and, ultimately, the combination with subject-specific MSK model-based dynamic simulation. In the following section, we will present work from our group showcasing how these methods have the potential to improve postoperative outcomes and the quality of life of patients by providing objective measurements of the dynamic functional abilities of the preoperative and postoperative patient and by increasing our understanding of the impact of ASD functional decline and support surgical decision making.

Combining complex MSK models with movement-related data from 3D motion capture allowed our group to upgrade the patient profiling currently used for surgical decision making by assessing the impact of ASD on spinopelvic and whole-body kinematics. More specifically, this approach allowed investigation of the effect of improved postoperative spinal alignment following spinal fusion surgery on spinopelvic kinematics and the consequent effect on postoperative functional abilities of patients. Therefore, our group developed and validated the first ASD-specific marker-based motion analysis method. \textsuperscript{70} This kinematic method corrects positions of skin markers with respect to their true anatomical position while taking into account subject-specific spinal deformities. This approach allows for accurate measurement of spinopelvic motion during various activities of daily living. As a result, we identified aberrant ASD-specific spinopelvic strategies during walking \textsuperscript{(Ahead of Print)} and sit-to-stand-to-sit, \textsuperscript{72} 2 functional tasks especially challenging for the spinopelvic complex in this population. Patients with sagittal spinal deformities presented increased trunk tilt and pelvic anteverision during walking but decreased lumbar lordosis and increased trunk inclination during sit-to-stand-to-sit. Interestingly, patients presenting only coronal deformities showed no differences in spinopelvic motion strategy compared with healthy controls. Likewise, patients with sagittal malalignment showed altered lower limb gait patterns to compensate for the aberrant ASD-specific spinopelvic movement strategies. These findings indicate that sagittal spinal malalignment is associated with more functional deterioration than coronal malalignment. In addition, we found that surgical treatments for the spinal deformities did not lead to gait improvements, indicating that further research on the underlying mechanisms for these kinematic differences is needed to improve our understanding of how ASD and its associated surgical treatment impact function for patients preoperatively and postoperatively.

Given the complex bony geometrical deformities in patients with ASD, patient-specific MSK models of the spine are a prerequisite for reliably estimating the spinal kinematics based on the 3D motion capture data collected during dynamic motions. These need to include personalized vertebral geometry as well as joint definitions to adequately relate the skin-marker motion to the relative movement of different individual vertebrae or even spinal segments. To this end, subject-specific spinopelvic bone geometries obtained from computed tomography images are integrated with personalized 3D weight-bearing spinal alignment based on upright biplanar radiography (EOS). Combining these patient-specific, complex MSK models with biomechanical assessment of posture allowed our group to upgrade the patient profiling currently used for surgical decision making based on insights on the impact of 3D spinal alignment and balance control. A novel instrumented 3D spinal parameter, the Transverse Gravitational Deviation Index, was proposed. \textsuperscript{73} This parameter quantifies the transverse plane position of any vertebra with respect to the gravity line, using full-body biplanar radiographic images (EOS) combined with the center-of-pressure movement during stance as measured by a force platform. This spinal parameter evaluates dynamic balance control while integrating measurement of spinal alignment to identify any compensation strategies associated with impaired balance control of ASD patients. This parameter can be used to help identify good candidates for surgical treatments, especially patients with combined coronal and sagittal spinal malalignments as they are typically more at risk for impaired balance performance and, thus, more at risk of suboptimal surgical outcomes associated with a decreased quality of life.

Building on these previous kinematic findings, our group is currently developing and validating a novel state-of-the-art modeling and simulation workflow to increase our understanding of the impact of ASD on function and elucidate the underlying mechanisms for the observed movement patterns during functional tasks, including evaluation of impaired neuromuscular control and muscle weakness. This additionally requires integration of patient-specific muscle force-generating capacity and muscle geometry (based on MRI) as well as an individualized representation of the complex nonlinear stiffness of intervertebral joints as recently piloted in healthy controls. \textsuperscript{74} Indeed, these parameters have an important impact on joint motion, muscle force distribution, and consequent joint loading in patients with ASD.

In combination with dynamic simulations of motion, these developments will—in future clinical research studies—allow unraveling of the 3D biomechanical fingerprint of patients with ASD during dynamic and functional assessments, thereby providing much-needed functional biomarkers, including joint loading and muscle recruitment pattern, which are not feasible to measure in vivo but which provide objective insights needed to improve current surgical decision making by assisting in patient stratification for specific surgeries and to develop targeted rehabilitation programs to improve postoperative outcomes.

