
Article:
van Veen, B.C., Mazza, C. orcid.org/0000-0002-5215-1746 and Viceconti, M. (2020) The uncontrolled manifold theory could explain part of the inter-trial variability of knee contact force during level walking. IEEE Transactions on Neural Systems and Rehabilitation Engineering, 28 (8). pp. 1800-1807. ISSN 1534-4320

https://doi.org/10.1109/tnsre.2020.3003559

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TNSRE.2020.3003559, IEEE Transactions on Neural Systems and Rehabilitation Engineering

The uncontrolled manifold theory could explain part of the inter-trial variability of knee contact force during level walking

Bart C. van Veen, Claudia Mazzà, and Marco Viceconti

***Abstract*—Accurate predictions of joint contact forces through computer simulation of musculoskeletal dynamics can provide insight, in a non-invasive manner, into the joint loads of patients with osteoarthritis and healthy controls. The current approach to assume optimal control, in terms of metabolic energy expenditure, remains a major limitation of the prediction of muscle activation patterns that determine joint contact forces. Stochastically optimal muscle control, in the form of a stochastic component superimposed to the optimal control, could potentially explain the inter-trial variability as observed in measured knee contact forces during level walking. A probabilistic approach was used to predict sets of possible muscle activation patterns within a 5 and 10% limit from the optimal muscle activation pattern. The knee contact forces determined by both the optimal and stochastically optimal muscle activation patterns were compared to the corresponding knee contact force patterns measured by an instrumented implant. The range of muscle control patterns captured the inter-trial variability of knee contact forces for most of the gait cycle, suggesting that the probabilistic approach used here is representative of a stochastically optimal control that accounts for co-contraction, whereas during some time intervals a more explicit representation of the motor control strategy is required. These findings underline the importance of stochastically optimal muscle control in the prediction of knee forces within a multi-body dynamics approach.**

***Index Terms*—knee contact force, level walking, muscle recruitment, musculoskeletal modelling, stochastically optimal muscle control**

I. Introduction

The relevance of the forces experienced by the articular surface of weight-bearing joints during activities of daily life to the onset and progression of joint degenerative diseases, such as osteoarthritis, has been discussed extensively in the literature, e.g. [1]. Experimental data on the forces experienced by the joints can typically only be obtained from a patient population with end-stage osteoarthritis through force sensors in a hip or knee implant. Alternatively, accurate predictions of joint contact forces through computer simulation of musculoskeletal dynamics can provide insight in the joint loads of early-stage patients and healthy controls, are relevant to study treatment effects in a non-invasive manner, and could potentially inform clinical practice. Open-source datasets from instrumented joint implants serve as an important validation for these predictive models [2], [3].

Numerous studies used publicly available experimental datasets to validate different approaches to simulate musculoskeletal dynamics and predict knee contact forces, such as the inclusion of complex and subject-specific joint contact models [4]–[8], force-dependent knee kinematics [9] and patient-specific musculoskeletal geometry in a segment-based model [10]. Experimental joint forces data has also been used to argue the importance of the discretization of large muscles into separate compartments and subject-specific muscle parameters in musculoskeletal dynamic simulations when predicting knee contact forces [11], [12]. A limitation to all the above studies is their assumption of optimal control to predict muscle activation patterns, assuming minimal metabolic energy expenditure [13]. Whereas this might be a valid assumption for healthy gait, it does not necessarily hold for pathological gait: overall metabolic energy expenditure, in fact, has been shown to increase in pathological gait [14]. Also, the amount of co-contraction observed during gait has been associated with painful joints [15], [16] and instability [17], [18], which logically leads to an increase in metabolic energy expenditure. However, the assumption of energetically optimal control does not account for co-contraction. Different approaches, such as EMG-driven forward dynamics and muscle synergies, successfully included experimental data to personalize muscle control in the estimation of knee contact forces [19]–[22]. However, the assumptions required for the translation from measurements of electrical activation to units of force, the cross-talking between muscles, and the limited information on the activation levels of deep muscles with surface electromyography remain a major limitation of such EMG-driven approaches.

One could argue that we aim for 'good enough' control rather than optimal control as "an organism uses trial-and-error learning to acquire a repertoire of sensorimotor behaviours that are known to be useful, but not necessarily optimal" [23]. This

This project was partly funded by the EPSRC Frontier Engineering Awards, United Kingdom Awards (Grant Reference No. EP/K03877X/1)

B. C. van Veen was with the Department of Mechanical Engineering and INSIGNEO Institute for *in silico* Medicine, University of Sheffield, UK,

C. Mazzà is with the Department of Mechanical Engineering and INSIGNEO Institute for *in silico* Medicine, University of Sheffield, UK (e-mail: c.mazza@sheffield.ac.uk).

M. Viceconti is with the Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna, Italy and the Medical Technology Lab, Rizzoli Orthopaedic Institute, Bologna, Italy (e-mail: marco.viceconti@unibo.it).

principle of 'good enough', or stochastically optimal control, partially explains the observed kinematic variability in repeated tasks, but kinematic variability has been argued to serve a purpose: variability in directions that are independent to task performance does not have to be controlled and could potentially provide stability to sudden changes or perturbations [24]. This theory of an uncontrolled manifold can equally be applied to muscle control, but only few studies have investigated the influence of such variability in muscle control on the loads experienced by the joints. A solution space of possible muscle activations and knee contact forces was obtained through a parametric variation of the contribution of agonist muscle groups and their individual muscles [25], [26]. However, a vectorized approach resulted in a larger possible variability in muscle activation and consequently a larger variability in hip contact forces [27]. A probabilistic approach to sample the solution space of muscle activations showed an even larger variability in muscle activations [28]. However, this study focused primarily on the range of possible muscle force patterns and it lacked a direct comparison to experimental measurements of joint contact forces. Therefore, the potential of a stochastically optimal control approach to improve the accuracy of joint contact force predictions remains unclear.

