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Design of Optimal Treatments for Neuromusculoskeletal Disorders using Patient-Specific Multibody Dynamic Models

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Abstract

Disorders of the human neuromusculoskeletal system such as osteoarthritis, stroke, cerebral palsy, and paraplegia significantly affect mobility and result in a decreased quality of life. Surgical and rehabilitation treatment planning for these disorders is based primarily on static anatomic measurements and dynamic functional measurements filtered through clinical experience. While this subjective treatment planning approach works well in many cases, it does not predict accurate functional outcome in many others. This paper presents a vision for how patient-specific multibody dynamic models can serve as the foundation for an objective treatment planning approach that identifies optimal treatments and treatment parameters on an individual patient basis. First, a computational paradigm is presented for constructing patient-specific multibody dynamic models. This paradigm involves a combination of patient-specific skeletal models, muscle-tendon models, neural control models, and articular contact models, with the complexity of the complete model being dictated by the requirements of the clinical problem being addressed. Next, three clinical applications are presented to illustrate how such models could be used in the treatment design process. One application involves the design of patient-specific gait modification strategies for knee osteoarthritis rehabilitation, a second involves the selection of optimal patient-specific surgical parameters for a particular knee osteoarthritis surgery, and the third involves the design of patient-specific muscle stimulation patterns for stroke rehabilitation. The paper concludes by discussing important challenges that need to be overcome to turn this vision into reality.

Keywords

Multibody dynamics; Biomechanics; Musculoskeletal models; Optimization

INTRODUCTION

When the human neuromusculoskeletal system is impaired, mobility is often limited, leading to a decreased quality of life [1]. Common clinical examples include osteoarthritis, stroke, cerebral palsy, and paraplegia. Planning of surgical and rehabilitation treatments for these disorders has historically been based on clinical experience, static anatomic measurements (e.g., x-rays), and dynamic functional measurements (e.g., gait analysis). To select a treatment and associated parameters, the clinician uses the available data to construct a

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"mental model" of the patient in his or her mind and runs the treatment options under consideration through this model. Thus, given the same clinical data for a particular patient, two different clinicians may make very different treatment decisions.

Due to the complexity of the human neuromusculoskeletal system, this subjective treatment planning approach has several negative consequences. First, existing treatments that are generally reliable may still be unreliable in a large number (though small percentage) of cases. For example, total knee replacement surgery is generally reliable, but a malpositioned component can result in pain, poor patient function, and eventually the need for revision surgery [2]. Second, existing treatment approaches that are unreliable but potentially valuable are avoided by clinicians; hence their benefits are not experienced by patients to the extent possible. For example, high tibial osteotomy surgery, where lower leg bone geometry is altered to make a "bow-legged" patient with knee osteoarthritis slightly "knock-kneed," has the potential to delay or even avoid the need for total knee replacement but is underutilized due to unreliable outcomes [3]. Third, new treatments are difficult to design since they are typically identified using a time consuming and costly trial-and-error experimental approach.

What, then, is the path to increased reliability and optimized functional outcome? One possibility is to replace the subjective mental models currently used in clinical practice with objective engineering models that obey the laws of physics and physiology. If engineering models can be constructed that accurately represent the neuromusculoskeletal systems of individual patients, clinicians could use these models to explore different treatment options prior to selecting the final intervention. By incorporating optimization principles into the exploration process, it may be possible to design personalized treatments that maximize clinical outcome on a patient-specific basis and that eliminate much of the subjectivity from the decision making process. Objective predictions of post-treatment function made by patient-specific engineering models would need to be validated before such models could be utilized clinically.

Multibody dynamic models have the potential to play a central role in the design of personalized treatments for neuromusculoskeletal disorders. The human neuromusculoskeletal system can be viewed as a servo-controlled multibody dynamic system. Bones serve as the rigid bodies, articular surfaces and ligaments form the joints, muscles are the actuators, and the central nervous system acts as the controller. A problem with the bodies, joints, actuators, or controller becomes evident in movement limitations of the system. For example, osteoarthritis involves problems with the bodies and joints, stroke and paraplegia involve problems with the actuators and controller, and cerebral palsy involves problems with the bodies, actuators, and controller. Regardless of the source of the problem, multibody dynamic skeletal models can serve as the underlying structure to which muscle-tendon actuator models, neural control models, and joint contact models are added. Thus, multibody dynamics provides a natural foundation for patient-specific modeling efforts.

