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Predictive Multibody Dynamic Simulation of Human Neuromusculoskeletal Systems: A Review

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Abstract Over the past decade, there has been a rapid increase in applications of multibody system dynamics to the predictive simulation of human movement. Using predictive "what-if" human dynamic simulations that do not rely on experimental testing or prototypes, new medical interventions and devices can be developed more quickly, cheaply, and safely. In this paper, we provide a comprehensive review of research into the predictive multibody dynamic simulation of human movements, with applications in clinical practice, medical and assistive device design, sports, and industrial ergonomics. Multibody models of human neuromusculoskeletal systems are reviewed, including models of joints, contacts, and muscle forces or torques, followed by a review of simulation approaches that use optimal control methods and a cost function to predict human movements. Modelling and optimal control software are also reviewed, and directions for future research are suggested.

Keywords Neuromusculoskeletal system models · Predictive dynamic simulation · Biomechanics · Optimal control · Human movement · Review

1 Introduction

Multibody dynamics formalisms and methods are well suited for studying the biomechanics of human movement. The human skeletal system is composed of bones connected by physiological joints, which can be modelled as a traditional mechanism formed by rigid links and mechanical joints. This human mechanism is actuated by muscle-tendon units and controlled by the central nervous system. The modelling of the human body as a mechanical multibody system allows its equations of motion to be derived using traditional formulations in mechanical engineering. To simulate human movements, these equations of motion need to be complemented by models of the muscular actuation and the neural control.

In his historical review paper on multibody system dynamics, Schiehlen observed a widespread application of multibody dynamics to automotive, aerospace, and machinery fields [1]. In contrast, biomechanics was listed as a "challenging application" requiring further research. Twenty-five years later, biomechanics is one of the leading areas of research within multibody dynamics. In fact, the number of published articles related to biomechanics in Multibody System Dynamics in the last ten complete years (2012-2021) is 98, which is 19 % of the total published papers (excluding editorials); thus, approximately one in five published articles in Multibody System Dynamics relates to biomechanics.

This growth in the volume of research related to biomechanics is thanks to events like the IUTAM Symposium on Human Body Dynamics: From Multibody Systems to Biomechanics that took place in Waterloo, Canada, and recently witnessed its tenth anniversary [2]. This event brought together leading researchers in biomechanical simulation and multibody dynamics for three intense days of research exchanges. The current paper highlights the advances in multibody biomechanical modelling in the 10 years since that symposium.

We found two recent review papers that focus on neuromusculoskeletal modelling and movement simulation. Fregly presents a personal perspective for how biomechanical models can become useful in current clinical practice [3]. The paper presents some future research challenges (e.g., model personalization and validation, among others), along with clinical, technical, collaboration, and practical issues that must be resolved before modelling and simulation can achieve clinical utility. Secondly, De Groote

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and Falisse review the latest studies on predictive simulations of human gait [4]. The paper presents different simulation approaches to predict walking, and challenges and future perspectives to increase the accuracy of simulations and to validate the simulated outcomes.

In this paper, we review predictive simulation approaches of general human movement using neuromusculoskeletal models, i.e., "what-if" simulations of human movement without tracking experimental data. The research papers classified in this review are neither restricted to clinical application [3] nor walking movements [4]. We present studies in different application fields, such as clinical, industrial, sport, or ergonomics. In the clinical field, we note the recent recommendation of the U.S. Food and Drug Administration (FDA) to replace time-consuming and expensive clinical trials with computer simulations [5]. The paper has two main sections: 1) Modelling section, including unique features of the multibody dynamic modelling of neuromusculoskeletal systems, such as nonlinear contact dynamics, non-ideal joints, and muscle geometry and dynamics, and 2) Predictive simulation section, including optimization approaches used to generate what-if simulations in the absence of experimental data, optimization cost functions and constraints, and applications. We conclude with some suggestions for future research directions.

2 Multibody biomechanical models

The level of detail in a multibody dynamic model of human movement depends on the desired predictions and analysis results. The human body can be driven with ideal joint torques, activations, or muscle excitations (Figure 1). In many predictive simulation studies, conceptual models with only a few degrees of freedom (DoF) and no muscles were used [4]. Musculoskeletal (MSK) models may also be used to represent the motion of the human body, or neuromusculoskeletal (NMSK) models that include models of the central nervous system (CNS), which adds more complexity to the system dynamics. In the following sections, the different modeling elements (skeletal, contact, neuromusculoskeletal, and human-device interactions) and modeling software packages are reviewed. A detailed description of each modeling element for the most relevant predictive simulations in the literature can be found in the Supplementary material.

2.1 Skeletal models

Multibody models represent the motion of each human body segment using rigid or flexible bodies. The segments represent a bone (or a group of bones) and the surrounding tissue that moves together (section 2.1.1). The joints and other interactions between segments can be represented by constitutive laws that model the elastic elements between them, such as the joint cartilage and the ligaments. Kinematic constraints can also be used to define the relative motion between segments (section 2.1.2). The skeletal

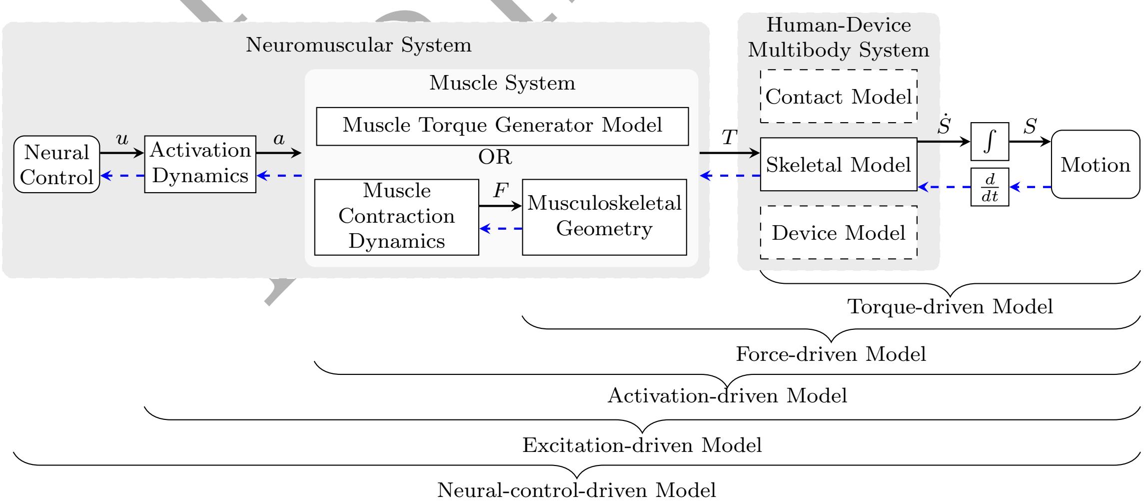

Fig. 1 Forward dynamic (FD) simulation (in solid arrows) of an NMSK system using joint torques (T), muscle forces (F), muscle activations (a), or muscle excitations (u) as the inputs. The state vector (S) consists of positions and velocities. An inverse dynamic (ID) simulation (in dashed arrows) follows the reverse path to the FD simulation. The muscle system can be modeled with muscle torque generators (MTGs), or a combination of muscle dynamics (e.g., Hill-type muscle model) and musculoskeletal geometry.

model can be driven with an ideal joint torque (T), as shown in Figure 1. If an NMSK model is used (section 2.3), it can be driven by muscle force (F), activation (a), or muscle excitation (u) from a neural controller (section 2.3.3).

2.1.1 Articulated-body models

The kinematic and dynamic model of the human body is usually represented as a series of rigid segments or articulated linkages that are connected together by joints [6, 7]. Based on the objective motion and study goal, a 2D or 3D model may be selected. For example, a 2D model was used for predicting sagittal plane biomechanics of lower body joints [8, 9], and a 3D articulated-body model was used for the prediction of 3D crutch-assisted walking patterns [10].

From a system topology viewpoint, the skeleton system is formed primarily by an open kinematic chain or, less frequently, by a closed kinematic loop (e.g., when both hands grasp a rigid object). A model with an open kinematic chain has been used for simulating the swing phase of human walking [11, 12, 13, 14, 15]. The open-loop model with serial kinematic connections, when using a minimum number of coordinates, results in an ordinary differential equations (ODEs) system [14, 16], and, when using dependent coordinates (e.g., natural coordinates), forms a differential algebraic equations (DAEs) system. For the double support phase of human walking, the joint variables are not all independent since the model contains a closed kinematic chain [17]. Another example of a closed loop is when the two feet of a cyclist are fixed to a crank or when the hand is attached to the handlebars [18]. Consequently, dynamic equations take the form of DAEs. The simulation framework becomes more difficult to solve for systems with closed kinematic chains [9].

Body positions are described by the generalized coordinates, which can be relative or absolute. Relative coordinates are primarily associated with internal motion (i.e., relative motion between consecutive segments), and absolute coordinates represent position and orientation relative to an inertial reference frame. For example, for a walking prediction study, the pelvis location relative to an inertial frame is defined by absolute coordinates, while the knee angle is considered as a relative or joint coordinate [19]. These generalized coordinates are used to form the system states.

Bodies are usually assumed to be rigid and segment properties (including length, the center of mass (CoM), mass, and moment of inertia) are frequently calculated based on anthropometric measurements (anatomical regression equations from the literature) and scaled to match the targeted subject [9, 18, 20, 21]. Motion capture data may be used to estimate segment lengths [9]. For fast motions, the segments may need to be modeled with non-rigid bodies ("wobbling masses") [22].

2.1.2 Joint models

The joints of the human body govern the directional mobility capabilities of body segments. For human movement modeling and analysis, ideal joints connect adjacent rigid segments by introducing DoF and consequently constraints to the system. The joints may be modeled with a range of simple 1-DoF revolute (pin) joints [23] to 6-DoF joints [19, 24].

Kinematic constraints are helpful in modeling anatomy that is difficult to explain using ordinary joints or that would otherwise require calibrated ligament and cartilage models to create the required features of the motion [25, 26]. Models of the knee, shoulder, and neck are examples of models with complicated anatomy achieved using kinematic constraints [27].

A joint can incorporate explicit contact and ligament models that limit the joint physiological motion [26]. Ligaments are fibrous tissue that joins two bones across a joint, ensuring that the joint angle remains within the functional range of motion (RoM) [28, 29]. Passive structures such as ligaments and cartilage can be explicitly modeled with complex equations or with lumped passive joint torques [22, 26]. These models of ligaments and cartilage resist movement and are activated during joint hyper-flexion or -extension [24, 28, 30]. Ligaments are often modeled as nonlinear spring-dampers that act as a soft or exponential limit on the joints [24, 28, 29, 29, 31, 32], and improve stability [26, 29]. Eskinazi et al. have shown that the ligament stiffness must be greater than some critical value in order for direct collocation optimal control to converge [24].

2.2 Contact models

The most common external contact considered and modeled in multibody human models is foot-ground contact (necessary for modeling walking, running, and jumping) and is the primary focus of this section.

Some other contacts of interest include posterior-seat contact (such as for sit-to-stand models [33, 34] and cycling models [18, 35]), crutch-ground contact [10, 36], and contacts at several points on the body for physical assistive devices [33] and exoskeletons [37, 38, 39].

2.2.1 Normal force models

Contact can be modeled in a variety of ways. These are mentioned in approximate order of model complexity, starting with the simplest.