This study aims to explore the limitations of optimal control in predictions of knee contact forces by answering the following questions: 1) Does at least one muscle activation pattern exist for which a subject-specific musculoskeletal dynamics model of level walking predicts the forces at the knee within measurement precision?; 2) Assuming such a solution exists, how different is it from an optimal control solution in terms of knee contact forces, but also in terms of muscle activation?; 3) How well can this difference be explained by a stochastic component superimposed to the optimal control, consistent with the uncontrolled manifold theory?

II. METHODS

Experimental data for one elderly participant (male, age: 83 years, height: 1.72 m, mass: 70 kg) with an instrumented total knee replacement on the right side was obtained from the sixth Knee Grand Challenge dataset [2]. This is an open-source dataset that includes knee contact force data measured with an instrumented implant alongside motion capture, ground reaction force, EMG, CT and X-ray data (https://simtk.org/projects/kneeloads). The musculoskeletal model, the dynamic simulations and the muscle activation solution that minimized the sum of muscle activations squared (J_{act}) as described for *p02* previously [29], were re-used for this study. The following section briefly summarizes the re-used data and methodology and presents the additional data and methodology in more detail.

A. Experimental data

Six trials of level walking at a self-selected speed (1.03 ± 0.02 m/s), defined from right heel strike to right heel strike, were included. The name and trial numbers from the original dataset ('*DM_ngait_og'*, trial *3, 4, 5, 6, 7* and *9*) were maintained to allow for comparison across studies. Two out of eight available trials were excluded because the foot strike was too close to the edge of the force plate. The forces and moments acting on the right knee joint were available from a six-axis load cell embedded in the stem of the tibial prosthesis (*eTibia;* [30]).
EMG data were available for 15 muscles of the right lower extremity: The Gluteus Maximus, the Gluteus Medius, the Adductor Magnus, the Tensor Fasciae Latae, the Sartorius, the Semimembranosus, the long head of the Biceps Femoris, the Vastus Medialis and Lateralis, the Rectus Femoris, the Gastrocnemius Medialis and Lateralis, the Soleus, the Tibialis Anterior and the Peroneus Longus muscles. The data for the Gluteus Medius and the Vastus Medialis muscles were identified to be of insufficient quality given the signals' small amplitudes, in accordance with an EMG-driven forward dynamics simulation study that used the same dataset [20]. Details on how the envelope trajectories and onset times were computed can be found in the supplementary materials (https://doi.org/10.0.59.27/shef.data.11370216).

B. Musculoskeletal model

The subject-specific musculoskeletal model of the right lower limb included five segments, 11 degrees of freedom and 43 actuators. The bone geometries, segment mass properties and orientation of joint axes were determined from the available CT images and point-cloud data of the implant. Further details on the model identification can be found in [29]. To allow for a direct comparison of the simulated knee contact force with the measured values from the instrumented knee implant, a knee contact joint was placed in the tibial tray aligned with the origin of the reference frame of the implant (Fig. 1). A massless body linked the articulating knee joint with the knee contact joint, which was in turn linked distally to the tibia segment. All six coordinates of the knee contact joint were locked such that the original orientation of the massless body and the tibia with respect to each other was maintained. The knee contact forces as predicted by the model and reported in the following sections were resolved around this knee contact joint.

C. Muscle activation patterns

Muscle activation patterns were obtained through two different methods: an optimization approach and a probabilistic approach.

1) Optimization approach

Muscle activation patterns for all trials were obtained by solving the optimization problem defined as [29]:

$$\begin{aligned} \min \quad & J(\vec{a}) \\ \text{subject to} \quad & \vec{T}(t) = B(q)\left(\vec{a}^T(t)\vec{F}_{max}\right) \\ & 0 \le \vec{a}(t) \le 1 \end{aligned} \tag{1}$$

where $\vec{a}$ is the vector of activations with its entries defined as $a_i(t) = F_i(t)/F_{max,i}$, $\vec{F}_{max}$ is the vector of m maximum actuator forces, F_i is the force of actuator i, $\vec{T}$ is the $n \cdot 1$ vector of forces and moments of force acting at the generalized coordinates and B is the $n \cdot m$ matrix of muscle moment arms. The variables required to define the optimization problem were obtained using the OpenSim API through MATLAB (v2017a, The MathWorks Inc., Natick, MA, USA).

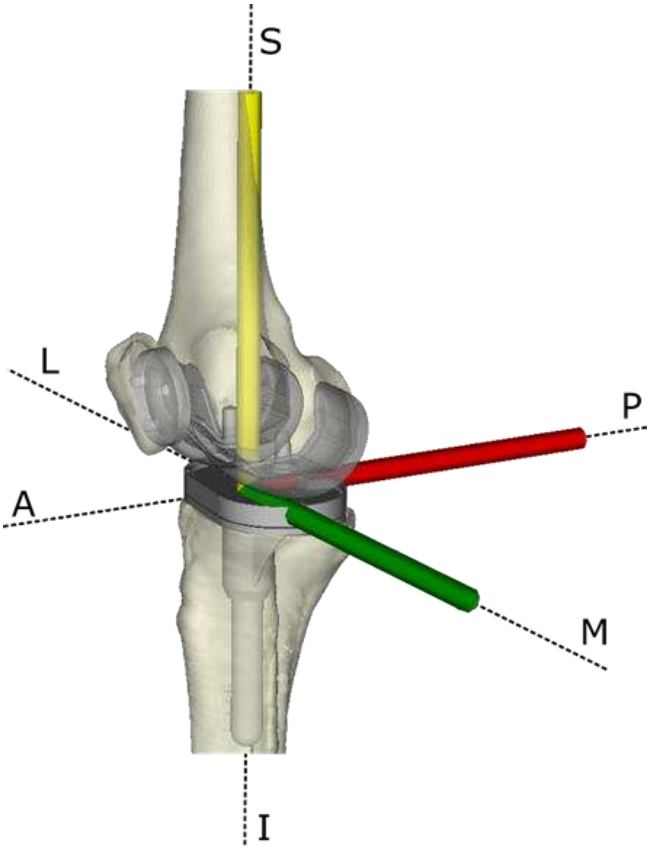

Fig 1: The coordinate system (anterior posterior (AP) axis (red), mediolateral (ML) axis (yellow) and superior-inferior (SI) axis (green)) fixed in the locked knee contact joint and used to resolve the simulated joint contact forces and moments.