This paper presents a vision for how patient-specific multibody dynamic models could be used to design new or improved treatments for clinical problems involving the human neuromusculoskeletal system. The ultimate goal is creation of high fidelity patient-specific multibody dynamic models that can be used to predict optimal treatments for individual patients. First, a computational paradigm is presented for constructing patient-specific multibody dynamic models. Next, three clinical applications are presented to illustrate how such models could be used in the treatment design process. Finally, the paper concludes by discussing important challenges that need to be overcome to turn this vision into reality.

CONSTRUCTION OF PATIENT-SPECIFIC MODELS

Patient-specific neuromusculoskeletal models are composed of several component models. At the core is a patient-specific skeletal model that accounts for the anatomic structure of the patient. Added to this model are muscle-tendon models that account for muscle force-generating characteristics and muscle lines of action around bones, neural control models that account for how the brain coordinates muscle forces, and joint contact models that account for how articular surfaces interact. State-of-the-art methods used to construct each of these component models are described below.

It is important to emphasize that not all of these component models are needed to address any particular clinical problem. The minimum complexity model that satisfies the needs of the problem at hand should always be selected. Thus, some clinical problems will not require models of muscle-tendon actuators. Other clinical problems will not require joint contact models. Yet other clinical problems will not require a neural control model. However, for every clinical problem discussed below, a patient-specific multibody dynamic model will serve as the foundation.

Patient-specific skeletal models

A patient-specific multibody dynamic skeletal model is basically a robotic linkage model whose joints are engineering constraint-based joints (e.g., pin, ball-and-socket) controlled by torque actuators. These actuators account for the net effect of all muscle, contact, and ligament forces applied across the joints. Thus, no models of individual muscles or their lines of action are included at this point.

The primary challenge of creating a patient-specific dynamic skeletal model is not deriving the equations of motion (which can be done using a variety of commercial or free software programs such as Autolev, SD/Fast, Pro/Mechanica, SimMechanics, or SimBody) but rather calibrating the model's parameter values to movement data collected from the patient. Two categories of model parameters are present at this stage: joint parameters defining the position and orientation of each joint in adjacent body segments, and inertial parameters defining the mass, mass center, and central principal moments of inertia of each body segment (also referred to as "body segment parameters" by some authors). A number of labs have developed methods for calibrating joint parameter values [4–14], and sensitivity studies have shown that joint torques calculated from inverse dynamics are sensitive to errors in joint parameter values [15–18]. Calibration of inertial parameter values for activities of daily living that do not involve "fast" movements (e.g., gait) appears to be less critical, as inverse dynamics joint torques are relatively insensitive to errors in inertial parameter values as long as a multibody dynamic model with joint constraints is used [15]. However, a similar conclusion may not apply to faster athletic movements such as running, jumping, throwing, and kicking.

Most methods for calibrating joint parameter values to a patient's movement data utilize numerical optimization [4–6, 8, 10]. First, a kinematic skeletal model is constructed with joint parameters that define the positions and orientations of the joints in the body segments and marker parameters that define surface marker locations in the body segments. This step requires an assumed skeletal model structure (e.g., assuming that the knee can be modeled as a pin joint). Next, experimental movement data are collected from the patient. To make the joint parameter values unique, calibration motions are required if the activity to be simulated does not exercise all functional axes sufficiently, where "sufficient" is approximately 25 deg of rotation [19]. For example, since gait does not exercise the ankle inversion-eversion axis, an ankle circumduction motion can be used to find a unique inversion-eversion axis [8]. Finally, a series of optimization problems is solved that finds joint and marker parameter

values such that markers on the kinematic model can be aligned as closely as possible with the experimentally measured marker locations. Optimization of the calibration trials is performed one joint at a time, followed by optimization of the functional activity trial (e.g., gait) [5]. One of the primary advantages of constructing patient-specific kinematic models in this fashion is that the resulting model parameter values are much less sensitive to selected marker placement locations on the skin than methods that depend on correct identification of anatomical landmarks [9, 10].