One method is to model the contact as a rigid joint. This is especially common for models where the body is in continuous contact with a surface, such as foot-ground contact during squatting [21], a hand rigidly grasping an object [18, 32], and foot-pedal and posterior-seat contact during pedaling [35, 40]. In cases where contact may be intermittent, a rigid contact can be modeled by only applying kinematic constraints and their reaction forces when the bodies are in contact. This results in different sets of equations being used at different simulation phases. In 2D models using rigid contacts, each foot contact typically uses two point constraints, representing the heel and the toe [14, 41, 42]. Depending on the foot model, 3D models have used one [43], two [13], four [16], or — when the foot is modeled as two segments — six [44, 45] point constraints per foot.

A rigid contact model may miss out on some foot motion that happens during contact. One improvement is to consider the "roll" of the foot, which may be done by modeling the foot as a rigid body that rolls without slipping. Ren et al. modeled the sole of the foot as a curved surface in their 2D model, fitted so that the ankle kinematics matched experimental data [17]. In Felis and Mombaur's 3D model, a sphere represented the heel, and a short line segment represented the forefoot, resulting in rolling motion during heel contact and 2D rotation during forefoot contact [7].

Outside of rigid contact, there are a number of deformable contact models. The simplest of these are point-contact models. In point contact, the normal forces will typically be modeled as linear or non-linear springs and dampers between the ground and one point on the contact surface. Normal force models used for point contact include linear spring-damper equations [29, 46], exponential spring-damper equations [47], and equations similar to or based on Hunt-Crossley [48, 49, 50, 51]. To better model contact across a large surface (as is the case in foot-ground contact), several point contacts may be used across the surface. Point contacts used per foot included 1 contact [29], 2 to 5 contacts (typically places at the edges of the foot) [46, 47, 49, 52, 53], and a larger number of contacts (e.g. 51 in [50] and 47 in [51]) distributed on a grid across the contact surface. In the case of [50], the number of elements (51) was chosen by increasing the number of point contacts until there were no more improvements in how well the model could match experimental data.

An alternative to using a large number of contact points is to use a single point of contact that can move relative to the foot, usually based on a geometrical representation of the contact surface. For example, the foot has been modeled using 2 to 8 spheres [54, 55, 56, 57], with the contact forces applied at the point on the sphere that is closest to the ground at a given time; being the forces computed using Hunt-Crossley (or other non-linear model) point contact equations. More complex geometries than spheres have also been used: Lopes et al. modeled foot-ground contact using a superellipsoid [58], and Millard and Kecskeméthy used a model based on disk-plane contact [59]. According to Lopes et al., the superellipsoid model was more computationally efficient than a similar model using many point contacts [58].

Another model that represents surfaces using analytical geometry is volumetric contact [60]. It uses elastic foundation theory to represent contact loads distributed over a surface, instead of acting at discrete points. Some initial work using volumetric contact in foot-ground contact has been done using spheres [61] and ellipsoids [62, 63], and it has also been used to model impacts in sports applications [32].

Finite element (FE) contact models have also been used for foot-ground contact. This is a computationally expensive approach compared to other models mentioned here, especially for predictive models that require many dynamic simulations, and there are few examples in the literature. Halloran et al. made use of an FE model for a study that was focused on ground contact pressure and reported that the contact model took 99.5% of the computation time [64]. As a more efficient alternative, Halloran et al. developed a surrogate model trained on the finite element (FE) model, which had similar results to the FE model at a 95% reduction in computation time [65].

The choice of contact model in existing works in the literature appears to be based on computational efficiency and appropriateness for the simulation, optimization, or control methodologies, rather than on which modelling method is most accurate for motion and contact forces. There are few direct comparisons of different contact models in the same type of simulation [58, 65]. Insight into the relative advantages of the different models could be gained from more studies comparing the relative accuracy and computational efficiency of different contact models for the same human model and motion.

2.2.2 Friction force models

When the contact is modeled as a rigid joint or a constraint, friction may be modelled as part of the constraint. To ensure that the friction forces do not exceed realistic limits, these models may add additional constraints or penalty functions to limit the friction forces (for example, they may be constrained based on Coulomb's law) [13, 42].

For deformable contacts, one way to model friction is using a velocity-based function based on the Coulomb friction model. In these "regularized" models, friction is a non-linear function of velocity, which approximates Coulomb friction, but with additional parameters to smooth the discontinuities in frictional forces.

For some examples of different equations used in these models, see [48], [51], and [53]. One disadvantage of velocity-based friction models is that equations tend to be stiff at low velocities, which is often the case for human motion; during gait or when jumping, the foot is not expected to slip across the ground during contact, and when grasping an object, the hand is typically not expected to slip either. Another disadvantage is that the model allows some tangential velocity during contact, even if no slip is expected.

An alternative friction model for deformable contacts is a position-based friction model. In position-based models (which includes bristle friction models), friction forces are modeled as tangential springs at the contact surface. This adds an additional state variable to the equations, resulting in more complex equations than those from velocity-based friction models. Unlike velocity-based models, position-based models do not allow additional slip during stiction, meaning that they are more accurate for experiments where stick-and-slip behavior is observed [66]. Examples of position-based foot-ground friction models can be found in [47, 67].

An aspect of contact that has received little attention in these models is the lateral flexibility of the contact surface (due to the soft tissue in the human body). For example, the bones and joints in a foot may be able to shift while the foot surface remains sticking (not slipping) on the ground. It is possible that position-based friction models could be used to model this flexibility. In existing position-based friction models, it is not clear if this was one of the intended purposes of using the model.

Aside from the models mentioned so far, another potential friction model is the Maw friction model [68]. This can model the effect caused by different regions of the contact surface having different stick and slip conditions, e.g. sliding at some areas and sticking at others, due to different normal and lateral forces across the contact surface. This may be relevant to biomechanical models such as foot contact during gait, since the contact area and contact forces have large changes throughout contact in gait.

2.3 Neuromusculoskeletal models

Many researchers have included the mechanical behavior of muscles in predictive simulations by using realistic MSK models, including an anatomically-detailed viscoelastic model of muscle mechanics, e.g. a Hill-type muscle model (section 2.3.1). To reduce the computational cost of predictive simulations, muscle torque generators (MTGs), which represent the resultant torques generated by muscle forces, can be used [18, 42, 69] (section 2.3.2). Furthermore, the muscle model may incorporate biologically-motivated neural control methods (section 2.3.3) such as muscle synergies, central pattern generators (CPGs), or stretch reflexes. The mechanical properties of muscles introduce limits to the maximal human performance [70], influence the simulation results [6, 31], and have an impact on validation accuracy [26].

2.3.1 Hill-type muscle models

The popular Hill-type model consists of: (1) a contractile element (CE) ($F_V(V)\,F_L(L)$) that models its force-length-velocity characteristic; (2) a nonlinear parallel elastic element with muscle fibers ($F_P(L,V)$) that mimics the stiffness or passive response; and (3) and a nonlinear series elastic element that characterizes the stiffness of the connected tendon with a stress-strain curve. The latter is serially connected to the muscle model (equation 1).

$$F(t) = F_A(u,t)\,F_V(V)\,F_L(L)\,F_{max} + F_P(L,V) \tag{1}$$

The force-producing qualities are influenced by the maximal isometric strength of the muscle (F_{max}) and its related optimal fiber length and pennation angle, the maximum shortening velocity of the muscle, and the rest length of the tendon [11, 26, 31]. Most of the model constant properties are based on data reported by literature. However, the musculoskeletal geometry model calculates the model variables, such as muscle length and velocity. The geometry path model of the muscles is made either by a set of straight lines or a combination of straight lines and space curves (wrapping) [24, 26, 47].

Due to the comparatively slow electrochemical process, muscles cannot be instantly contracted or relaxed. The muscle's force-velocity property partly explains this behavior, but is also a function of muscle activation's time course. Primarily, a first-order differential equation ($F_A(u,t)$) relates the time rate of change of muscle activation to muscular excitation.

The use of high-dimensional complicated models in predictive simulations is typically prevented by the tremendous computational cost necessary to solve the accompanying optimal neuromuscular control problem [11]. Due to numerical issues, static optimization of muscle redundancy can only accommodate simplified Hill-type muscle models [71]. However, using the biologically-based muscle model in the predictive simulations allows estimation of metabolic energy expenditure of human muscle actions [49, 72, 73, 74].

2.3.2 Muscle torque generators

Using anatomically-detailed muscle models in simulations can provide insights into individual muscle and joint loads; however, these muscle models increase the computational cost of the predictive simulation. An alternative approach is to use physiological torque actuators to represent the resultant torques being generated by muscle forces [18, 42].

In this approach, each joint is driven by a pair of agonist-antagonist parametric MTGs [9] (equation (2)) that mimic the flexor ($^+$) and extensor ($^-$) groups surrounding the joint [32, 75]. The MTG consists of active and passive elements. Active components include angle-dependent ($\tau_\theta(\theta)$) and angular velocity-dependent ($\tau_\omega(\omega)$) torque production capacities at each joint [42], which represent the physiological muscle force-length and force-velocity relationships [18]. To account for both concentric and eccentric muscle contractions, the scaling functions are piecewise [18]. The passive component ($\tau_p(\theta,\omega)$) is modeled as a nonlinear rotational spring and damper that represents the passive forces produced by the stretching of muscle tissue, tendons, and ligaments around the joint [18]. The curves describing the MTGs torque generation capacity are normalized by the maximum isometric torque and are usually characterized from experimental dynamometer data [75]. Similar to conventional muscles, a differential equation ($\tau_a(u,t)$) relates the time rate of change of muscle activation (a) to muscular excitation (u).

$$T(t) = \tau_a^+(u^+,t)\,\tau_\omega^+(\omega)\,\tau_\theta^+(\theta)\,\tau_0^+ + \tau_a^-(u^-,t)\,\tau_\omega^-(\omega)\,\tau_\theta^-(\theta)\,\tau_0^- + \tau_p(\theta,\omega) \tag{2}$$

NMSK models and dynamic simulations are simplified by using MTGs, since the number of model parameters and input variables is reduced [18]. By using MTGs in place of line-type muscles, there is no need to solve for redundant muscle forces, resulting in faster simulations and easier interpretation of the numerical results [75]. Since MTGs are continuous to the second derivative, gradient-based optimization is facilitated by their use [75]. Moreover, the MTGs are easier to fit to specific subjects since they simulate groups of muscles rather than multiple line-type muscles [75]. However, joint reactions cannot be computed from an MTG-driven model [69]. In the event of co-contraction of the flexor ($^+$) and the extensor ($^-$) MTG components, one is again faced with a redundancy problem to resolve; it seems that no papers have been published on the resolution of MTGs in the case of co-contraction.

2.3.3 Neural controls

The CNS is thought to coordinate body motion by bundling individual muscles into groups [23]. Similarly, in the human model, a large number of independent muscle activations can be controlled via a low-dimensional set of synergy activations [51, 76]. The synergy controls (lower-dimensional set of time-varying signals) can be obtained by decomposing a high-dimensional set of processed electromyography (EMG) signals. For decomposition, non-negative matrix factorization with an optimization approach is often used [77]. The synergy weights define the contribution of each synergy control to the processed EMG signals [51, 76, 78, 79]. Utilization of muscle synergies reduces the complexity and size of the neuromuscular control problem [23, 76, 80, 81], simplifies the control process [76, 81], improves the prediction results [82], and improves computational speed and convergence of the optimal control algorithm [51, 78].

Table 1 Summary of how different neuromusculoskeletal impairments have been modelled in predictive simulations.