One muscle activation pattern for each trial was available from the previously defined J_{act} solution [29]:

$$J_{act}(\vec{a}) = \sum_{i=1}^{m}(a_i(t))^2 \quad (2)$$

A second muscle activation pattern was obtained with an objective function aimed to minimize the difference between the measured and estimated knee resultant force:

$$J_{Fmatch}(\vec{a}) = w_1\left(\frac{\|\vec{F}^K_{exp}(t)\| - \|\vec{F}^K(\vec{a},t)\|}{\|\vec{F}^K_{exp}(t)\|}\right)^2 + w_2 \mathrm{R}(\vec{a},t) \quad (3)$$

where $\|\vec{F}^K_{exp}(t)\|$ is the magnitude of the experimental knee resultant force, acting on the tibia segment, as measured by the instrumented knee implant and $\|\vec{F}^K(\vec{a},t)\|$ is the magnitude of the resultant force acting on the tibia in the knee joint as predicted by the musculoskeletal model, $R(\vec{a},t)$ is a regularization term and w_1 and w_2 are constant weights that define the relative contribution of both parts to the objective function. The regularization term $R(\vec{a},t)$ was included to prevent the optimization problem from being ill posed, as some muscles do not contribute directly to the first part of the objective function [29]. MATLAB's nonlinear programming *fmincon*, leveraging on the interior-point algorithm, was used to solve the problem.

The weight ratio $w_1{:}w_2$ was set to 10:1, based on the asymptotic behaviour of the objective function value with an increasing weight ratio in a preliminary sensitivity analysis. The initial guesses for the minimizations were set to $\vec{0}$ after a preliminary bootstrap study confirmed the uniqueness of the solution, regardless of the initial value.

2) Probabilistic approach

A probabilistic approach was used to draw two sets of possible muscle activation patterns $\{[\vec{a}^M(t)]_1, [\vec{a}^M(t)]_2, \dots, [\vec{a}^M(t)]_N\}$ from the following probability distribution:

$$\pi\left(\vec{a}^M(t)\middle|\vec{T}(t)\right) \propto \pi_{pr}(\vec{a}^M(t))\pi\left(\vec{T}(t)\middle|\vec{a}^M(t)\right) \quad (4)$$

where $\pi_{pr}(\vec{a}^M(t))$ is the prior term that represents the constraints on the muscle activations, $\pi\left(\vec{T}(t)\middle|\vec{a}^M(t)\right)$ is the likelihood term that represents the probability of the known generalized torques, $\vec{T}(t)$, given a vector of muscle activations $\vec{a}^M(t)$ and $\pi\left(\vec{a}^M(t)\middle|\vec{T}(t)\right)$ is the posterior distribution that represents the probability of a vector of muscle activations that satisfies the dynamic equilibrium:

$$\vec{T}(\mathrm{t}) = B(q)\left(\vec{a}(t)^T\vec{F}_{max}\right) \quad (5)$$

The constraints on the muscle activations were set to a limit radius r around the J_{act} solution:

$$\max\{\vec{a}_{act}(t) - \mathrm{r}, \vec{0}\} \leq \vec{a}(\mathrm{t}) \leq \min\{\vec{a}_{act}(t) + \mathrm{r}, \vec{1}\} \quad (6)$$

where $\vec{a}_{act}(t)$ is the vector of muscle activations that resulted from the minimization of J_{act}. Two sets of 1×10^5 muscle activation patterns were sampled using Bayesian statistics to estimate the posterior probability density functions (PDF) of the unknowns of interest, and then generate samples from this distribution by means of a Markov Chain Monte Carlo (MCMC) algorithm (Metabolica, [31]), implemented in MATLAB and used to sample muscle activation patterns before [28], [32]. The limit radius of the first set was defined as 0.05, or 5% of the maximum activation of 1, and the limit radius of the second set was defined as 0.1, or 10%.

D. Data analysis

The contact forces at the knee joint were computed, leveraging on the implementation in OpenSim through the MATLAB API, for each muscle activation pattern that was obtained as an optimization solution or as a sample from the solution space. The root-mean-square error (RMSE) and the coefficient of determination (R^2) values were the suggested measures of comparison for the Knee Grand Challenge, so allowed for comparison with previous studies [2]. RMSE and R^2 values were obtained for the J_{act} and J_{Fmatch} solutions of each trial.

III. RESULTS

The magnitude of the knee contact force for the J_{Fmatch} solutions matched the measured values throughout the gait cycle, except for an overestimation during the loading response phase (0-10 % of the gait cycle) of trial 3 and 5 and during the terminal stance phase (30-50 % of the gait cycle) of trial 9 (Fig. 2, Table 1).

The J_{act} solutions underestimated the knee force at initial contact, during the mid-stance phase (10-30% of the gait cycle) and during swing phase (except for the final 8% of the swing phase in trial 4) and overestimated the knee force during the loading response phase for each trial. The differences between the predicted and measured values were less consistent throughout trials for the first peak and during terminal stance (Fig. 2, Table 1).