For the functional activity optimization, joint parameters that are not exercised can be handled one of two ways. Either the values of these parameters can be constrained to those found by the calibration trials, or else changes in these parameter values can be minimized by the cost function to avoid finding unrealistic solutions [5]. For example, joint parameters specifying the medial-lateral position of the hip center are not well defined by gait data. If these parameter values are adjusted during optimization of a gait trial, noise in the marker data may produce a slightly lower cost function value by moving the hip center laterally off the pelvis, even though such a change is physically unrealistic.

Each optimization can be formulated as either a one-level or two-level problem [5, 6]. In the two-level formulation, both levels seek to minimize the sum of the squares of the errors between model and experimental marker coordinates. The outer-level optimization adjusts design variables related to joint and marker parameter values, while the inner-level performs a separate optimization for each time frame by adjusting the model's generalized coordinates given the current guess for the joint and marker parameter values. The primary disadvantage of this approach is that performing repeated inner-level optimizations can be computationally costly [6]. In the one-level formulation, adjustment of the model's generalized coordinates is moved to the outer level by parameterizing the joint trajectories using B-spline or polynomial plus Fourier coefficients [20, 21]. Though this additional parameterization step imposes an assumed smoothness on the experimental data, it significantly reduces computation time compared to the two-level formulation. With either formulation, the motions of the generalized coordinates are found as a byproduct.

As an alternative to optimization, several studies have utilized Kalman filtering techniques (e.g., extended Kalman filters and unscented filters) to find joint and marker parameter values and joint motions simultaneously [11–14]. Since multibody dynamic models of human movement are highly nonlinear, these methods are significantly faster computationally than optimization-based approaches, making them a better choice for clinical applications where patient-specific models would need to be constructed during a single office visit. Though filtering methods have not achieved widespread use in the biomechanical modeling and simulation community, they are gaining recognition.

Patient-specific muscle-tendon models

Creation of patient-specific muscle-tendon models requires calibration of musculoskeletal geometry (i.e., muscle origins/insertions and moment arms) and muscle force generating properties. With current capabilities, calibration of musculoskeletal geometry is best achieved using magnetic resonance (MR) imaging data. Scanning parameters can be selected to enhance the brightness of fatty tissue so that the muscle boundaries are easily visible [22, 23]. The boundaries of anatomic structures of interest (e.g., muscles, bones, articular surfaces) can be segmented using commercial image processing software (e.g., SliceOmatic, Mimics, Analyze, Matlab, 3D Doctor) and the resulting point clouds converted to geometric surfaces using commercial reverse engineering software (e.g., Geomagic, Rhinoceros).

Converting the geometric surface models into multibody dynamic models requires identifying muscle origins and insertions on the bones and the way muscles wrap around bones and other muscles. Though muscles attach to bones over an area, most musculoskeletal models assume that they attach to bones at a point, necessitating the use of multiple muscle lines of action to represent broad muscles such as gluteus maximus. Even narrower muscles such as tibialis anterior may require multiple lines of action to eliminate sensitivity of predicted motions to small errors in muscle insertion points. Musculoskeletal modeling software (e.g., SIMM, AnyBody, LifeMOD, OpenSim) provides built-in functionality for defining muscle lines of action as a series of line segments with parameterized muscle wrapping surfaces represented by spheres, cylinders, and ellipsoids [24, 25]. Muscle paths modeled with this method have been validated against experimental moment arm data reported in the literature [26]. The primary challenges with this methodology are the cost of obtaining the MR scan data, determination of appropriate scanning parameters, the time and expertise required to segment the anatomic structures of interest from the resulting images, and the time and effort required to convert the resulting geometric models into a parameterized multibody model. Though less accurate, an alternative to using patient-specific geometry is to scale a nominal musculoskeletal model to match measurements made from the patient [27].