Type of impairment	Modelling	References
Muscle weakness	Reducing maximal isometric force	[57, 89]
	Limiting maximum hip abduction moment (constraints)	[46]
Muscle contracture	Reducing a muscle's optimal fiber length	[57]
Cerebral palsy	Subject-specific muscle torque generators	[9]
	Personalized geometries (from MRI images), personalized muscle-tendon parameters (optimal fiber lengths and tendon slack lengths), spasticity model–personalized feedback gain estimation, and reduced neuromuscular control complexity modeled through muscle synergies	[80]
Spinal cord injury	A weakness factor limits the maximum neural excitation of those denervated muscles	[14]
Nonspinal knee injury	Subject-specific parameters and torque generator functions were implemented in the model from dual X-ray absorptiometry and human dynamometer measurements	[90]
Stroke	Subject-specific muscle-tendon parameters, musculoskeletal geometries, muscle synergy controls	[51, 76]
Knee osteoarthritis	Subject-specific joint and inertial parameters Subject-specific cost function weights	[12, 15, 19]
Amputee	Remove muscles Add passive stiffness at the ankle	[41, 53, 74, 89, 91]
	Reduce the mass of the lower leg and foot segments to mimic the prosthesis	[89]

As an alternative to synergy-based approaches, machine learning methods can be used to map processed EMG signals to muscle excitations [83, 84].

Human locomotion arises from a rhythmic interaction between the CNS, the MSK system, and the environment [28]. A CPGs is a network of brain cells; in the absence of sensory feedback, it may form synchronized rhythmic motor signals of neural activity without rhythmic inputs [28, 43, 67]. CPGs could play a role in human locomotion in terms of stability against perturbations and speed control [28]. They are primarily used for gait (walking and running) optimal control simulations [28].

The NMSK model may incorporate a set of biologically-motivated stretch-reflex-based control rules that produce muscle excitation signals determined by the current kinematics, muscle states, and environment conditions [54]. Each muscle is activated in proportion to its normalized fiber length via stretch feedback controllers [54] or via a proportional-derivative controller [85]. The stretch-reflex-based control laws are utilized for disturbance rejection, and precision control in human limbs [85].

2.4 Subject-specific and impairment modeling

A MSK model of the human body can be developed using values taken from the literature for the different parameters that define the skeletal model (inertial and geometric parameters), the muscle-tendon (MT) models, and the foot-ground contact models. They are usually estimated based on experimental measures from cadaver specimens [86, 87]. Depending on the objective of the study, and especially for clinical applications, these parameters may be further specified towards individual characteristics, to develop patient-specific models [9, 19] (Table 1). Having a subject-specific model of the patient under investigation is crucial for obtaining meaningful simulation results and can also serve as the foundation for an objective treatment planning approach [88]. For that, it is important to identify these parameter values accurately.

2.4.1 Skeletal models

Body segment properties (mass, length, inertia properties) and joint centers and axes are usually adapted from a generic model to a specific subject model using regression equations. This is the usual approach for most predictive simulation studies [14, 41, 53, 57, 82], where segment lengths are measured using reflective markers and are used to compute scaling factors to scale the anthropometric properties [92, 93]. Depending on the purpose of the study, population-specific models can be used, e.g., female-male, young-adult-old adult. In [94], running is predicted for four different groups: a young adult female, a young adult male, an older adult female, and an older adult male. In [33], the optimal way of supporting sit-to-stand transfers of geriatric patients is predicted, and mass and inertial parameters are taken from percentiles 20/50/80 of the male and female geriatric population. However, linear scaling presents some limitations and may not be accurate enough when having a subject that is far away from the mean population values, e.g., children with cerebral palsy [80] or paralympic athletes [95].

Medical imaging, such as magnetic resonance imaging (MRI) [80, 96], computed tomography (CT) imaging [97, 98], biplanar X-ray [99] and dual-energy X-ray absorptiometry (DXA) [95], has been used to create subject-specific models. In [96], the authors developed software for creating subject-specific bone geometries, joints, muscle paths, and wrapping surfaces in OpenSim. They tested the software by developing an MRI-based musculoskeletal model of the lower limb. In [97], subject-specific bone geometries from a subject wearing a total knee replacement (TKR) implant were segmented from CT images. In [99], subject-specific masses and 3D locations of the CoM of body segments were determined using biplanar X-rays for six children and six adults. In [95], the authors aimed to define body segment parameters of paralympic athletes (e.g., individuals with spinal cord injuries and lower extremity amputations). Two-dimensional body segment parameters (i.e., mass, length, position vector of the CoM, and principal mass moment of inertia about the CoM) were quantified from DXA. The previous studies presented new methods [95, 96, 99] or used a subject-specific model for simulation [97], but without predicting new motions. In [80], a 3D MSK model with personalized geometries was created from MRI images of a child with cerebral palsy (CP), which presents bony deformities, and was used to predict walking motions of that specific child.

Other studies use dynamic measurements (e.g., marker trajectories and ground reaction forces) together with optimization methods to calibrate model joint and/or inertial parameters. In [15], a method for estimating hip, knee, and ankle joint centers and axes, together with full-body inertial parameters, was developed. Based on this method, the authors have predicted the walking motions of an osteoarthritic knee subject using a 3D ideal torque-driven model, with the aim of designing patient-specific gait modifications for knee osteoarthritis rehabilitation [12, 19]. The same group has also predicted the gait of a post-stroke subject walking at different speeds [51] and has designed a treatment to improve propulsive force symmetry during the post-stroke gait of a stroke subject, using a 3D muscle-synergy-driven model [76].

Although some methods have been developed for constructing medical image-based MSK models of the lower limb, these personalized models have rarely been used in predictive simulations. One reason may be that more development is needed to improve the existing modeling methods, as they have been applied only for one joint [98], the lower body [15], or have been tested in only one subject [80, 96, 97]. Moreover, the existing model personalization processes for predictive simulations require a large learning time [3].

2.4.2 Muscle models

To determine muscle forces, it is important to correctly identify muscle geometry (e.g., muscle attachment points, muscle paths) and MT parameters (describing the Hill-type muscle model). Personalized bone shapes and muscle attachments are especially important in cases where bone deformities are present, such as in children with cerebral palsy [80]. MT parameters describing the Hill-type muscle model are often collected from cadaver studies. The maximum isometric force is usually linearly scaled, together with the skeletal model parameters (segment mass, length, inertia). However, the MT parameters are subject-specific and values vary widely across subjects [87].

Different approaches have been proposed to estimate personalized MT parameters that combine measurements and optimization techniques. Different techniques that take into account differences in subject size were examined in [100], and the authors found that scaling by maintaining muscle operating range (force-generating characteristics) throughout the range of joint motion was the approach that worked best. In [101], the previous method was generalized and used to adjust lower limb muscle parameters following linear scaling of a generic model and to estimate muscle parameters "from scratch" in a subject-specific model of the hip joint created from medical images. In [87, 102], angle-torque relationships measured from functional movements (marker trajectories and dynamometer measurements) were used to estimate Hill-type MT parameter values. Motion data and EMG measurements, together with optimization techniques, have been used to identify muscle tendon parameters [61, 80, 103]. MTG parameters have also been identified using dynamometer measurements [9, 75, 104].

Muscle impairments

Muscle weakness and muscle contracture are deficits that can be found in different NMSK disorders, such as cerebral palsy, stroke, muscular dystrophy, and spinal cord injury. The usual approach in predictive simulation studies is to model muscle weakness by assuming a weakness factor (or percentage of use) with respect to the "healthy" condition that limits the maximum force that can be produced by a specific muscle or group of muscles [14, 46, 57, 89, 105]. To model muscle contracture, in [57], the muscle's optimal fiber length is reduced by different percentages with respect to the "healthy" condition. In all these studies, the main goal is to test if the prediction framework can predict the expected trends correctly when simulating impaired walking, rather than trying to find a treatment for a specific subject [14, 46, 57, 89]. When the motion of a specific subject is predicted, then MT parameters that describe the Hill-type model are personalized based on experimental data. In [9, 104], MTGs are used to produce the combined effect of all muscles spanning each joint, and maximum isometric torque is personalized based on experimental data collected for the specific subject under study. MT parameters can be estimated through optimization, including optimal fiber lengths and tendon slack lengths [51, 76, 80], and additional parameters describing the activation dynamics [76]. EMG-driven modeling has also been used to adjust surrogate representations of a patient's musculoskeletal geometry to improve prediction of lower extremity joint moments during walking [106].

Aging

Aging results in progressive loss of mobility, mainly caused by muscle weakness [107], and an increase in stiffness and tone [108]. There are few predictive simulation studies focused on elderly subjects. In [34], sit-to-stand was predicted and compared for virtual healthy young and elderly individuals using population-specific models (each of the digital healthy young and elderly groups had five digital male and five digital female individuals). For the elderly models, a reduction rate of 20% to the isometric strength was assumed and applied. In [33], sit-to-stand transfers of geriatric patients were predicted in order to design the best physical assistive devices. However, the model was driven by ideal joint torques, and no limit was applied to the torque that each joint could produce.

2.4.3 Neural control models

Motion data and EMG measurements, together with optimization techniques, have been used to identify muscle synergy parameters [51, 76, 109]. However, neural control and muscle behavior in NMSK impairments present some differences with respect to healthy subjects. In clinical applications, it is crucial to model the deficits correctly if one wants to obtain meaningful results for a specific subject.

Neural control impairments

Spasticity is a common impairment in cerebral palsy and stroke and is characterized by exaggerated stretch reflexes. However, the mechanisms underlying spasticity and its influence on gait are still not well understood. In [110], a model of the lower leg as a torque-driven single-link pendulum was used to gain insight into physiological mechanisms of spasticity, and in [111], a spasticity model based on feedback from muscle force was developed. This model was applied in a predictive simulation case study of a child with CP in [80]. High muscle co-contraction is often seen in subjects with neurological impairments. In these cases, model-based optimization techniques that consider EMG measured information can be used to solve the muscle redundancy problem, to find more realistic agonist and antagonist muscle forces [112]. Finally, reduced neuromuscular control complexity has been modeled through muscle synergies, imposing a lower number of synergies in the case of a child with CP [80].

2.4.4 Foot-ground contact models

When foot-ground contact is modeled using spring and damper elements, Hunt-Crossely models, or volumetric contacts, these model parameter values need to be specified. One approach used in predictive simulation studies is to hand-tune them to fit an experimental measurement [48, 53, 54, 70]. Another approach is calibrating those values for a specific subject solving an optimization problem where the difference between simulated and measured data (motion and ground reaction forces) is minimized [37, 76, 82, 89]. In [62], pressure data is included in the optimization procedure.

Some assumptions can be made to reduce the number of parameters to calibrate. For instance, usually symmetry between values of both feet is assumed [51, 113, 114]. Other approaches include in the cost function the minimization of the difference between individual spring stiffness (or damping coefficient) and mean stiffness (or damping coefficient) for all springs [114], or approximate the stiffness distribution across the entire shoe sole by a three-dimensional parabolic surface [51]. Another way of reducing variables is considering some constant parameter values for all spring-damper units, like the damping coefficient [51] or the friction coefficient [114].

In [115], contact model parameter values were calibrated using experimental data from five subjects (performing 15 trials at different walking speeds each), and it was found that the vertical and anterior-posterior position of the visco-elastic units is specific for each subject. In [114], a sensitivity study was performed, and the authors found that the free moment of both feet exhibited moderate sensitivity to the change in stiffness values, while all other ground reaction quantities exhibited little sensitivity to changes in model parameter values. However, validation was only done using gait for one subject and at the same cadence. In [62], data was collected for one subject at three different speeds: one speed for calibration and two other speeds for validation. However, the model was not evaluated by running a predictive simulation, and data were collected for only one subject. In [89], the authors compared the results of a 3D full-body musculoskeletal model using a generic model from the literature [116] with results using an optimized contact model. Despite large differences in contact geometry, using a generic model instead of an optimized contact model had little influence on the predicted gait pattern, except for a small offset in the ankle angle. All these results lead to some open questions: if these parameter values are really subject-specific or not, and which of them are more critical for accurate predictive simulations.