**Discussion**

Within this review, we presented MSK modeling combined with dynamic movement simulation as an integrated framework in transition from a pure research tool to a promising clinical decision support tool to assist medical doctors and physical therapists to improve MSK function in numerous patient populations. Based on the selected clinical applications, we showcased proof-of-concept use of in silico biomarkers (eg, joint loading and muscle–tendon shortening) that relate to the origin and nature of MSK dysfunction during relevant locomotor activities. The integration of relevant patient-specific factors in this in silico framework (eg, altered movement patterns, muscle weakness, and presence of bony deformity) is a prerequisite in documenting biomechanical factors underlying MSK conditions and their role in functional decline. As such, the potential of the integrated in silico framework for contributing to clinical needs, such as early identification of disease, more in-depth patient assessment, and more informed treatment pathways, has been confirmed (Figure 1). Finally, the
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ultimate ambition for using such a framework for addressing “what-if scenarios” to predict locomotor function is becoming increasingly feasible but is clearly still less well developed and tested on “real-life” clinical cases. Nevertheless, the realization of such predictive simulation frameworks with accurate modeling of the impact of therapeutic interventions on the patient-specific MSK system would address a highly relevant clinical need given its relevance in numerous patient-specific treatment choices to improve locomotor function.

However, the authors acknowledge that it is fair to recognize that, despite the potential in clinical research studies described earlier, actual clinical implementation and—by extension—impact remain low. Whereas high computational, mathematical, and technological complexity of dynamic simulations might have for long limited transfer to nonengineering users, the development of dedicated and more accessible simulation environments, independent from large high-performance computing services and infrastructure, should—at least in theory—have addressed this barrier. Based on our aforementioned experiences, the authors of this review would like to discuss the barriers to clinical integration and positioning of these in silico technologies within standard clinical care paths in the light of 4 specific challenges.

The first challenge relates to the assumptions made when modeling the structures and processes that underlie healthy and pathological locomotor function. Indeed, the validity of the modeling approaches to represent specific MSK structures and control processes underlying locomotion is only documented to a limited extent. Even in some of the more current models, their validity remains totally undocumented, let alone that they adequately represent the pathological conditions studied. This inherently limits the fidelity of MSK model-based parameters as clinical biomarkers representative of clinical outcomes. We see 3 major gaps. First, the representation of muscles in MSK models is very simple. Three-dimensional muscle structures are represented by line segments, which might affect moment arm estimations and, thereby, muscle and contact force estimations. Muscle mechanics are commonly described by phenomenological muscle models that do not capture the underlying physical processes that are important, for example, to understand the response of muscles to stretch when assessing spasticity. Second, whereas MSK models are powerful tools to capture the relation between movement patterns and joint loading, models that relate joint loading to tissue adaptation are less well established but needed to predict disease progression. Third, predicting movement patterns requires a model of both the MSK system and motor control. Yet, most movement simulations combine relatively detailed models of the MSK system with simple assumptions about motor control; for example, humans move in a way that minimizes effort. The neural pathways underlying motor control are not explicitly modeled, hindering our ability to, for example, accurately capture the motor control deficits in CP. Tracking the measured electromyography can be used to partially address this issue in inverse simulations, but data-independent forward (predictive) simulations need a better model of the neural system to accurately simulate motor control deficits in CP. Continued fundamental research in motor control, as well as in mechanobiology, is needed to experimentally describe these processes and how they are affected by pathology or treatment to inform future generations of MSK and neuro-MSK models.