Calibration of muscle force generating properties is challenging as well. Most multibody dynamic models that include models of individual muscles use a Hill-type muscle-tendon model. This model treats muscle as a contractile element in parallel with a passive elastic element, with the muscle attached in series and at an angle (called the pennation angle) with a passive elastic tendon [28, 29]. Five parameter values are required to calibrate a Hill-type model to a particular muscle of a specific patient: 1) peak isometric force, 2) corresponding optimal muscle fiber length, 3) pennation angle, 4) tendon slack length, and 5) maximum shortening velocity. Thus, for a complex musculoskeletal model with 54 muscles [30], $5 \times 54 = 270$ patient-specific muscle-tendon model parameter values need to be determined, which is an extremely challenging task. In addition, a first order activation dynamics model, which converts a neural control signal (i.e., electromyographic activity, or EMG) into the activation signal input to the muscle-tendon model, is often used and possesses additional unknown parameter values that need to be determined [28].

Researchers have proposed a two-phase nested optimization method for calibrating three of the five muscle-tendon parameter values to strength data collected from an individual patient [31]. In phase one, joint angles and muscle activation levels are found by maximizing the isometric torque developed by each degree of freedom at each joint in the model. In phase two, the unknown muscle-tendon parameter values are found by matching the joint torque profile of the model to that measured for the patient using isometric dynamometer tests. Within each phase, peak isometric force is calculated as the ratio of measured muscle volume to estimated optimal muscle fiber length. The calculated values of peak isometric force, optimum muscle fiber length, and tendon rest length are often evaluated qualitatively by comparison with published values from anatomic studies. Values of the two remaining parameters are normally taken from the literature [29].

For EMG-driven muscle-tendon models, researchers have proposed a different optimization method that uses functional data to calibrate the same three muscle-tendon parameter values along with parameter values related to activation dynamics (i.e., EMG-to-activation characteristics) [28, 32, 33]. These models utilize experimentally measured EMG signals as inputs. Rather than matching just the isometric joint torque profiles of the patient, this method matches the patient's functional, isokinetic, and isometric joint torque profiles [34, 35]. A variety of movement trials are used to cover a range of contractile conditions of the patient's muscles, including the functional activity to be simulated (e.g., gait) and passive,

maximal effort, and submaximal effort eccentric and concentric trials on an isokinetic dynamometer. An optimization problem is solved to adjust the muscle-tendon and activation dynamics parameter values for each muscle to match the joint torques measured from the different movement trials [35]. Once the model is calibrated, it can be used to predict joint torques (and hence the extent of muscle co-contraction) during other tasks for which EMG data are available from the patient [34, 36].

Patient-specific neural control models

For applications where prediction of individual muscle forces is necessary, a neural control model is needed. Since there are more unknown muscle forces than degrees of freedom in the skeletal model, prediction of muscle forces for experimental or simulated motions is an indeterminate problem [37]. The most common neural control models used to predict muscle forces fall into two categories: 1) optimization methods and 2) EMG-driven methods. A third category called reduction methods eliminate unknown muscle forces until the number of muscle forces to be found equals the number of equations available from inverse dynamics [38], but these methods ignore the fact that muscle co-contraction occurs in real life.

Optimization methods assume that the neural control system minimizes some cost function (e.g., sum of squares of muscle activations [37, 39]) when producing human movement. The cost function makes the solution unique and makes up for missing equations. Optimizations methods themselves can be divided into two sub-categories: inverse dynamic (often called “static”) and forward dynamic (often called “dynamic”) optimization [40]. Static optimization requires experimental motion (and ideally external load) inputs and solves the dynamics equations algebraically for the net forces and torques at the joints (i.e., inverse dynamics). Muscle forces consistent with these net joint loads are then predicted by solving a separate optimization problem for each time frame of the motion. In contrast, dynamic optimization does not require experimental motion or load inputs and solves the dynamics equations via numerical integration for the motion produced by the muscle forces (i.e., forward dynamics). Muscle forces and associated motion are predicted by solving a single optimization problem over all times frames simultaneously. The problems with optimization methods are first, that the “correct” form of the cost function being minimized by the neural control system is unknown [41], second, that the weight factors on the individual terms in the cost function are unknown [42, 43], and third, that the optimality assumption of the neural control system may not apply to neurologically impaired individuals (e.g., cerebral palsy and stroke) [44].