2.5 Human-device models

To design devices that interact with humans, it is necessary to model the device alongside the human. Human-device modeling and predictive simulation provide insight into immeasurable variables [42], help to improve the design of augmentative devices [32, 39], are useful tools to identify the optimal device characteristics and personalize the device parameters [9, 82], shorten the prototyping period [41], study the device performance and interaction feel [39, 85], and increase athletic performance [18, 32, 40]. Examples of human-device predictive simulations include passive assistive devices (e.g., crutch [10] and wheelchair [90]), wearable robots or exoskeletons [37, 38, 39, 39, 75], passive or active orthoses [9, 14, 74, 82, 89], bicycles [18, 40], golf clubs [32, 104]), and vehicles [85].

Human-device interaction models range from very simple to highly detailed. In a simple model example, only the resulting active and passive joint torque of a wearable robotic device was considered for studying human jump performance within an optimization framework [42]. In contrast, a comprehensive high-fidelity vehicle dynamics model in combination with a neuromuscular driver model was used to study the driver's control performance, steering feel, and the human effect on vehicle control and stability [85].

The device may be modeled with rigid or flexible bodies based on the study goal and the device's mechanical properties. For example, an exoskeleton can be modeled as a rigid-body mechanism coupled to the wearer through kinematic constraints to predict how the exoskeleton will affect the movement of the human [38, 39, 75]. Improvements to golf swings and clubs were found using direct orthogonal collocation and a multibody dynamic model that included MTG models of muscles and a Rayleigh beam model of the flexible golf shaft [32, 104].

In some applications, not only should the device be modeled, but also the interaction of the device with the environment or human. For example, in addition to the exoskeleton model, linear or rotational spring-and-damper elements were used to model the human–exoskeleton interface in an optimal control framework to assess user comfort and effectiveness of the interaction [37]. A crutch-ground contact model was included in a crutch and human model to predict different three-dimensional crutch-assisted walking patterns [10]. A Pacejka model of tire forces and moments was used in a bicycle model for predictive dynamic simulations of standing starts of a two-legged cyclist [18].

Some devices are powered and provide external actuation from motors and mechanical transmissions. Those devices also include a control system to define the device assistance during a motion task. For example, an active (or powered) knee-ankle-foot orthosis model was used in an optimal control-based predictive simulation approach for personalizing knee trajectory parameters during walking [82]. García-Vallejo et al. modeled the active orthoses as external devices attached to the lower limbs for predicting orthosis-assisted human gait, while optimizing ankle stiffness (device design parameter) [14]. Usually, very simple models of the actuation system (motor and mechanical transmission) have been employed in these studies [14, 82].

2.6 Modeling software packages

Several commercial (e.g., MapleSim, AnyBody, MuJoCo, and LifeMOD/Adams) and open-source (e.g., OpenSim and BiomechZoo) multibody dynamic programs have been used to model and simulate human

MSK systems. These programs provide models of joints and Hill-type muscles for human motion simulation. We describe those that have been used for predictive simulation. MapleSim is based on symbolic computing, which provides analytic derivatives when needed, e.g. for optimization or sensitivity studies, while AnyBody, MuJoCo, LifeMOD, and OpenSim use numerical programming.

OpenSim (SimTK, Stanford, CA, USA) is a widely-used open-source biomechanical modelling and simulation environment that relies on the Simbody dynamics engine; it was developed at Stanford University [117]. It provides an explicit formulation of the dynamic equations of motion [55] and uses a 5th-order Runge–Kutta integration method with a variable step size [55] or semi-explicit Euler integrator [57, 78]. OpenSim provides tools for generating tracking simulations [118], such as the scale model tool (for scaling the OpenSim generic model to the target subject's dimensions using surface marker data [76, 82]), the inverse kinematic analysis tool (to obtain joint coordinates of the human model from marker trajectories [10, 37, 82, 91]), the inverse dynamic (ID) analysis tool (to obtain the resultant net joint moments [37, 76, 82]), and the muscle analysis tool (calculates MT lengths and muscle moment arms [51, 76]).

The AnyBody Modeling System [119] (AnyBody Technology, Aalborg, Denmark) provides a generic MSK model, which is constructed from anatomical studies. AnyBody consists of two graphical user interfaces and a console that can be called from other programs. It uses a dynamic trial to scale individual segments. AnyBody is restricted to ID simulation; it calculates muscle forces using ID-based optimization methods to minimize the polynomial muscle recruitment criterion [46, 119].

MapleSim (Maplesoft Inc., Waterloo, ON, Canada) is a multibody dynamics simulation software that supports the modelling of MSK systems. MapleSim's multi-domain capabilities allows human and device (e.g., bicycle [18], vehicle [85], rehabilitation robot [120], or wheelchair [90]) models in the same software. The symbolic models and optimized simulation code can be exported from the MapleSim environment as DAEs or ODEs for computationally efficient forward dynamic (FD) models [18, 85, 90, 104].

3 Human movement predictive simulation in biomechanics

3.1 Biomechanical simulation approaches

Once a biomechanical model for a human is selected, a solver is required to simulate the model's movement for a specific task. Simulation solvers use predictive simulation approaches, including optimization-based methods and feedback-control methods. Optimization-based methods use "*trajectory optimization*" or "*optimal control*" for task analysis. Feedback-control methods benefit from straight-line programming or non-optimal controllers to solve the simulation problem of a specific task. In this paper, we focus on optimization-based methods as well as those feedback-control methods that use optimization to guide their controllers (e.g., model-predictive control).

3.1.1 Optimization-based methods

Trajectory optimization and optimal control, commonly-used optimization-based methods, are often confused and used interchangeably. In trajectory optimization, static parameter values are identified to optimize a given performance index. In contrast, in optimal control, time-variant inputs to a system and, optionally, static parameters are estimated to optimize a given performance index. Optimal control methods are divided into two categories: indirect and direct methods [121].

Indirect methods use the calculus of variations to obtain analytical expressions of optimal control that are adjoint differential equations. Thus, boundary-value problems should be solved to obtain the optimal solution. However, finding an initial guess for adjoint variables is challenging since most of the variables are not physically meaningful. Furthermore, adjoint differential equations are highly nonlinear; hence, backward integration of those differential equations can be numerically unstable.

In direct methods, it is not required to solve boundary-value problems. Instead, the controls and/or states are parameterized, and the optimal control problem is solved as a nonlinear programming problem (NLP). Systems with large-scale NLP (e.g., optimal control of human movement) can be solved using different software packages such as interior point optimizer (IPOPT) and sparse nonlinear optimizer (SNOPT). Direct methods are divided into two methodologies: direct shooting and direct collocation.

In the direct shooting method, the optimization design variables are model controls. In this method, forward dynamic equations are explicitly integrated, and each time frame is solved sequentially by time marching. The shortcoming of this method is that numerical integration problems may lead to the prediction of unstable movements. Thus, a stabilizing feedback control would be required to predict stable movements using the direct shooting method.

To cope with the shortcoming of the direct shooting method, researchers have exploited the direct collocation method in which the optimization design variables are both model controls and states. In this method, forward dynamic equations are solved implicitly, and all time frames are solved simultaneously. Although this method leads to a large nonlinear optimization problem, it can predict stable movements under novel conditions without facing numerical integration problems.

3.1.2 Feedback-control methods

In feedback-control methods, a forward dynamics model and a feedback controller are used with/without an inverse dynamics model. Using the controller, the joint actuator values (torques or muscle forces) are updated by comparing with reference motion data. A classic feedback-control method is the proportional-integral-derivative (PID) control. PID controls the plant model by feeding back the past error.

Due to numerical differentiation errors and inaccurate model parameters, feedback-control methods may predict unrealistic joint torques or muscle forces. Some studies have used the feedback controller in conjunction with model predictive control (MPC) to improve the results.

MPC can be considered as a practical optimization-based method that uses an internal model to estimate/predict the output, compare it with the reference data, and finally predict control inputs of the plant model by minimizing a cost function. The cost function can contain a data-tracking error. Not only does MPC provide stability for the model, but it also has predictive features [23]. MPC is a fast near-optimal controller that seems well-suited to real-time biomechatronic applications [120].

3.2 Components of biomechanical predictive simulations

In this subsection, we describe the components of the optimization formulations (mainly optimal control approaches) for motion prediction: simulation inputs, initial guesses, constraints, and cost function. It is believed that the CNS optimizes performance during motion (i.e., minimizes the metabolic cost of transport, muscle activity, effort, or other criteria), and different cost function terms have been proposed to represent these optimal principles mathematically [4, 11, 43, 52, 122]. Additionally, some simulations include some task requirements (like reaching a target position) that may not be directly related with an optimal principle [123], or include a clinical-related goal [3, 80]. A special mention should be made to sports-related predictive simulations, where the goal is to maximize performance instead of minimizing effort [32, 42, 104, 124]. A detailed description of each of the components of the optimization formulations for the most relevant predictive simulations in the literature can be found in the Supplementary material.

3.2.1 Control and state variables

Torque-driven models

Predictive simulations using torque-driven models following an ID-based algorithm, use as inputs generalized coordinates [17, 44, 45, 125] or generalized coordinates and ground reactions [12, 15, 19]. These references use parameter optimization or sequential quadratic programming (SQP) for solving the optimization problem. When a FD-based algorithm is used, the inputs for the optimization problem are joint torques, together with the initial values for generalized coordinates and/or velocities [7, 33, 42, 43]. These references use dynamic optimization (covariance matrix adaptation) or direct multiple shooting to solve the problem. Finally, in direct collocation approaches, both joint torques and generalized coordinates and velocities are inputs for the optimization algorithm [16, 104]. Other variables that are used as controls in direct collocation approaches are joint jerk [10, 37, 82] and joint torque change [10, 82]. A study that predicts walking in a stochastic environment [126], defines the generalized coordinates as states and velocities and the state feedback control law parameters as controls.

Muscle- and synergy-driven models

Predictive simulations using muscle-driven (and synergy-driven) models use as controls muscle excitations, muscle activations, or muscle forces. In FD-based methods, controls are usually muscle excitations [9, 11, 20, 49, 65], followed by muscle activations [71, 75, 81] and muscle forces [41]. The initial values for states (muscle activation, muscle length, generalized coordinates, and velocities) can be imposed or treated as unknowns in the problem. When they are imposed or known, they can be obtained from experimental data (e.g., assuming static equilibrium) [20, 65, 124] or they can be optimized previously [47]. In [11], initial conditions for generalized coordinates and velocities are imposed from experimental data, but they are included as variables for muscle activations. García-Vallejo et al. use a parameter optimization approach, where both muscle forces and generalized coordinates are design variables [13, 14].

In direct collocation approaches, most studies define muscle excitation as controls, and muscle activation, muscle length (CE length), generalized coordinates and velocities as states [35, 48, 55, 74, 118]. In [23], muscle length is not included as a state variable, and in [127], muscle force is used as a state instead of muscle length. Other types of controls used in muscle-driven simulations are activation/deactivation times for muscle torque generators [32], muscle synergy controls [51], combination coefficients [78], joint jerks [24, 51, 76], and time derivatives of muscle activations, tendon forces and velocities [80, 89]. Predictive simulations using control laws for the actuators that are based on the muscle-reflex controller introduced by Geyer and Herr [128], define as design variables the controller parameters [28, 67, 72, 129], or the controller parameters together with the initial values for generalized coordinates and velocities [30, 54, 57].