For a limit radius of 0.05, the measured knee contact forces were outside of the range of forces estimated by the sampled muscle activation patterns for larger intervals (Fig. 2). Therefore, this set of muscle activation patterns was not analysed any further.

For a limit radius of 0.1, the measured knee contact forces were within the range of forces estimated by the sampled muscle activation patterns for most of the gait cycle, except for a time interval during the loading response phase when all sampled muscle activation patterns overestimated the measured knee force. Also, for trial 4, 6 and 9, all sampled muscle activation patterns overestimated the measured knee contact force during a time interval in the terminal stance phase, whereas for trial 6 all samples underestimated the measured knee contact force around 30 % of the gait cycle (Fig. 3).

Except for the first 10% of the gait cycle, the muscle activations as predicted by the J_{Fmatch} solutions were within the range sampled by Metabolica (Fig. 4 for trial 3, figures in supplementary materials for other trials).

Overall, the agreement between activation patterns from the J_{Fmatch} solutions and EMG onset data for muscles spanning the knee changed minimally and non-consistently across muscles when compared to the J_{act} solutions for each trial (Fig. 4 for trial 3, supplementary material for other trials). One difference between the EMG data and the J_{Fmatch} solutions was consistent across trials: predicted activations did not capture the EMG activity of muscles that span the knee during the loading response.

IV. DISCUSSION

This study investigated, firstly, the capability of a subject-specific musculoskeletal dynamics model of level walking to match the measured knee contact forces within measurement precision and, secondly, the difference of such a best-match solution from an optimal control solution in terms of both muscle activation and knee contact forces. Lastly, this study assessed the suitability of stochastically optimal control (a stochastic component superimposed to optimal control) to explain this difference in muscle activation required to accurately predict physiological knee contact forces.

The reported results showed that the model, with its idealisations and methods used to identify its input, is compatible with the experimental observations over multiple repeated trials. In fact, for each trial a muscle activation pattern (J_{Fmatch}) existed for which the corresponding knee force tracked the force measured with an instrumented implant; only during a brief time interval during terminal stance in one trial a difference in knee force occurred. The J_{Fmatch} solutions, given their uniqueness, serve as a reference activation pattern for solutions obtained in a blinded manner.

The mean RMSE and R^2 values of the J_{act} solutions (0.5 BW and 0.61, respectively) were comparable to the values reported for blinded predictions of the total knee force in various studies that assumed optimal control in simulations of different trials (normal and instructed 'bouncy' and 'smooth' gait) from the same Knee Grand Challenge dataset: 0.4 – 0.8 BW and 0.54 – 0.74, respectively [4], [8], [10], [12]. In each of these studies, the objective functions to obtain muscle activation patterns included a term comparable to J_{act}: the minimization of the sum of muscle activation squared. It should be noted that some of these studies included some form of a contact force term in the objective function [4], [12] and for most studies only one or two trials of smooth and bouncy gait were included compared to the six trials of normal, level walking included in this study. Hence, the model described in this study showed predictive accuracies against this particular validation experiment comparable to those achieved by other published models. The agreement of the predicted muscle activation patterns with the EMG onset timing did not change notably between the J_{act} and J_{Fmatch} solutions. This result raises questions on the capability of EMG-driven approaches to identify the activation patterns that best match the measured knee forces. We made no quantitative comparison between the EMG data and predicted muscle activations because of the evident qualitative differences.

A probabilistic approach explored the solution space of stochastically optimal muscle activation patterns within a 5 and 10% limit radius from the solution for optimal control. For all trials, a 5% limit radius did not capture the measured knee contact forces during large parts of the gait cycle. However, the probabilistic approach with a 10% limit radius captured the best-match solutions in terms of both knee force and muscle activation for most of the gait cycle: only during limited time intervals during the loading response phase (all trials) and the terminal stance phase (three out of six trials) did the low knee contact force not appear in the set of stochastically optimal solutions. The range of sampled knee forces was larger compared to a study that explored potential variability in muscle control with a parametric approach in a different Knee Grand Challenge dataset [25]. The tendency of the probabilistic approach to sample higher knee forces compared to the optimal control solution corresponded to the range of hip forces found in a previous study that used the same approach on a different dataset [28]. The wide range of muscle activations that resulted in accurate predictions of knee contact forces suggest that the probabilistic approach used here is representative of a stochastically optimal or 'good-enough' control that accounts for co-contraction and captures the inter-trial variability in knee forces during most of the gait cycle, whereas in the interval immediately before and after heel strike a more explicit representation of the motor control strategy is required. In this specific case, the minimization of the knee force might provide a more accurate prediction during the loading response phase.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TNSRE.2020.3003559, IEEE Transactions on Neural Systems and Rehabilitation Engineering