EMG-driven methods avoid these problems by using muscle EMG measurements as additional experimental inputs [28, 32, 34, 35, 45]. Similar to static optimization, these methods require experimental motion inputs, and similar to dynamic optimization, they can predict net joint loads for quantitative evaluation. The two primary drawbacks of EMG-driven methods are first, that it is unclear how to incorporate deep muscles for which EMG measurements cannot be made, and second, that muscle force predictions cannot be made if experimental EMG and motion measurements are not available. The main strength of EMG-driven methods is that they apply equally well to normal and neurologically impaired individuals, since they utilize a patient-specific neural control strategy by design. Furthermore, once the method is calibrated to a set of functional, isokinetic, and isometric trials, the predictions can be tested quantitatively by predicting net joint loads for other trials not used in the calibration process [34, 36].

To address the issue of unknown weight factors in optimization methods, recent studies have investigated identification of patient-specific cost functions [5, 42, 43]. With this approach, the form of the cost function must be pre-supposed, but the weights on the various terms in

the cost function are identified on a patient-specific basis. Conceptually, a two-level optimization problem is formulated. The outer level minimizes a cost function that tracks some combination of experimental measurements by varying design variables that define the weight factors in the inner-level cost function. The inner level minimizes a cost function that uses the current weight factors specified by the outer level by varying design variables related to the muscle activations, joint moments, joint motions, and/or applied loads (e.g., ground reactions). The two levels are iterated until the inner level optimization predicts a solution that matches the experimental data being tracked at the outer level as closely as possible. In essence, this approach yields an inner level optimization result that closely reproduces the experimental data without tracking it directly. Though this approach has promise for patient-specific clinical applications, it has yet to be investigated extensively.

A simpler neural control model assumes “minimum control change” between the patient’s pre-treatment motion and his or her post-treatment motion [5, 43, 46, 47]. The underlying assumption is that the patient’s neural control strategy after treatment will be similar to his or her neural control strategy before treatment. This concept eliminates the need to determine what (if anything) the patient’s neural control system is minimizing and instead seeks a “neighboring solution” to the patient’s existing motion and control. An advantage of this approach is that it allows optimization methods to be applied to patients who are neurologically impaired, since no assumptions are required about the quantities being minimized in an absolute sense.

Patient-specific joint contact models

For some clinical applications, such as those related to osteoarthritis or joint replacement wear, patient-specific articular contact models may be necessary. Historically, computational cost has limited the feasibility of incorporating such models into a larger multibody dynamic skeletal model. For forward dynamic and static simulations, elastic foundation contact models (i.e., bed-of-springs models) require significantly less computation time than do finite element contact models (i.e., minutes compared to hours or days [48]). Nonetheless, even minutes of CPU time is prohibitive for applications that require thousands of repeated simulations, such as optimizations that predict muscle forces and movement simultaneously.

One alternative to an elastic foundation or finite element contact model is a surrogate contact model [49–51]. A surrogate model is a computationally cheap model that reproduces the input-output characteristics of a computationally expensive model. Surrogate model development involves four steps: 1) design of experiments, 2) computational experiments, 3) surrogate model selection, and 4) surrogate model evaluation [52]. Design of experiments defines combinations of inputs (i.e., sample points) that cover the allowable range, computational experiments calculate the outputs from the computationally expensive model for each sample point input, surrogate model selection determines the process for fitting the input-output relationships, and surrogate model evaluation quantifies how well the final surrogate model matches the input-output relationships of the original model for sample points not used in the fitting process.