Static parameters

Besides control and state variables, some prediction studies include static parameters to be optimized, such as full (or half) cycle duration [33, 82, 89, 124], stride/step duration [48, 70], the duration of different motion phases [13, 30, 33, 45], stride/step length [14, 82], and walking speed [7]. Other parameters that have been used are foot orientation angles, and mediolateral distance between ankles at heel strike [13], angular stiffness of metatarsophalangeal (MTP) joint [52, 70], and linear spring-damper parameters to mimic the compliance and damping properties of muscles, ligaments and passive tissues [7, 43].

Assisted motions

A special mention should be made for studies in which an assisted motion is predicted. The prosthesis or orthosis motor torque [14, 41] or the subject-exoskeleton contact forces [37] can be considered control inputs. Moreover, when optimization is used for assistive device design, orthosis design parameters such as spring stiffness [9, 14, 42] or equilibrium position [42] can be added as design variables. The gains and parameters of controllers of an upper limb exoskeleton were optimized in [130]. Finally, in [76] the stimulation amplitude and timing of a fast functional electrical stimulation (FES) treatment for a post-stroke patient are optimized.

3.2.2 Initial guess

Initial guess definition

The initial values for states in FD-based methods can be obtained from experimental data [29, 75], imposing specific poses, like standing posture [42], or finding an optimal steady state [65]. They can also be assigned random values [28], or be set as zero, especially velocities [16, 42, 75]. Controls are given constant values [65, 75] or are hand-tuned until a first "good" solution is found [42, 54, 67, 72]. In methods where both controls and states are variables, initial guesses for a certain number of time points are given. One approach is to define these initial guesses from experimental data [9, 19, 104], or from a forward dynamic simulation [55, 118]. Some works use experimental data of gait at normal (or self-selected) speed and predict gait for higher and lower speeds [51, 89, 131]. It is also possible to give only initial and final states [18, 37]. Some researchers give as initial guesses random, quasi-random, or arbitrary values [8, 30, 73, 124, 132].

The most common approach is to use as an initial guess the solution from a previous tracking or predictive problem. In tracking problems, the reference motion can be obtained from experimental data from published studies [48, 122], or it can be collected from healthy subjects [48, 56, 94, 122] or from patients [51, 76]. Another option is to use as an initial guess the solution obtained in a previous simulation [23, 57, 122, 126], especially in cases where to help convergence, some constraints are "loosened" in the first simulations and are then "tightened" little by little [21, 73]. In other cases, a first prediction for nominal conditions (e.g., mean speed or normal walking) is generated, and it is then used as the initial guess for predicting motion under different conditions [42, 51, 67, 74]. Alternatively, a first prediction can be started from a random initial guess, and each solution is used as the initial guess for the following prediction, in which some tolerances are tightened [73].

Sensitivity analysis and global optimum

Some studies used different initial guesses to determine the sensitivity of the optimal control solution to a change in the initial guess [55], and to demonstrate the robustness of their simulations against the initial guess [89, 132]. In [18], it was found that the initial and final guesses only seemed to influence the CPU time and did not seem to influence the optimal solution. However, in [81], it was found that the method was clearly sensitive to the initial guesses, and multiple runs were performed to obtain the mean and variability of the results.

It is difficult to be sure that the obtained solution is a global optimum. In [124], they found that the algorithm converged to the same solution regardless of the initial guess. In [41], authors only considered solutions that could be discovered from multiple initial seeds. However, the previous studies predicted a 2D jump and a 2D lower body gait motion; and for 3D walking, in general, different initial guesses converge to different solutions, and the solution with minimum cost function value is the one considered the optimal solution [8, 28, 30, 40, 48]. These references ran each simulation with 2 to 10 different initial guesses and found different solutions per each different initial guess. In [126], they used 100 random initial guesses, for a simple one DoF pendulum swing-up problem. Depending on the degree of complexity of the model and problem, the amount of different initial guesses that can be tested is limited.

3.2.3 Constraints

In optimization approaches, constraints can be classified into dynamic constraints, algebraic equality constraints, and algebraic inequality constraints [133]. Algebraic constraints have also been classified in the literature as interior or terminal path constraints [6], and as time-dependent or time-independent constraints [44]. In optimal control approaches, the system dynamics (which may include skeletal dynamics, activation dynamics, and contraction dynamics) is usually defined as differential equations in explicit formulations [43] and as algebraic equality constraints in implicit formulations [91].

Task-related constraints

In predictive simulations, different task constraints have to be stated to define the motion that has to be predicted. For walking, a target mean speed is often imposed as a constraint [48, 65, 89, 91]. Moreover, cycle or step duration [17, 21, 94, 125], step or stride length [7, 10, 43], or step width [46] can be also known or imposed. Usually, bilateral symmetry is assumed in walking predictive simulations. This is usually done by predicting only a half cycle [11, 73, 89, 122]. Moreover, periodicity is imposed in most predictive simulations of walking [13, 44, 51, 94]. For other predicted movements different than walking, final (or endpoint) constraints define a prescribed final point [21, 127], or specific conditions on position and/or speed [104]. Additionally, initial and final state may be imposed within a specific tolerance [10, 22, 71, 118].

Physical constraints

In addition to skeletal dynamics, other physical constraints that have to be included in predictive simulations are those that define the contact conditions, which can be kinematic constraints or dynamic equations. Some works model the foot-ground contact through kinematic constraints [33, 75], that define feet point position for specific periods of time [10, 14, 43, 125], or add conditions on foot ground penetration [16, 17] and/or ground clearance [13, 41, 44]. Sometimes, zero velocity is imposed at foot strike [43, 125] or at the start of phases [9]. Forces and dynamic equations are also considered in works that model the foot-ground contact through kinematic constraints, as imposing normal forces to be always positive [13], centre of pressure to be within the boundary of the foot [44], or imposing some limits (e.g. $F \leq \mu N$) on friction [17, 45]. Other contacts that have been modeled through kinematic constraints in predictive simulations include contact with a chair [33], with a bicycle seat [18], hand contact with a box [75], contact between a human and an exoskeleton [75], and bounding the hand position on a treadmill handlebar [76]. In walking, sometimes constraints are added to avoid collision between feet [45, 89] or to avoid body penetration [44, 89]. Finally, in [14], a knee-ankle-foot orthosis (KAFO) actuation is modeled through constraints: the knee is locked during the stance phase, and a Klenzak ankle joint constrains ankle plantarflexion.

Physiological constraints

In predictive simulations of human movements, constraints defining realistic or physiologically feasible movements are added: limits in joints RoM [16, 41, 48, 125], avoiding joint hyperextension [17, 124]; or bounding neural excitations and activations between zero and one [6, 21, 56, 81], between a lower value greater than zero and one [65, 89], or between zero and a maximum value adapted to weakened impaired conditions [14]. Other constraints related to muscle forces include the condition of muscle forces to be always positive [124] or to be bounded to a maximum value [85], and joint torques being limited using variable bounds [44, 104] or through contraction dynamics [72]. Physiological constraints include the excitation-activation dynamics and the muscle contraction dynamics (force-length and force-velocity properties defined by the Hill-type muscle model [134]]). The latter can be modeled with more or less complex equations. Other constraints related to neural activity include limits on neural transmission speed [67] and muscle excitation timing [50]. Finally, reflex-based controllers add realistic constraints on the control space by modeling physiological feedback loops, and sensors [57].

Constraints versus penalty terms in the cost function

Some constraints are enforced using penalty terms in the cost function. For instance, avoiding joint hyperextension has been formulated as a constraint [6, 13, 124] or as a penalty term in the cost function [47], and tracking synergy controls has been imposed using constraints [76] or penalty terms in the cost function [51]. A possible drawback of using penalties to enforce constraints is that they can create local minima [40].

3.2.4 Cost function terms

Optimality terms

Metabolic cost

One of the most accepted approaches to predict walking and running is to minimize metabolic cost, using 2D [28, 30, 52, 73] and 3D [11, 56, 67, 72] models. This cost function term has also been used to predict bicycle pedaling [40]. In some works, minimizing metabolic cost has been considered as a single objective in the cost function [28, 56, 73, 94], but in others has been combined with other terms [8, 14, 54, 129].

Muscle effort and fatigue

A second group of terms widely used for motion prediction is those related to muscle effort and fatigue, quantified through minimization of weighted muscle excitations, activations, forces, and stresses. Minimization of squared activations [48, 89, 91, 122] and cubed activations [48, 94, 122, 132] are used to minimize muscle effort or fatigue. Minimization of activations to a power of 10 [48, 80, 94] approximates the minimization of the largest muscle excitation integral and thus avoids excessively activating any single muscle [135]. Squared activations can be weighted by muscle volume [48], muscle mass [94] or by travelled distance [9]. Motion prediction has also been done by minimizing squared excitations [23, 35, 53, 94], squared muscle forces [94, 127] or time derivative of muscle force [21, 40], squared muscle stress [52, 94], stress to a different power [40, 94], or divided by muscle mass [94]. In some works, squared excitations [80, 89], activations [24, 75], or time derivatives of activation [104] are minimized for reserve or muscle torque actuators. It is interesting to note that some researchers have performed a comparison of different muscle effort/fatigue-related terms [40, 48, 94], but have not found a clear advantage of one specific cost function formulation over another. Minimizing muscle effort/fatigue related terms has worked for 2D [40, 73, 104, 118] and 3D [24, 49, 78, 81] simulations, and has also been used as a single objective [9, 21, 73, 118] or combined with other optimization terms [24, 71, 89, 104]. Besides walking and running [73, 94, 122, 132], different activities have been predicted using muscle effort or fatigue-related terms: squatting [21, 123, 127], bicycle pedalling [35, 40], manual wheelchair propulsion [104], weight lifting with an exoskeleton [75], arm motion [23, 71, 78, 81] and finger tapping [20].

Joint torque

The minimization of joint torque has been defined as a minimization of energy [29, 125] or dynamic effort [44, 72] criterion, especially in torque-driven simulations, but also in some muscle-driven simulations. In some 3D walking torque-driven simulations, minimization of squared joint torques has been used as a single-objective cost function [29, 44, 125], while in others, it has been combined with other criteria [43, 126, 136]. In [33], minimization of squared joint torque is used together with other terms for designing physical assistive devices to support sit-to-stand transfers of geriatric patients. Some muscle-driven simulations include minimization of all squared joint torques [85], of ideal joint torques in the upper body [72], or of passive joint moments that model ligaments and other passive structures [8, 80, 89].

Stability and balance

Stability/balance-providing terms have always been used combined with other criteria, in both torque-driven [7, 33, 43] and muscle-driven [30, 54, 57, 72, 132] simulations. The most common way of defining stability is by minimizing the motion of the head [43, 57, 72], which can be done by minimizing head angular velocity [7, 33] or head acceleration [30]. Another option is to minimize distance, or relative forward velocity, between the head and the body CoM [54], or between the head and the center of the base of support [132].

Mechanical and kinetic terms

Other mechanical or kinetic objectives used for motion prediction are minimizing mechanical energy, angular momentum, or contact forces, and encouraging smoothness of movement. Minimization of mechanical energy in torque-driven models was used in different motions, e.g., as a single term in 2D walking [17], or as a combined term in 3D crutch walking [10] and 2D sit to stand transfer [33]. Minimization of system angular momentum expressed at the CoM [7] or the sum of the squared norms of the local angular momenta [10] was used, combined with other criteria, in 3D torque-driven models. Other terms related to contact forces and ground reaction forces that are minimized are: joint contact forces in running [94], reaction forces in the wrist joint in steering tasks [85]; foot–ground impact in walking: ground reaction forces (GRFs) derivative [30], an impulse at the foot on touch-down [43]; sum of the hand forces in manual wheelchair propulsion [104]. Finally, there are other terms related to the smoothness of movement: minimize squared joint velocities at the last time step [78], minimize joint accelerations [80, 89], or minimize jerk costs for the CoM [132].