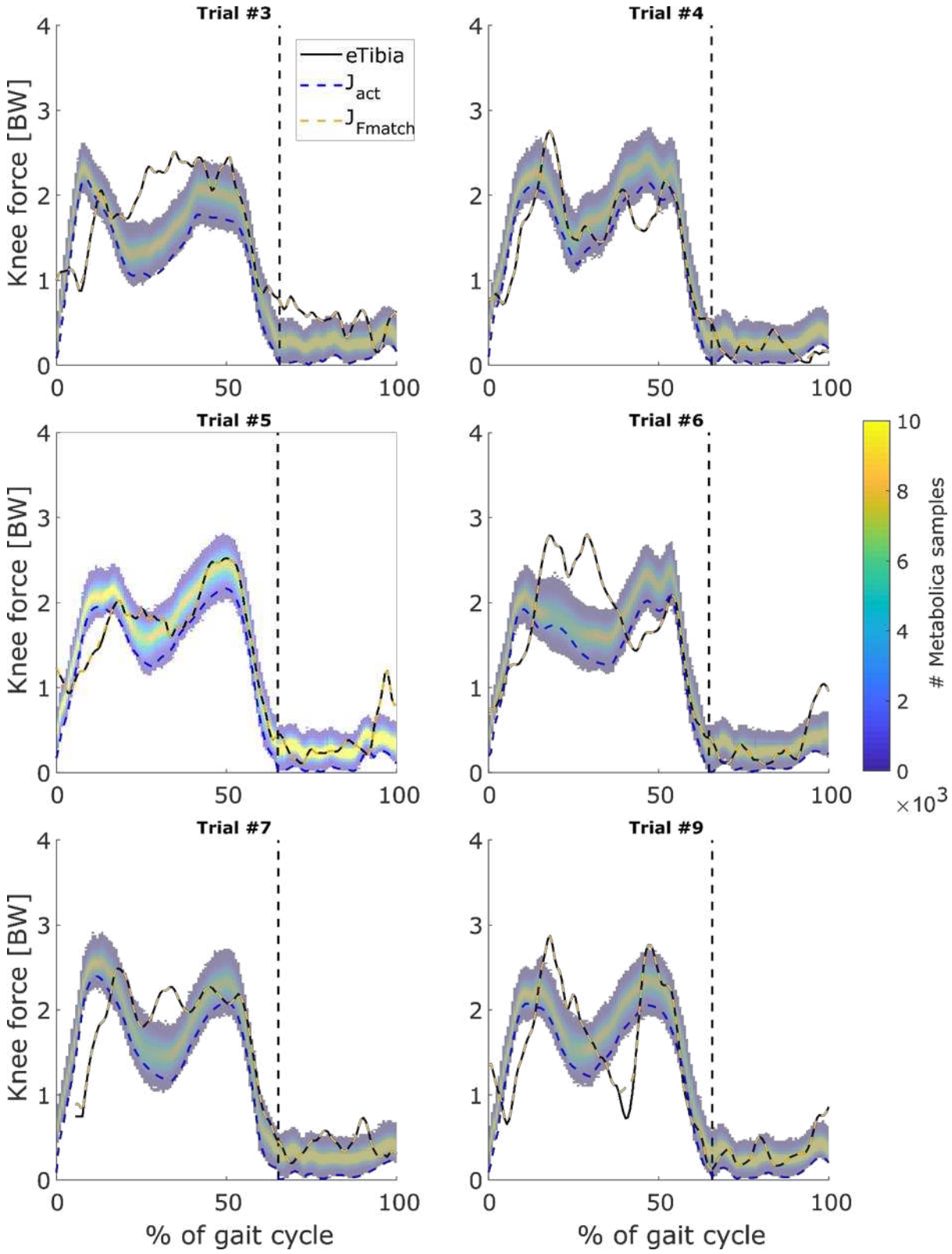

Fig. 2: Knee contact force trajectories in bodyweight (BW) for all trials; the sampled values from Metabolica, with a limit radius of 0.05, are shown as a range for which the colour indicates the number of samples that resulted in the corresponding knee force (see colour bar); the values from the instrumented implant (eTibia; black, solid), the J_{act} (blue, dashed) and J_{Fmatch} (yellow, dashed) solutions are shown as lines. The vertical dashed line indicates the time instant when toe off occurred.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TNSRE.2020.3003559, IEEE Transactions on Neural Systems and Rehabilitation Engineering