Though these steps apply to the creation of any surrogate model, development of surrogate contact models poses unique challenges. For an elastic contact model, inputs are the position (3 translations) and orientation (3 rotations) of one contacting body relative to the other, and outputs are the net force (3 components) and net torque (3 components) that prevent the bodies from interpenetrating excessively. Other outputs of interest (e.g., maximum contact pressure, wear volume) can be fitted as well. When allowable ranges of the 6 inputs are sampled, a large number of unrealistic outputs are generated where the bodies are either out of contact or deeply interpenetrating. Because realistic combinations of inputs form a thin

hypervolume in 6-dimensional design space, special techniques are needed to generate feasible sample points and to perform the surrogate model fitting process [50, 51].

The computational benefits of this approach were recently demonstrated by simulating a multibody dynamic artificial knee model that includes both the tibiofemoral and patellofemoral joints [51]. The sample points required for surrogate model creation were generated by performing repeated static analyses with an elastic foundation contact model, and the surrogate model fitting process was performed using Kriging [53]. Once surrogate contact models of the tibiofemoral and patellofemoral joints were created, they were incorporated into a three-dimensional, 12 DOF (i.e., 6 DOFs for the tibiofemoral joint and 6 DOFs for the patellofemoral joint) multibody dynamic model of the artificial knee. The femoral component was fixed to ground and the tibia and patella were allowed to move relative to it. Knee flexion-extension was prescribed to match a one-cycle gait motion and the remaining 11 DOFs were numerically integrated under the influence of a quadriceps force (3 lines of action) applied to the tibia, a patellar ligament force (3 lines of action) applied to the patella and tibia, and an anterior-posterior force and internal-external rotation torque applied to the tibia. With the elastic foundation contact model, the forward dynamic simulation required approximately 30 minutes of CPU time, while with the surrogate contact model, it required only 15 seconds. Furthermore, the predicted motions and loads were nearly identical for the two models. The computational speed of the surrogate contact modeling approach is more than adequate for use in biomechanical optimizations that require repeated forward or inverse dynamic simulations.

DESIGN OF PATIENT-SPECIFIC TREATMENTS

To use patient-specific multibody dynamic models to design clinical treatments for a neuromusculoskeletal disorder, we require one additional piece of information – a "clinically useful locomotion measure" [54]. Brand defines a clinically useful locomotion measure as a quantity that "predict[s] a different outcome than would be predicted without the measure" or that "change[s] the clinician's choice of treatment." Locomotion measures that meet these two criteria will be highly correlated with some direct measure of clinical outcome, such as slowing of disease progression, decrease in pain, or increase in function. Thus, a patient-specific multibody dynamic model must be able to calculate or predict a clinically useful locomotion measure for the model to have clinical applicability.

Below we consider three illustrative examples where a patient-specific multibody dynamic model can be used to design clinical treatments based on knowledge of a clinically useful locomotion measure. The first two examples relate to knee osteoarthritis, while the third relates to stroke.

Knee osteoarthritis

Knee osteoarthritis (OA) affects the quality of life of millions of patients in the United States and Europe. The inner (or medial) side of the knee is the region most commonly affected, often due in part to a "bow-legged" alignment of the leg. The external knee adduction torque, which is caused primarily by the moment of the ground reaction force vector about the knee center, has been identified as a "clinically useful locomotion measure" for surgical and rehabilitation treatments of medial compartment knee OA [55]. The peak value of this torque during the stance phase of gait has been shown to be highly correlated with disease progression [56, 57], pain [58], and the long-term outcome of high tibial osteotomy surgery [59, 60]. Ideally, patient-specific multibody dynamic models could be used to design patient-specific gait modifications or leg alignment corrections to reduce the external knee adduction torque in an optimal fashion.