The second challenge relates to determining model complexity and level of personalization to capture clinical outcomes. It is often unclear what level of MSK model complexity and personalization is needed to accurately represent the clinical condition and, therefore, capture a specific clinical outcome. This is important as more complex models typically require higher processing times, have more parameters, and require higher levels of personalization based on more extensive input data that are often hard to obtain. Indeed, many of the clinical applications we presented in this review require nonstandard-of-care data that are hard to obtain, which might induce longer experimental protocols, in turn placing an additional burden on patients and/or additional costs in an already challenged health-economic environment. For example, creating detailed models of bone, cartilage, and muscle geometry might require medical imaging modalities such as MRI, which are not part of the current clinical practice. To mediate this challenge, sensitivity analyses can help to elucidate how model-based biomarkers or outcome predictions are influenced by model complexity and the level of personalization. Importantly, they also offer a way to quantify the uncertainty on modeling outcomes due to unknown patient features. In addition, statistical or machine learning-based methods are increasingly becoming available to allow us to estimate model parameters based on standard-of-care data or data that can be more easily collected; for example, statistical shape modeling can be used to estimate bone geometry from incomplete or lower resolution data as well as their changes throughout the disease progression. Likewise, lower quality input data from wearables can be augmented with population-based movement profiles obtained based on principal composition decomposition of 3D motion capture data in a specific clinical population.

The third challenge relates to the difficulty of validating MSK modeling approaches using existing, longitudinal clinical data sets. MSK modeling approaches used in research often require inputs that are not available in standard-of-care data sets. Therefore, historical data sets can often not be leveraged to validate the added value of MSK modeling. This drastically hinders clinical acceptance. Indeed, in view of double-blinded randomized clinical trials on large patient cohorts being the current gold standard, MSK modeling will only be adopted in clinical practice after thorough validation. This presents a “catch-22” situation. As the data needed for MSK modeling are currently not being collected in the clinic, it is unlikely that MSK-based model parameters will become available as predictors of clinical outcome in a sufficiently sized and representative historical cohort of which, for example, the clinical outcome is known. This would, however, yield the ultimate verification experiment, allowing us to show superiority and, therefore, added value of MSK model parameters above currently used clinical parameters. To mediate this challenge, different approaches can be envisioned: Continued efforts should be dedicated to fully exploiting the benefits of new modeling and simulation developments by combining and more efficiently using the few and often incomplete (historical) data sets available. Even if we know that historical data sets do not contain sufficient information for high-accuracy predictions, applying modeling techniques might still be attempted by enhancing the information from available (low-resolution) information. For example, we could use available data for model personalization (eg, radiographs) while filling in missing data on joint contact surfaces based on statistical shape models from another data set that contains information from population distributions determined on MRI. The estimated MSK model-based outcomes will be more uncertain than when using fully personal models but might still yield additional information on clinically relevant markers or outcomes. This approach has the big advantage of requiring little alterations in clinical practice. Alternatively, setting up new clinical research studies...
that integrate MSK model parameters and invest in creating high-quality data collection even in a smaller cohort of patients might still lead to changes in clinical practice. Although this path offers a lot of flexibility, our experiences have shown that it requires dedicated clinical collaborators and is also costly and slow due to the need for collecting novel data sets.

The fourth and final challenge relates to the actual implementation of MSK modeling in clinical practice. Available MSK modeling workflows commonly require expert knowledge, hindering their implementation in clinical practice. Therefore, the ease of use of these MSK modeling workflows should be improved, which will probably require the development of software tools tailored to specific applications. In addition, dedicated training programs need to be developed with specific attention to standard operational protocols for data collection and standard reporting customized to the clinician’s needs to facilitate quality assurance and interpretation by the clinician. To maximize clinical adoption, this will require close interaction with clinicians to leverage insight of the actual clinical benefit and consequent buy-in of the professional bodies. Of course, this would require “proof-of-concept” trials to demonstrate the added value of the model-based assessment in terms of patient stratification, monitoring of treatment outcome, and consequent personalization of the interventions. In addition, given legal requirements imposed by the Medical Device Regulation on the use of software for medical purposes and liability issues, uncertainty associated with parameter outcomes will need to be expected addressed using dedicated risk analyses and economic cost–benefit analyses before actual clinical implementation can be considered.

In conclusion, and despite the challenges listed earlier, the authors remain confident on the—to be expected—clinical impact of MSK model-based approaches in defining in silico biomarkers for motor dysfunction. Comparable with the impact of the 3D motion capture system, the use of state-of-the-art MSK modeling and simulation in clinical research studies might already lead to guidelines for patient selection that are broadly applicable, that is, even by clinicians that do not use modeling and simulation. Although the complexity of laboratory-based settings—requiring dedicated staff and infrastructure—for now—limits the access for use in the standard clinical care or rehabilitation paths, emerging technologies and advanced data curation methods are promising in leveraging the use of more mainstream wearable technologies and model personalization based on standard-of-care input data.

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