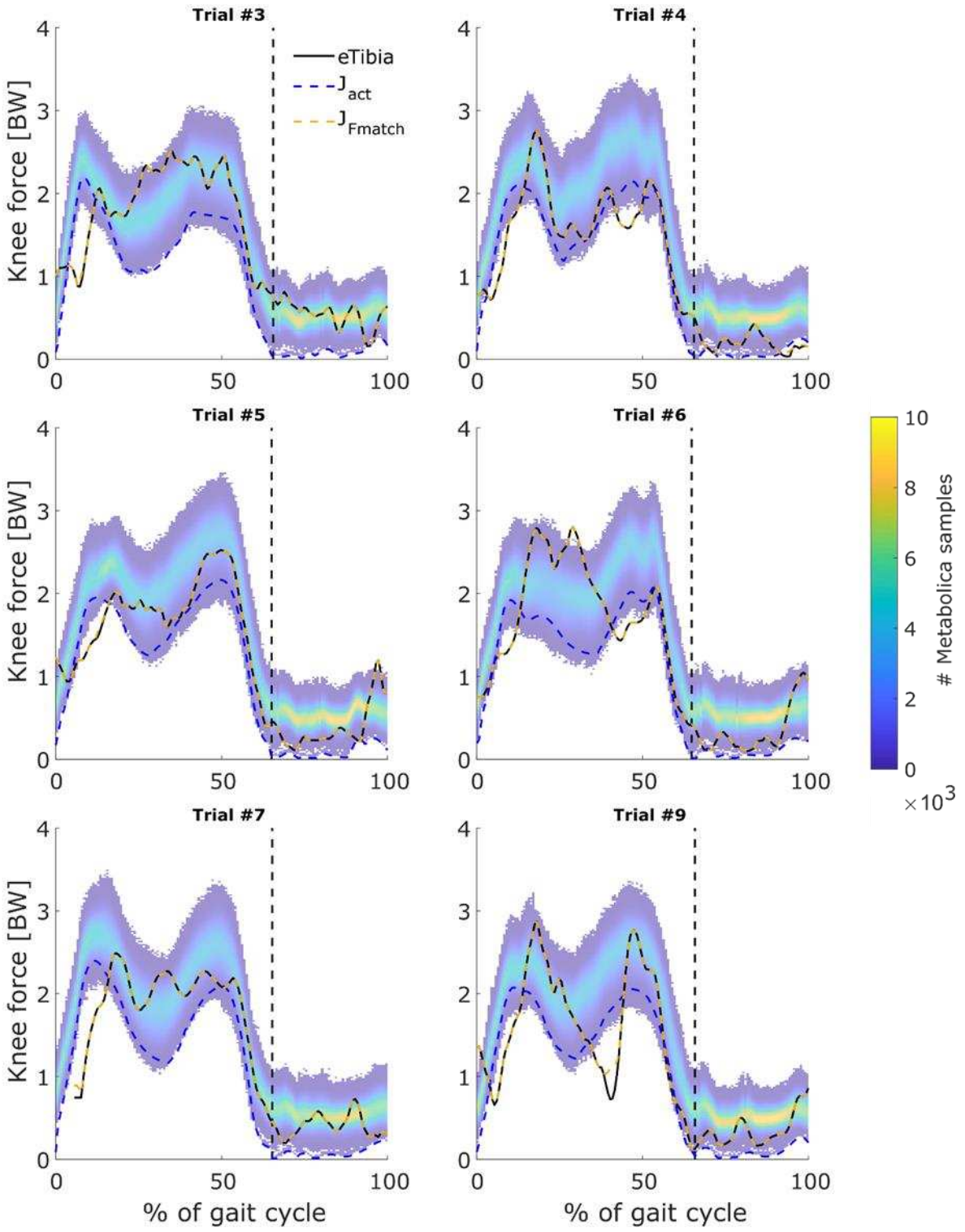

Fig. 3: Knee contact force trajectories in bodyweight (BW) for all trials; the sampled values from Metabolica, with a limit radius of 0.1, are shown as a range for which the colour indicates the number of samples that resulted in the corresponding knee force (see colour bar); the values from the instrumented implant (eTibia; black, solid), the J_{act} (blue, dashed) and J_{Fmatch} (yellow, dashed) solutions are shown as lines. The vertical dashed line indicates the time instant when toe off occurred.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TNSRE.2020.3003559, IEEE Transactions on Neural Systems and Rehabilitation Engineering

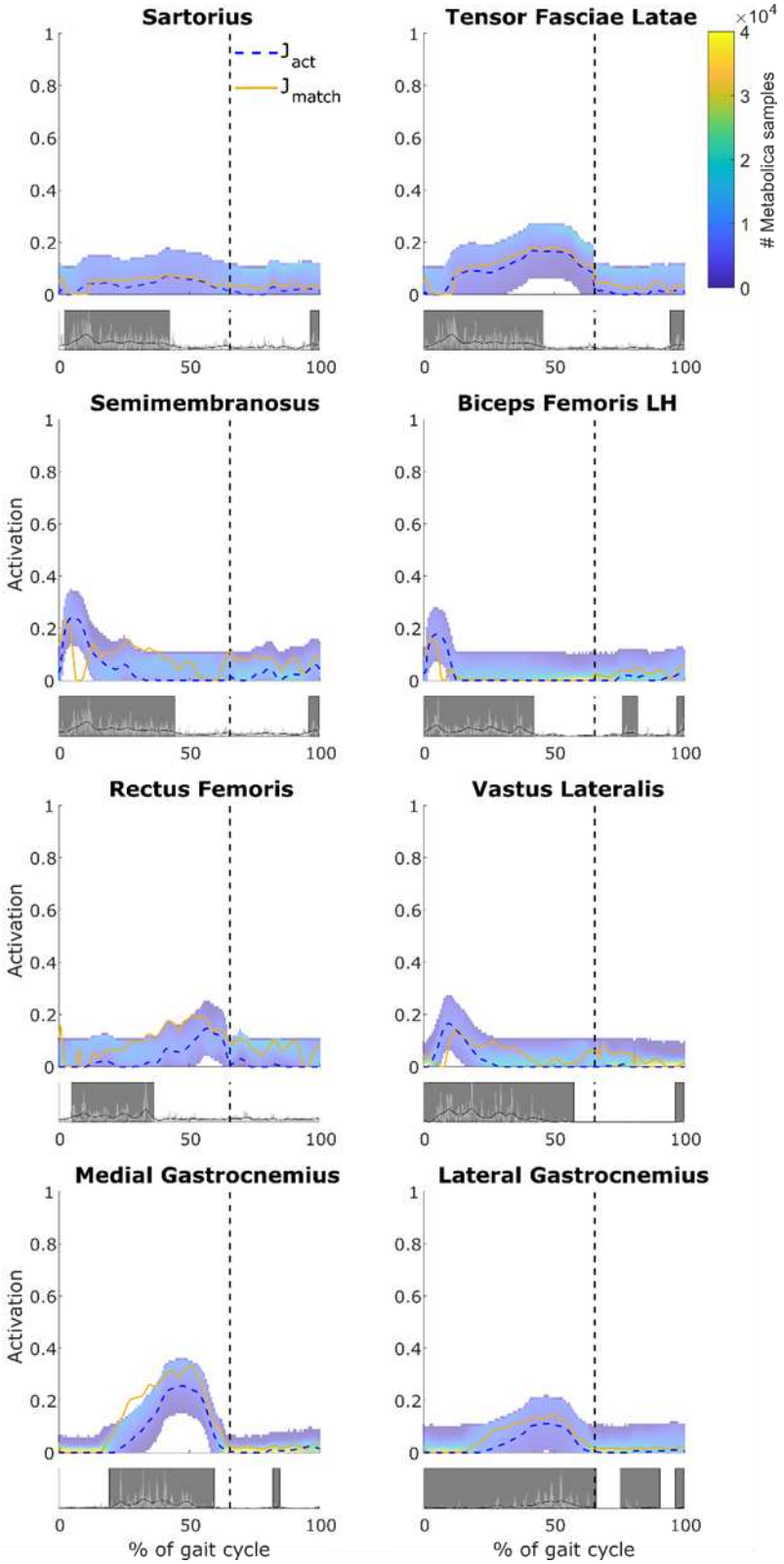

Fig. 4: Trial 3, the activation patterns of the muscles that span the knee for which EMG data were available. For each muscle, the top graph shows the J_{act} (blue, dashed) and J_{Fmatch} (yellow, solid) solutions as lines and the sampled muscle activation patterns as a range for which the colour indicates the number of samples (see colour bar); the bottom graph shows the EMG data: the rectified values in light grey, the envelope in black and the onset timing as dark grey boxes. The vertical axis of the bottom graph was normalized to the maximum value in the rectified EMG data. The vertical dashed lines indicate the time instant when toe off occurred.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TNSRE.2020.3003559, IEEE Transactions on Neural Systems and Rehabilitation Engineering