Optimization of a patient-specific multibody dynamic model was recently used successfully to design a customized rehabilitation treatment for a specific patient with medial compartment knee OA [46]. Walking data collected from the patient were used to construct a full-body, patient-specific multibody dynamic model. Joint and inertial parameter values in the model were calibrated to the patient's walking and isolated joint motion data. An inverse dynamics optimization problem was formulated to predict a new walking motion that minimized both knee adduction torque peaks, was similar to the patient's normal walking motion, and satisfied a minimal control torque change criteria. The optimization predicted a "medial thrust" gait motion that brought each knee toward the midline of the body during stance phase, thereby reducing the knee adduction torque by 30 to 40%, a clinically significant amount. The kinematic changes predicted by the optimization were implemented by the patient, who achieved comparable reductions when measured in the gait lab [46]. For this particular application, torque actuators were sufficient to predict a clinically useful rehabilitation treatment. Whether a medial thrust gait pattern will work well for other patients is currently being investigated by research labs in the United States and Australia [61–63].

A similar computational approach has been used to predict the outcome of high tibial osteotomy (HTO) surgery [5]. Given pre-surgery gait data from a patient with medial compartment knee OA and an associated patient-specific multibody dynamic model, the patient's post-surgery knee adduction torque was predicted via optimization for a typical range of HTO surgical parameters. However, rather than predicting how the patient *should* walk as in the gait modification example above, this optimization predicted how the patient *would* walk, which is a more difficult problem. This problem was addressed by creating a patient-specific neural control model in the form of calibrated weight factors in an optimization cost function. The patient was asked to perform different walking motions that modified the external knee adduction torque. Weight factors in the cost function were calibrated so that the optimization accurately predicted the patient's knee adduction torque curve for walking with the toes pointed outward, and the calibrated weight factors were tested using walking with the feet wide apart. The calibrated model and cost function were then used to predict the patient's knee adduction torque curve for changes in his lower leg bone geometry produced by simulated HTO surgery. The predicted changes were clinically realistic, though they could not be evaluated quantitatively since the surgery was not performed on the patient. Nonetheless, the study demonstrated the feasibility of using a patient-specific multibody dynamic model to predict post-surgery functional outcomes.

Stroke

Stroke is a neurological disorder that affects the ability to move one side of the body and hence the ability to walk. Weakness of the muscles in the affected leg and spasticity of the ankle extensor muscles often hinder support during stance phase, propulsion during toe off, and foot clearance during swing phase [64–67]. The ankle flexion-extension torque during gait has been identified as a "clinically useful locomotion measure" for developing stroke rehabilitation treatments. Abnormalities in this torque have been shown to be negatively correlated with walking speed and the ability to ambulate independently in the community [64, 67, 68]. Since muscle forces can only be increased and not decreased through external means (e.g., functional electrical stimulation), patient-specific multibody dynamic models could potentially be used to design patient-specific ankle muscle stimulation patterns to produce optimal correction of abnormal ankle torque profiles, thereby improving gait speed and symmetry.

Researchers have recently initiated the development of such an approach using patient-specific neuromusculoskeletal models [47]. The goal is to identify optimal patient-specific muscle stimulation patterns that will make the ankle motion and torque profiles of stroke

patients match those of normal subjects. First, gait data are collected from the stroke patient, and an inverse dynamics analysis is performed to calculate his or her ankle flexion-extension torque over the gait cycle. Next, a patient-specific EMG-driven neuromuscular model is constructed whose muscle-tendon and activation dynamics parameter values are calibrated to gait and isokinetic dynamometer data collected from the patient. Once the EMG-driven model is able to reproduce the patient's measured ankle flexion-extension torque curves, a new optimization problem is solved that seeks to match normal ankle motion and torque profiles during gait while minimizing activation increases in the ankle muscles. Though the predictions have yet to be tested in actual patients, the approach provides a well-defined path for implementing the predicted patient-specific activation increases via functional electrical stimulation [69] and evaluating whether they result in clinically significant increases in gait speed and symmetry on a patient-specific basis.