Sports applications

In sports, the goal is usually defined as an objective function, as says the original Olympic motto *"Citius, Altius, Fortius"* ("Faster, Higher, Stronger"). Examples of "faster" can be found in maximizing speed for sprinting [70] and maximizing distance in bicycle standing start [18]. Examples of "higher" can be found in maximizing jumping height [47, 65, 124] or jumping distance [42], and maximizing carry distance in golf drives [32, 104]. These objectives are usually the only criterion considered in the cost function [6, 18, 55].

Clinical applications

In clinical applications, the cost function usually contains different criteria, and one of them is related to the treatment goal, as minimization of knee contact force [8] or adduction moment [19, 50], minimization of maximum knee flexion angle [8], minimization of anterior-posterior force [76], or minimization of joint moment [53] asymmetry. In human walking with assistive devices (e.g., active orthoses and prostheses), device-related costs can be included in the cost function, as minimizing the root mean square (RMS) power [14] or actuation torque [14, 41] from the assistive device, or minimizing the human–exoskeleton interaction energy [37]. In some wearable robotic systems, prosthesis and orthosis design and tuning simulations, usually parameters from the devices are optimized, but without considering additional terms in the cost function [9, 42].

Task-related and optimization supporting terms

There are some terms that are included in the cost function for predicting motion, not for being optimality principles, but task-related (desired or imposed speed), penalty terms to avoid undesirable motions, regularization, and optimization-supporting terms.

Task-related objectives used in predictive simulations related to angle or position include covering at least a certain distance [28], minimizing steering wheel angle [85], imposing the pedal cycle travel [40], or reaching a desired position (e.g., vehicle lateral position [85], or hand end position [23, 78]). Task-related objectives related to speed include reaching a target velocity [28, 35, 67, 72] or angular velocity [40], or a target stride/cycle duration [53, 74, 126]. Other terms include encouraging periodicity in kinematic state [49, 50] or encouraging steady speed [70].

Penalty terms are used to avoid undesirable motions, as hyperextension of the joints to avoid ligament injury [30, 57, 70, 78], or deviation of the trunk from an upright posture during walking [45, 72]. Other

Table 2 Terms that are tracked (x) in simulations that predict new motions using multi-objective cost functions, which include tracking one or more quantities.

Reference	Motion	Dimension	Control	Angles/orientation	Joint torques	Residual loads	GRFs	CoP	Footpath/Foot angles	Activations/synergy controls	Excitation timing	Stride/step time
[35]	Pedalling	2D	Hill-type muscles						x			
[127]	Raising up from squat	2D	Hill-type muscles		x							
[12, 19]	Walking (knee OA)	3D	Ideal torque actuators	x	x	x	x	x	x			
[15]	Walking (knee OA)	3D	Ideal torque actuators	x	x	x		x	x			
[64]	Walking	2D	Hill-type muscles	x			x					
[91]	Walking (prosthesis)	2D	Hill-type muscles	x			x					
[13]	Walking (one-side disorders)	3D	Hill-type muscles	x			x					
[46]	Walking (weak hip abd.)	3D	Ideal torque actuators	x								
[50]	Walking (gait retraining)	3D	Hill-type muscles								x	
[51]	Walking (post-stroke)	3D	Muscle synergies	x	x					x		
[14]	Walking (SCI subject with KAFO)	2D	Hill-type muscles	x			x					
[53]	Walking (prosthesis)	2D	Hill-type muscles	x			x					x
[20]	Finger tapping	2D	Hill-type muscles	x								
[74]	Walking (unilateral transtibial)	2D	Hill-type muscles	x			x					x
[132]	Walking	2D	Hill-type muscles	x			x					
[81]	Arm motion	3D	Muscle synergies	x								
[37]	Sit-to-stand (with exoskeleton)	2D	Ideal torque actuators		x		x	x				
[126]	Walking	2D	Ideal torque actuators	x			x					x

undesirable effects that are avoided are falling [54, 57, 67, 72] or slipping [42, 136]. Finally, model torque production has been limited by penalizing rapid activation and deactivation [41].

Some authors add regularization terms (or optimization supporting terms) to avoid singular arcs, i.e., situations for which controls are not uniquely defined by the optimality conditions [133]. Regularization terms include minimization of joint jerks [10, 24, 51, 76], joint torques [7], joint torque change [10], external forces [33], time derivatives of activations [89], time derivatives of tendon forces [89], and joint accelerations of the arms [89]. Some works correlate jerk to the smoothness of motion [137, 138], but it remains unclear if it is one of the optimality principles that guide human motion.

Data-tracking terms

Some simulations include tracking terms in the cost function (Table 2). The tracked quantities can be obtained from experimental data, from the literature, or from previous simulations. Quantities that are tracked include joint angles or body orientation [19, 51, 91, 132], joint torques [15, 37, 51, 127], residual loads at the pelvis [12], ground reaction forces [13, 53, 74, 91], centre of pressure (COP) [19, 37], footpath or foot angles [15, 35], activations/synergy controls [51], excitation timing [50], or stride/step time [74, 126]. Some references track only one type of magnitude (e.g., only joint angles or only forces) [35, 94], whereas others track different types of magnitudes at the same time [14, 19, 74, 126]. Tracking can be done also through equality constraints [24, 71, 76].

Some authors have used tracking terms to answer specific research questions. In [31], it was found that the contact force could be reduced while maintaining a normal knee joint motion, but at the cost of using a slightly slower speed and a shorter stride length. In [80], results showed that upright (close to healthy) walking was less optimal than walking in a crouch for a child with cerebral palsy.

3.2.5 Cost function design

An important aspect of predictive simulations is finding the terms included in the cost function, as well as the weighting factors for each of these terms. Generally, the cost function is assumed a priori, based on previously published studies or some hypotheses, and the weighting factors are manually adjusted [47, 54, 91, 127]. Another approach for determining the cost function is to compare the predicted motion using different cost functions. Some works compare different single-term cost functions [48, 94] in order to gain insights into each term, or the same cost function but with different mathematical formulations (e.g., in [49], five different energy models to calculate the metabolic cost term in the cost function were compared). In other works, this comparison is made with the aim of finding a combined cost function that improves the results compared to the single-term cost functions [10, 30, 82]. Other published studies determine the cost function from among a family of possible cost functions, by an inverse optimal control problem [139]. These studies include a small (three in [132], five in [140]) or large (twelve in [141]) number of different terms. The difference between the solution and experimental data or a synthetic motion is minimized, and in this way, the weighting factors are found. A weight close to zero or even zero may indicate that the specific term does not need to be included in the cost function. When the cost function is assumed a priori, weights can be manually adjusted, as stated previously; can be determined following a formal comparison [12, 19, 33], e.g., computing a Pareto front [30, 41]; or can be determined using an optimization procedure [15, 29].

The combination of subject-specific models with optimal control approaches is a promising tool for designing patient-specific treatments [3], but finding the correct optimal control problem formulation for the generation of new impaired or assisted walking motions is a current challenge [4, 89, 142]. Some researchers make the assumption that the cost function is the same for healthy subjects and impaired subjects (e.g., amputee, one-sided impairments, spinal cord injury (SCI) subjects) [13, 82, 89, 91]. Other authors formulate a hypothesis and test it by performing predictions. For example, in [53], the authors hypothesize that subjects with unilateral transtibial amputation can walk with more symmetric joint moments at the cost of increased effort or abnormal kinematics; and, in [80], the authors investigate whether a child with CP adopted an impaired crouch gait pattern because of neuro-mechanical constraints or because it was more optimal. A common finding is that the optimized cost function includes different criteria, as the use of multiple criteria leads to improved results [10, 89, 132, 143]. This is usually done by having a combined cost function optimizing multiple criteria simultaneously, but it can also be done by having single-term cost functions that are optimized one after the other [28]. In the case of multiple-objective cost functions, a critical aspect is finding the weighting factors, and interpreting those values, as they may include the scaling of the cost function terms, and a term that dominates the others in the cost function may not necessarily be the most important factor [89, 132]. In addition, it is an open research question whether these weights (and even some cost function terms) are subject-specific [12, 15, 80], which would be of high importance in the case of clinical applications [3].

3.3 Validation of simulation results

Validation of results is a critical step in predictive simulations to corroborate that those results are representative of the physical system, and they can be applied in real scenarios (Table 3). Hicks and co-workers [26] suggested a seven-stage process for verification and validation of models and simulations. However, such a rigorous (or a similar) validation of MSK models is not usually done, mainly because of its technical difficulty [144, 145]. Some researchers publish their predictive simulation results without validating them against experimental data, discussing them qualitatively based on what they expected to find (e.g., if the gait looks natural [43]). Usually, it is because the authors aim to evaluate the feasibility of a new approach, rather than analyzing some specific tasks or motions [21, 81, 118], or because they are more interested in comparing different methods [16, 78] or different problem formulations (e.g., different cost functions [48, 53]) among them.

When results are validated, this validation is often weak [3]. Some researchers validate their results qualitatively by "visualization" or taking into account the researcher's or clinician's experience [33]. Another approach is to validate results by comparing them against published data [14, 55, 122, 129]. In this approach, the validation is usually done qualitatively (e.g., by checking the trends or if results fall within the mean and 1 or 2 standard deviations). While this approach allows one to check if the predicted results look realistic or natural, it cannot be used in subject-specific applications, where a more strong validation is required [3].

The most used approach for validating predictive simulation results, is to compare them against experimental data collected for one [7, 18, 29] or more than one [11, 49, 74, 104] subject. Collected data are in almost all cases marker trajectories [15] and ground reaction forces [15], and some works include also EMG measurements [76, 80] or pulmonary gas exchange rates [49]. Validation is usually done more extensively when subject-specific models (i.e., some model parameters are identified beyond just anthropometric scaling) are used, and in this case, data are collected for the specific subject under study [9, 15, 51, 76, 80, 104].

There are also a few research studies that have published extensive human movement data sets, including motion, ground reaction forces, and EMG data, along with in vivo hip or knee contact force data that can be used for model validation purposes [146, 147]. Some studies use these datasets for validating their predictive methods [24, 56]. Moreover, a novel shear wave tensiometer has been recently developed to measure tendon forces in vivo [148]. These novel techniques are promising for measuring internal forces with non-invasive methods. However, despite this considerable progress in the movement measurement capabilities, there is still no extensive movement data for clinical use (e.g., patient movements before and after treatments) in the literature [3].

3.4 Domain of applications

Predictive simulations using neuromusculoskeletal models have been used for clinical purposes (Table 4), in sports, and in industrial/ergonomics applications (Table 5). The Food and Drug Administration has recently endorsed the use of computer simulation to support medical device design [5]. The use of computer simulation instead of (or together with) clinical trials could reduce time and costs in the design of medical devices and interventions. As mentioned in section 3.2.4, the original Olympic motto *"Citius, Altius, Fortius"* ("Faster, Higher, Stronger") is well suited for predictive simulations in sports. Finally, there are some studies that show the potential of using predictive simulations in some industrial applications to avoid work-related injuries, to increase productivity and/or to reduce discomfort.

3.4.1 Clinical

Proof-of-concept studies

Some researchers show the potential application of their predictive framework to clinics by including some additional results as a proof-of-concept, where some impairment, disorder and/or assistive device is modeled. In [91] and in [13], the waking motion of an amputee and an individual with one-side disorder, respectively, are predicted. Both studies use a generic model and include multiple tracking terms in the cost function. In [46] a Trendelenburg gait (with weakened hip abductors) was simulated, and the model was able to predict a small increase in lateral trunk sway as a compensatory strategy. In [89], the capability of a fully predictive framework using a 3D full body model, muscle-driven (trunk and lower body), is demonstrated by predicting the walking of a subject with muscle weakness and a subject with a prosthesis.