Table 1: Root-mean-square errors (RMSE; in bodyweight (BW)) and coefficients of determination (R^2) for each trial and the mean values over trials for the J_{Fmatch} and J_{act} solutions.

	RMSE (BW)							R^2						
Trial #	3	4	5	6	7	9	mean	3	4	5	6	7	9	mean
J_{Fmatch}	0.0	0.0	0.0	0.0	0.0	0.1	0.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00
J_{act}	0.7	0.3	0.4	0.6	0.5	0.5	0.5	0.23	0.85	0.76	0.59	0.58	0.65	0.61

Other approaches, such as an EMG-driven approach, have previously underlined the importance of muscle control in the predictions of joint contact forces. Such an approach could provide a subject-specific muscle activation pattern representative of possible pathological muscle control, as opposed to the assumption of optimal control. The probabilistic approach would then assume a level of stochastic optimality of muscle control around this muscle activation pattern. The level of stochastic optimality would, for example, be representative of the uncertainty in the muscle activation prediction resulting from the EMG-force calibration. However, one could question the difficulty to validate the model predictions qualitatively when EMG is already included in the model definition and measured joint contact forces data are not available.

This study suffered of three main limitations: firstly, the study included only one participant and therefore the conclusions drawn here are only valid for this specific participant. However, the measured knee-contact forces show a particularly high variability between trials. Therefore, the authors believe that our findings indicate a research direction for this complex problem despite the single case they are based on. Nonetheless, current work should be expanded to other datasets that include measured joint contact forces to confirm the generalizability of the current approach. Also, it remains an open question how to validate approaches that predict joint contact forces when no experimental data on joint contact forces, through instrumented implants, is available. Secondly, the force-length-velocity relationship was not considered when determining the force producing capacity of the muscles, which ultimately defined the 5 and 10% limit radius of the solution space. However, the relationship can in most cases not be measured for ethical or experimental limitations and no consensus currently exists on a standardized method to accurately predict this relationship for each muscle individually. Therefore, the authors decided not to include the force-length-velocity relationship to prevent an influence of poorly estimated muscle parameters on the outcomes of the study. Thirdly, only the resultant force and not the direction of the forces experienced by the knee were considered. Given the relatively large contribution of the axial component to the resultant force and the small mediolateral and anterior-posterior orientation of the muscle lines of action with respect to the joint during the stance phase, no difference in the obtained results was expected if the directional components of the contact force were included separately. Nonetheless, future work should study the influence of muscle control on the distribution of loads over different compartments of the knee joint.

In conclusion, the results presented in this study underline the importance of stochastically optimal muscle control in the prediction of knee forces within a multi-body dynamics approach. A subject-specific musculoskeletal dynamics model, built according to the current best practice, was compatible with the experimentally measured knee forces during level walking. In case of pathological gait, such as studied here, the assumption of optimal motor control was not representative of the considerable level of inter-trial variability. A probabilistic approach that assumed an uncontrolled manifold of 10% around the optimal control solution did capture this variability for most of the gait cycle. In cases when the motor control strategy is severely sub-optimal or when a higher level of accuracy for the predicted joint contact forces is required, the authors believe the only solution is to include an explicit model of control. A mechanistic model would for example allow for the differentiation between hierarchical levels of motor control such as the involuntary spinal control and the cognition-driven anticipatory control.

REFERENCES

[1] T. P. Andriacchi, A. Mündermann, R. L. Smith, E. J. Alexander, C. O. Dyrby, and S. Koo, "A Framework for the in Vivo Pathomechanics of Osteoarthritis at the Knee," *Ann. Biomed. Eng.*, vol. 32, no. 3, pp. 447–457, Mar. 2004, doi: 10.1023/B:ABME.0000017541.82498.37.

[2] B. J. Fregly *et al.*, "Grand challenge competition to predict in vivo knee loads," *J. Orthop. Res.*, vol. 30, no. 4, pp. 503–513, Apr. 2012, doi: 10.1002/jor.22023.

[3] W. R. Taylor *et al.*, "A comprehensive assessment of the musculoskeletal system: The CAMS-Knee data set," *J. Biomech.*, vol. 65, pp. 32–39, Dec. 2017, doi: 10.1016/j.jbiomech.2017.09.022.

[4] Y. Jung, C.-B. Phan, and S. Koo, "Intra-Articular Knee Contact Force Estimation During Walking Using Force-Reaction Elements and Subject-Specific Joint Model 2," *J. Biomech. Eng.*, vol. 138, no. 2, p. 021016, Jan. 2016, doi: 10.1115/1.4032414.

[5] M. W. Hast and S. J. Piazza, "Dual-Joint Modeling for Estimation of Total Knee Replacement Contact Forces During Locomotion," *J. Biomech. Eng.*, vol. 135, no. 2, p. 021013, 2013, doi: 10.1115/1.4023320.

[6] D. G. Thelen, K. Won Choi, and A. M. Schmitz, "Co-Simulation of Neuromuscular Dynamics and Knee Mechanics During Human Walking," *J. Biomech. Eng.*, vol. 136, no. 2, p. 021033, Feb. 2014, doi: 10.1115/1.4026358.