CHALLENGES TO PATIENT-SPECIFIC ADVANCES

A number of practical challenges need to be overcome before patient-specific multibody dynamic models achieve widespread clinic application. One of the primary challenges is development of methodologies that can accurately calibrate model parameter values to data collected from individual patients. Skeletal model parameter values can already be calibrated to a patient's movement data with reasonable accuracy [4–6, 9, 10]. Nonetheless, further evaluation of joint parameter estimates [70] and improvement of inertial parameter estimates for "fast" movements would be valuable [71]. Muscle-tendon model parameter values remain challenging to calibrate, as current methods can fit experimental joint torque measurements but do not guarantee that the resulting parameter values are correct. Though MR data can be used to calibrate muscle moment arm parameter values [72], an automated approach is needed for converting imaging data to parameterized models. Calibration of neural control model parameter values for optimization-based muscle force predictions will likely require significant research effort to identify appropriate cost function forms. Joint contact model articular geometry for individual patients can be obtained from MR data, but parameter values related to tissue material properties and adaptation over time require development of new measurements and calibration methods.

A related challenge is development of sensitivity analyses to determinate which model parameters should be calibrated accurately to predict treatment outcome reliably. Due to the complexity of many neuromusculoskeletal models, it is often difficult to perform a sensitivity analysis of how the clinically useful locomotion measure predicted by the model is influenced by errors in model parameter values. For the knee osteoarthritis applications described above, Monte Carlo analysis revealed that the external knee adduction torque was sensitive to errors in joint parameter values, which could be calibrated accurately from experimental data, but not to errors in inertial parameter values, which could not be calibrated accurately [5]. For clinical applications that require estimation of individual muscle forces, few sensitivity analyses have been performed of how muscle-tendon model parameter values affect the predicted outputs of interest [73–75]. Computationally efficient methods for performing sensitivity analyses, such as the advanced mean value method [76], may prove useful in this regard.

Validation of patient-specific model predictions is another critical challenge. Muscle force predictions in particular are difficult to validate, since direct measurement of muscle forces during human movement is possible only under special circumstances [77–81]. Most often, predicted muscle forces are evaluated only qualitatively by comparing predicted and measured muscle activation patterns [26, 30, 82]. Quantitative evaluations have been performed by comparing predicted and measured joint contact forces, as correctly predicted contact forces are a necessary (but not sufficient) condition for correctly predicted muscle

forces. Such evaluations have worked well for the hip [83], and a recent evaluation for the knee shows promise [84]. More extensive quantitative evaluation using instrumented implant data collected under a wide variety of movement conditions could play a valuable role in the validation process.

Yet another challenge is determination of the appropriate level of patient-specific model complexity for any given clinical application. A prime example is whether patient-specific joint contact models are needed to predict accurate muscle forces. While patient-specific articular geometry is probably not critical for a geometrically simple joint such as the hip, it is likely to be critical for the complex geometry of the knee, as evidence exists that an overly simplistic model of a complex joint leads to incorrect prediction of muscle forces [85]. Current methods of predicting muscle forces across the knee do not utilize contact models and typically match only the flexion-extension torque, thereby utilizing only one of the six available inverse dynamic loads at the knee. This load is chosen since it is the only one where it seems justifiable to assume that contact forces do not contribute significantly (though the validity of this assumption has not been evaluated). Inclusion of contact forces in the muscle force prediction process would allow the other five inverse dynamics loads to be used as constraints as well, reducing the level of indeterminacy in the solution process. The high computational cost of contact problems has prevented the development of methods that solve for muscle and contact forces simultaneously, and surrogate contact models may provide a solution to this dilemma. Advances in fluoroscopic imaging of natural and artificial joints may also be critical for providing accurate bone or implant motion inputs [86–92].

A final challenge is identification of “clinically useful locomotion measures” as defined by Brand [54]. Multibody dynamic neuromusculoskeletal models can only be used for clinical treatment planning when the model is able to predict a clinically useful locomotion measure. For the vast majority of clinical applications, such measures have yet to be identified. Determination of such measures is an important research area where collaborative efforts between engineers and clinicians have the potential to make a significant clinical impact in the future.

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