Investigation of a clinical question

Predictive simulations have been used to gain insights into a specific clinical problem. In these cases, the model used is generic, and usually 2D, and includes only the lower body, as the main goal of the research is not to find a result for a specific subject but to understand better an underlying mechanism or to find possible treatments for a general population. In [57], the authors explored gait adaptations due to ankle plantar flexor muscle weakness and contracture, which occur commonly in conditions such as cerebral palsy, stroke, and muscular dystrophy. Both the development and progression of knee osteoarthritis have been associated with the loading of the knee joint during walking. In [8], walking patterns that minimize the axial knee joint contact force were predicted. These results could help to develop strategies for changing walking biomechanics to offload the knee joint without resorting to surgery. In [50], the authors use a 3D lower body model to explore the relationship between knee adduction moment reduction and changes in medial knee joint contact force. In [53], they tested the following hypothesis: people with a unilateral transtibial amputation can walk with more symmetric joint moments at the cost of increased effort or abnormal kinematics. The hypothesis was confirmed using predictive simulations of gait. In [74], the authors tried to understand the relationship between changes in strength and gait energetics in subjects with transtibial amputation, and their results suggested that maintaining muscle strength may prevent an increase in the metabolic cost of walking following unilateral transtibial limb loss.

Subject-specific treatment design

Fregly et al. have used a computational model to predict how an individual with medial knee osteoarthritis should walk differently to reduce medial knee contact force and relieve pain [19]. They developed a patient-specific cost function to predict the influence of foot path on the knee adduction torque during gait [12], and compared how two treatments for knee osteoarthritis —gait modification and high tibial osteotomy surgery— altered the external knee adduction torque for a specific patient [15]. In these three studies, the model used was a torque-driven 3D full body model, which was personalized

Table 3 Different approaches for validation of predictive simulation results. If the authors use data collected from a previous study but with the same authors, this is considered as "against experimental data". When results are evaluated against experimental data, we indicate by "n" the number of subjects (usually, more than one trial is collected per subject, but we do not provide information on the number of activities or trials).

		Torque-driven		MTG-driven		Muscle/synergy-driven	
		2D	3D	2D	3D	2D	3D
Not validated			[43, 45]			[21, 71, 118]	[81, 85]
Weak validation	Qualitative evaluation	[33]					
	Comparison among solutions or methods		[16]			[48, 53, 65, 127]	[78]
	Against literature results	[126]	[44, 125]	[42]		[6, 14, 20, 22, 28, 35, 40, 55, 57, 64, 73, 91, 122, 129]	[67, 78]
Strong validation	Against exp. data (n=1)	[17, 37]	[7, 10, 12, 15, 19, 29]	[9, 75, 90]	[18]	[23]	[13, 51, 76, 80, 89]
	Against exp. data (n>1)		[46]		[32, 104]	[8, 30, 52, 54, 70, 74, 94, 124, 132]	[11, 47, 49, 50, 72]
	Against datasets						[56]

Table 4 Overview of predictive simulations with clinical application. A simulation is considered "fully predictive" when no tracking terms are included in the cost function (or in tracking constraints). If tracking terms are included, then we indicate if they are included in the cost function (cf) or in constraints, and if in the cost function, if only one type of quantity is tracked (single) or more than one (multi). Regarding validation of results, if the authors use data collected from a previous study but with the same authors, this is considered as "against experimental data". When results are evaluated against experimental data, we indicate by "n" the number of subjects (usually, more than one trial is collected per subject, but we do not provide information on the number of activities or trials).

Ref.	Motion/subject (study type)	Dim. (control)	Subj-spec?	Method	Fully predictive?	Validation?
[91]	Amputee (Proof-of-concept)	2D lower (muscle)	no	Direct collocation	semi (cf-multi)	literature results
[89]	Amputee, muscle weakness (Proof-of-concept)	3D full (muscle)	no	Direct collocation	yes	exp. data (n = 1)
[13]	One-side disorder (Proof-of-concept)	3D lower (muscle)	no	Parameter optimization	semi (cf-multi)	exp. data (n = 1)
[46]	Weak hip abductors (Proof-of-concept)	3D lower (torque)	no	Kinematic feedback controller	semi (cf-single)	qualitatively
[57]	Muscle weakness and contracture (Gain insight)	2D lower (muscle)	no	Single shooting	yes	literature results
[8]	Knee OA (Gain insight)	2D lower (muscle)	no	Simulated annealing	yes	exp. data (n = 21)
[50]	Gait retraining (Gain insight)	3D lower (muscle)	no	Simulated annealing	semi (cf-single)	exp. data (n = 14)
[53]	Amputee (Gain insights)	2D lower (muscle)	no	Direct collocation	semi (cf-multi)	solutions/methods
[74]	Amputee (Gain insight)	2D lower (muscle)	no	Direct collocation	semi (cf-multi)	exp. data (n = 26)
[10]	Crutch-walking (First prediction)	3D full (torque)	no	Direct collocation	yes	exp. data (n = 1)
[19]	Knee OA (Subject-specific treatment)	3D lower (torque)	yes	Trajectory optimization	semi (cf-multi)	exp. data (n = 1)
[12]	Knee OA (Subject-specific treatment)	3D full (torque)	yes	Trajectory optimization	semi (cf-multi)	exp. data (n = 1)
[15]	Knee OA (Subject-specific treatment)	3D full (torque)	yes	Trajectory optimization	semi (cf-multi)	exp. data (n = 1)
[51]	Stroke (Subject-specific treatment)	3D full (muscle)	yes	Direct collocation	semi (cf-multi)	exp. data (n = 1)
[24]	TKR (Subject-specific treatment)	3D lower (muscle)	yes	Direct collocation	semi (constraints)	datasets
[76]	Stroke (Subject-specific treatment)	3D full (muscle)	yes	Direct collocation	semi (constraints)	exp. data (n = 1)
[80]	CP (Subject-specific treatment)	3D full (muscle)	yes	Direct collocation	yes	exp. data (n = 1)
[14]	SCI (Assistive device design)	2D lower (muscle)	no	Parameter optimization	semi (cf-multi)	literature results
[41]	Amputee (Assistive device design)	2D lower (muscle)	no	Direct multiple shooting	yes	
[33]	Geriatric patients (Assistive device design)	2D full (torque)	population	Direct multiple shooting	yes	qualitatively (clinicians)
[9]	Gait abnormalities (Assistive device design)	2D lower (MTG)	yes	Direct multiple shooting	yes	exp. data (n = 1)
[82]	SCI (Assistive device design)	3D full (torque)	no	Direct collocation	yes	exp. data (n = 2)

Table 5 Overview of predictive simulations with industrial and sports application. A simulation is considered "fully predictive" when no tracking terms are included in the cost function (or in tracking constraints). If tracking terms are included, then we indicate if they are included in the cost function (cf) or in constraints, and if in the cost function, if only one type of quantity is tracked (single) or more than one (multi). Regarding validation of results, if the authors use data collected from a previous study but with the same authors, this is considered as "against experimental data". When results are evaluated against experimental data, we indicate by "n" the number of subjects (usually, more than one trial is collected per subject, but we do not provide information on the number of activities or trials).

Application	Reference	Motion/Subject	Dimension (control)	Subj-spec?	Method	Fully predictive?	Validation?
Assistive Device	[85]	Steering tasks	3D upper (muscle)	no	MPC + PD controller	semi-one	not validated
	[37]	Sit-to-stand (exo.)	2D lower (torque)	no	Direct collocation	semi (cf-multi)	exp. (n = 1)
	[75]	Weight lifting (exo.)	2D full (MTG)	yes	Direct multiple shooting	yes	exp. (n = 1)
Sports	[35]	Pedaling	2D lower (muscle)	no	Direct collocation	semi (cf-single)	literature results
	[22]	Kicking	2D lower (muscle)	no	Direct collocation	fully	exp.
	[70]	Sprinting	2D lower (muscle)	no	Simulated annealing	yes	exp. (n = 12)
	[52]	Running	2D lower (muscle)	no	Simulated annealing	yes	exp. (n = 12)
	[72]	Running	3D lower (muscle)	no	Trajectory optimization	yes	exp. (n = 20)
	[42]	Assisted jump	2D full (MTG)	no	Dynamic optimization	yes	literature results
	[32]	Golf swing	3D upper (MTG)	no	Genetic algorithm	yes	exp. (n = 10)
	[40]	Pedaling	2D lower (muscle)	no	Simulated parallel algorithm	yes	literature results
	[18]	Bicycle standing start	3D full (MTG)	yes	Direct collocation	yes	exp. (n = 1)
	[104]	Golf swing	3D upper (MTG)	no	Direct collocation	yes	exp. (n = 10)
Clinical/Sport	[90]	Wheelchair basketball athlete	2D upper (MTG)	yes	Direct collocation	yes	exp. (n = 1)
	[94]	Running	2D lower (muscle)	population	Direct collocation	yes	exp. (n = 14)

to the subject by calibrating joint centers and axes. The cost function included some tracking terms. A limitation in these studies was that the cartilage wear was not included in the model when it may be important in patients with knee osteoarthritis. Additionally, the knee joint was modeled as a single DoF joint, without considering the secondary kinematics of the tibiofemoral and patellofemoral joints, nor the ligament forces. In [24], a computational framework that includes a more complex model of the knee joint, which simultaneously estimates muscle and joint contact forces and body motion using optimization and surrogate modeling, was developed. This framework represents a promising tool for future studies.

Subject-specific treatment design has been predicted for a stroke patient. In the study of Meyer et al. [51], stroke patient walking was predicted at different speeds. In this work, in addition to minimizing joint jerk, the cost function included various tracking terms (upper body joint angles and lower body joint torques, muscle activations, or synergy activations), following the assumption that under different conditions, the subject would try to find a solution close to what he did in the nominal case. In [76], a personalized functional electrical stimulation treatment for fast-speed treadmill training was designed for an individual post-stroke. In that study, the cost function included minimization of joint jerk and minimization of inter-limb propulsive force asymmetry, which was the targeted gait improvement parameter. In [80], a case study to support clinical decision-making to choose the appropriate treatment for a child with cerebral palsy was reported. The authors explored the influence of altered muscle-tendon properties, reduced neuromuscular control complexity, and spasticity on the gait pattern. They concluded that altered muscle-tendon properties were the primary cause of the crouch gait pattern observed for the child under study, which matched with the clinical examination.

Assistive device design

Optimal control has recently been used to identify the optimal spring characteristics of an ankle-foot orthosis that minimizes muscle effort for a child with gait abnormalities [9]. In [33], an assistive device was designed to best support the sit-to-stand transfer of geriatric patients. The models used were based on percentiles 20/50/80 of male and female geriatric populations. In [14], a semi-predictive simulation has been used to identify the parameters of an active KAFO for SCI subjects. Febrer-Nafría et al. [10] recently found that a multi-term cost function combining minimization of joint jerk, joint torque change, joint mechanical power, and angular momentum predicted four-point crutch walking without tracking any experimental data [10]. Based on this problem formulation, the authors predicted crutch-orthosis-assisted walking of an SCI subject, with the aim of finding the best controller parameters of the robotic orthosis [82].

An interesting application is predicting walking with a prosthesis. Some researchers have attempted to predict gait for transtibial amputees. In such studies, the ankle muscles are usually removed, a passive stiffness is added at the ankle, and limb mass and inertial properties are maintained [41, 53, 74, 91]. In some cases, limb mass and inertial properties are reduced to mimic the prosthesis [89]. In these studies, the patient's neural control strategy is not modeled explicitly, which limits the reliability of those simulations. Including the neural control in the model would help to improve our understanding of how the surgery affects the mechanics and control of the ankle muscles that are partially retained in transtibial amputation surgery [74]. A review of emerging model-based methodologies for personalized neurorehabilitation technologies, which includes an example of designing a biomimetic variable stiffness transfemoral prosthesis, can be found in [149]. Predictive simulations could be used to improve the design of the prosthesis controllers.

3.4.2 Sports

Some sports movements, such as rising up from squatting position [21] or kicking [22], have been chosen as applied examples to demonstrate the effectiveness of the problem formulation or an improvement in computational time when compared to previous methods.

Running

Following what has been discussed in section 3.2.4, it is still an open question which cost function describes the human performance correctly in running. In [72], the authors suggested that metabolic energy expenditure (as a measurement of effort) can be used for both walking and running optimization. In [89], the authors used the same multi-criteria cost function (which includes the cost of transport (COT), i.e., metabolic energy consumed per unit distance traveled) for predicting walking and running. In this case, their results suggested that the cost function may not capture all goals during running, as the predicted walk-to-run transition speed and the stance phase duration were slightly greater/longer than expected. In [52], the authors explored different cost functions, which were minimizing the COT, the total muscle activation, and the total muscle stress. While minimizing the COT naturally predicted the lowest COT, minimizing activation predicted a more realistic COT in comparison with the experimental mean. All these studies have predicted periodic running at a constant speed, which might not be completely realistic, as they do not take into account changes in time as fatigue (which is not included in the current metabolic energy expenditure models). More research is needed regarding the cost function for running, as it might be different for sprinting, trail running, or running a marathon, for instance.

Besides the cost function, other aspects have been studied regarding running. These same authors have used fully-predictive simulations of running using a generic 2D muscle-driven lower body model to gain insights into different aspects of running. They found that the force-velocity relationship is the most important contractile property of muscle regarding limits to maximum sprinting speed [70], and that rear-foot striking is the optimal footfall pattern for a large number of goals (or cost functions) [94].

Cycling

Research on modeling and simulation of cycling has mostly focused on seated pedaling. One of the first semi-predictive simulations solves a steady-state pedaling problem using a 2D muscle-driven model [35]. The computed muscle activations compare well with experimental EMG data. In [40], the authors compared different fully-predictive cost functions for bicycle pedaling, and found that the simulations based on minimizing muscle activation and muscle stress were the ones that matched most closely the experimental pedaling data. Recently, a 2D muscle-driven model has been used for predicting standing starts, when the cyclist starts from rest and attempts to accelerate to top speed as quickly as possible [18]. The cost function consisted in one single term: to achieve the maximum distance in the given time period. The predictive simulations aligned well with the experiments and replicated key aspects of the standing start technique. The authors suggested that this model could be used to investigate optimal cycling techniques and equipment.

Golf

The golf swing has been predicted using a 3D upper body model, driven by MTGs, and a fully-predictive single-term cost function (maximizing ball carry distance), using a genetic algorithm [32] and direct collocation [104]. These simulations provide a deeper understanding of the interaction between golfer biomechanics and the physical properties of golf clubs, which can be used to improve the design of golf clubs.

Clinical aspects of sports

Human motion prediction can be used to find ways of reducing the risk of developing injuries in sports. In [94], the optimal footfall pattern was studied in relation to running performance and injury risk. Another application example can be found in wheelchair sports. A 2D model of the upper body driven by MTGs was used to predict the manual wheelchair propulsion of a basketball athlete who suffered severe, non-spinal lower body knee injury [90], and a 2D torque-driven full-body model was used to predict wheelchair curling of a Paralympic athlete with a spinal cord injury [95].

3.4.3 Assistive devices for healthy populations

A 3D muscle-driven arm model has been used to simulate steering tasks during driving [85]. Realistic driver models, which include modeling of muscle loads, fatigue and co-contraction, can play an important role in developing new driver assistance technologies. Moreover, simulation can aid in the design of performance-enhancing technologies, as it has been suggested by the predictive simulation of an orthosis-assisted long jump [42], and by the predictive simulation of subject-exoskeleton combined motion when lifting a box using a lower back exoskeleton [75]. The framework used in these studies is applicable for simulating a large range of robotic-assisted human motions, but the human-exoskeleton interaction is modeled through kinematic constraints, which may limit the validity of those simulations. Modeling correctly contact forces is an important aspect of human-exoskeleton interaction. It has been found that the calibration of those contact force models is critical to predicting the correct collaborative movement and interaction forces between a subject and exoskeleton during sit-to-stand movements [37]. We can conclude that in the industrial/ergonomics domain, a limited number of predictive simulation studies can be found, but they show the potential use of those simulations to increase performance and/or to avoid injuries.

3.5 Optimal control software

Although some researchers have programmed their own optimal control algorithms for specific NMSK and MSK models, there exist optimal control software packages that can be employed for general computational models. The most popular of these general-purpose software packages are described in the following paragraphs. Other toolboxes or software include CasADi, an open-source tool for nonlinear optimization and algorithmic differentiation [150] (it uses the IPOPT solver), the recursive integration optimal trajectory solver (RIOTS) (a MATLAB toolbox from the University of California, Berkeley, USA), the open-source software for predictive simulation of biological motion (SCONE) [151], Bioptim, which is a Python framework based on IPOPT [152], and musculoskeletal optimal control (Moco), which can perform tracking and predictive simulations using OpenSim models [27].

Researchers have obtained predictive simulations of MSK movement by combining OpenSim models with optimization algorithms in MATLAB (The MathWorks, Inc., MA, USA) [55, 118] or SCONE [57]. MATLAB can call the OpenSim multibody dynamics engine using MEX files that communicate data between the shared memory and OpenSim's C++ API [51, 55, 76, 118, 153]. Eskinazi and Fregly have developed an interface between MATLAB and OpenSim with code parallelization capabilities for direct collocation whereby multiple queries are created instantly [24].

The optimization toolbox of MATLAB software has optimization algorithms that are widely used in the literature. The common algorithms are: Levenberg–Marquardt nonlinear least-squares (model fitting) optimization [15, 19]; SQP algorithm [17, 65], which may run the constrained nonlinear optimization algorithms (fmincon) routine [20, 71, 127]; interior-point algorithm available within the fmincon [55, 118]; and Nelder–Mead algorithm, which run by bounded constrained multivariable function (fminsearchbnd) using a derivative-free method [71].

MATLAB can also integrate with the open-source IPOPT [154] or commercial SNOPT [155] toolboxes. By using sparsity in the constraint Jacobian matrix that develops when the system dynamics are translated to a wide set of algebraic equality constraints, IPOPT and SNOPT have the potential to significantly exceed fmincon [118]. When a good initial guess is unavailable, IPOPT is favored [18, 24, 51, 104], whereas SNOPT is preferable when a series of related problems has been solved, and early guesses are already near to the solution [91].

The multiple shooting code (MUSCOD-II) [156] is used as a direct multiple-shooting-based reduced SQP method for the solution of mixed-integer nonlinear constrained optimal control problems. By discretizing continuous controls on a grid and solving the resulting boundary value issue, MUSCOD-II reduces the infinite-dimensional problem into a finite-dimensional nonlinear problem.

The general-purpose optimal control MATLAB software version II (GPOPS-II) is a commercial toolbox for direct collocation (simultaneous) multiple-phase optimal control that implements variable-order Gaussian quadrature orthogonal collocation algorithms [157]. GPOPS-II uses the hp-adaptive mesh refinement approach to optimize the individual interval widths and polynomial degrees to attain a final optimal solution. GPOPS-II parameterized both states and inputs into a sparse nonlinear programming problem. IPOPT and SNOPT solvers are available within the GPOPS-II toolbox. For dynamic constraints, GPOPS-II does not support implicit dynamics and needs the usage of explicit dynamics [10].

4 Conclusion

In the past 25 years, multibody system dynamics has seen a rapid increase in applications to the simulation of human movement. New models of joints, muscles, and contacts have been combined with optimal control methods to develop predictive dynamic simulations of humans without relying on data from costly and time-consuming experiments. These what-if simulations hold great promise for the rapid and safe development of new medical interventions and assistive devices, and preliminary applications have included prostheses and orthoses, surgery assessment, wearable robotics, and sports optimization.

However, there are still many significant challenges to overcome before predictive human simulations become widely accepted and adopted. First and foremost, the accuracy of these computer simulations must be firmly established, especially for the subject-specific models that are needed for personalized treatments. These subject-specific models will require systematic methods to convert non-invasive measurements (e.g. from wearable sensors or markerless motion capture using AI-based pose estimation) into the many parameters in the model. Studies that compare different models of joints, muscles, and contact forces (including human-device interactions) are needed to develop guidelines for choosing the most appropriate model for a given application. Fast and accurate solutions to the muscle redundancy problem should be researched, especially in the presence of co-contraction of muscles or muscle torque generators. More studies are needed to determine if and when a human moves so as to minimize some cost function, and what mathematical terms should be included in that function.

Predictive human simulations are time-consuming, mainly because optimal control methods must run many dynamic simulations in their search for optimal movements and devices. Methods to improve their computational efficiency are needed, especially for clinical practice in which decisions must be made quickly. Muscle synergies offer one approach to reduce the number of inputs and therefore the size of the optimal control problem, while machine learning might be used to increase the speed of the dynamic simulation and control algorithms. Model-predictive control is another promising approach to the fast simulation of near-optimal human movements.

Another future research direction is to investigate how one can model the recovery of the neural control system during rehabilitation, and the adaptation of a human to an assistive or rehabilitative device (and vice-versa, in the case of devices with model-based controllers). To simulate altered walking or reaching patterns, research into how the neural control of muscle coordination adapts to different neuromuscular conditions, such as spinal cord injury or stroke, is needed. The effects of aging on muscles and cognition should also be included in predictive dynamic simulations, for both clinical practice as well as sports applications. The latter also requires better models for muscle dynamics, particularly energy expenditure and fatigue, in order to boost performance and avoid injuries.

The growth in multibody dynamics of human movements over the past 25 years has been remarkable, and the authors expect that research in predictive dynamic simulation of human motion will continue its exponential growth until computer simulations become commonplace in clinical practice, sports, and biomedical engineering companies.

5 Declarations

Ethical Approval Not applicable.

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Availability of data and materials A detailed description of each modeling element and of each of the components of the optimization formulations for the most relevant predictive simulations in the literature can be found in an Excel file in the Supplementary material.

Glossary

CE contractile element.
CNS central nervous system.
CoM center of mass.
COP centre of pressure.
COT cost of transport.
CP cerebral palsy.
CPG central pattern generator.
CT computed tomography.
DAE differential algebraic equation.
DoF degrees of freedom.
DXA dual-energy X-ray absorptiometry.
EMG electromyography.
FD forward dynamic.

FE finite element.
FES functional electrical stimulation.
GPOPS-II general-purpose optimal control MATLAB software version II.
GRF ground reaction force.
ID inverse dynamic.
IPOPT interior point optimizer.
KAFO knee-ankle-foot orthosis.
Moco musculoskeletal optimal control.
MPC model predictive control.
MRI magnetic resonance imaging.
MSK musculoskeletal.
MT muscle-tendon.
MTG muscle torque generator.
MTP metatarsophalangeal.
MUSCOD-II multiple shooting code.
NLP nonlinear programming problem.
NMSK neuromusculoskeletal.
ODE ordinary differential equation.
PID proportional-integral-derivative.
RIOTS recursive integration optimal trajectory solver.
RMS root mean square.
RoM range of motion.
SCI spinal cord injury.
SNOPT sparse nonlinear optimizer.
SQP sequential quadratic programming.
TKR total knee replacement.

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