[7] H. J. Kim, J. W. Fernandez, M. Akbarshahi, J. P. Walter, B. J. Fregly, and M. G. Pandy, "Evaluation of predicted knee-joint muscle forces during gait using an instrumented knee implant," *J. Orthop. Res.*, vol. 27, no. 10, pp. 1326–1331, Oct. 2009, doi: 10.1002/jor.20876.

[8] C. R. Smith, M. F. Vignos, R. L. Lenhart, J. Kaiser, and D. G. Thelen, "The Influence of Component Alignment and Ligament Properties on Tibiofemoral Contact Forces in Total Knee Replacement," *J. Biomech. Eng.*, vol. 138, no. 2, p. 021017, Jan. 2016, doi: 10.1115/1.4032464.

[9] M. A. Marra *et al.*, "A Subject-Specific Musculoskeletal Modeling Framework to Predict In Vivo Mechanics of Total Knee Arthroplasty," *J. Biomech. Eng.*, vol. 137, no. 2, p. 020904, Feb. 2015, doi: 10.1115/1.4029258.

[10] Z. Ding, D. Nolte, C. Kit Tsang, D. J. Cleather, A. E. Kedgley, and A. M. J. Bull, "In Vivo Knee Contact Force Prediction Using Patient-Specific Musculoskeletal Geometry in a Segment-Based Computational Model," *J. Biomech. Eng.*, vol. 138, no. 2, p. 021018, Jan. 2016, doi: 10.1115/1.4032412.

[11] G. Serrancolí, A. L. Kinney, B. J. Fregly, and J. M. Font-Llagunes, "Neuromusculoskeletal Model Calibration Significantly Affects Predicted Knee Contact Forces for Walking," *J. Biomech. Eng.*, vol. 138, no. 8, p. 081001, Jun. 2016, doi: 10.1115/1.4033673.

[12] F. Moissenet, L. Chèze, and R. Dumas, "Influence of the Level of Muscular Redundancy on the Validity of a Musculoskeletal Model," *J. Biomech. Eng.*, vol. 138, no. 2, p. 021019, Jan. 2016, doi: 10.1115/1.4032127.

[13] F. C. Anderson and M. G. Pandy, "Static and dynamic optimization solutions for gait are practically equivalent," *J. Biomech.*, vol. 34, no. 2, pp. 153–161, Feb. 2001, doi: 10.1016/S0021-9290(00)00155-X.

[14] R. L. Waters and S. Mulroy, "The energy expenditure of normal and pathologic gait," *Gait Posture*, vol. 9, no. 3, pp. 207–231, Jul. 1999, doi: 10.1016/S0966-6362(99)00009-0.

[15] T. L. Heiden, D. G. Lloyd, and T. R. Ackland, "Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait," *Clin. Biomech.*, vol. 24, no. 10, pp. 833–841, Dec. 2009, doi: 10.1016/j.clinbiomech.2009.08.005.

[16] J. D. Childs, P. J. Sparto, G. K. Fitzgerald, M. Bizzini, and J. J. Irrgang, "Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis," *Clin. Biomech.*, vol. 19, no. 1, pp. 44–49, Jan. 2004, doi: 10.1016/j.clinbiomech.2003.08.007.

[17] W. J. Hurd and L. Snyder-Mackler, "Knee instability after acute ACL rupture affects movement patterns during the mid-stance phase of gait," *J. Orthop. Res.*, vol. 25, no. 10, pp. 1369–1377, Jun. 2007, doi: 10.1002/jor.20440.

[18] S. Hirokawa, M. Solomonow, Z. Luo, Y. Lu, and R. D'Ambrosia, "Muscular co-contraction and control of knee stability," *J. Electromyogr. Kinesiol.*, vol. 1, no. 3, pp. 199–208, Sep. 1991, doi: 10.1016/1050-6411(91)90035-4.

[19] J. P. Walter *et al.*, "Muscle Synergies May Improve Optimization Prediction of Knee Contact Forces During Walking," *J. Biomech. Eng.*, vol. 136, no. 2, p. 021031, Feb. 2014, doi: 10.1115/1.4026428.

[20] S. S. Razu and T. M. Guess, "Electromyography-Driven Forward Dynamics Simulation to Estimate In Vivo Joint Contact Forces During Normal, Smooth, and Bouncy Gaits," *J. Biomech. Eng.*, vol. 140, no. 7, p. 071012, May 2018, doi: 10.1115/1.4038507.

[21] P. Gerus *et al.*, "Subject-specific knee joint geometry improves predictions of medial tibiofemoral contact forces," *J. Biomech.*, vol. 46, no. 16, pp. 2778–2786, Nov. 2013, doi: 10.1016/j.jbiomech.2013.09.005.

[22] K. Manal and T. S. Buchanan, "An Electromyogram-Driven Musculoskeletal Model of the Knee to Predict in Vivo Joint Contact Forces During Normal and Novel Gait Patterns," *J. Biomech. Eng.*, vol. 135, no. 2, pp. 1–7, Feb. 2013, doi: 10.1115/1.4023457.

[23] G. E. Loeb, "Optimal isn't good enough," *Biol. Cybern.*, vol. 106, no. 11–12, pp. 757–765, Dec. 2012, doi: 10.1007/s00422-012-0514-6.

[24] J. P. Scholz and G. Schöner, "The uncontrolled manifold concept: identifying control variables for a functional task," *Exp. Brain Res.*, vol. 126, no. 3, pp. 289–306, May 1999, doi: 10.1007/s002210050738.

[25] H. J. Lundberg, C. Knowlton, and M. A. Wimmer, "Fine Tuning Total Knee Replacement Contact Force Prediction Algorithms Using Blinded Model Validation," *J. Biomech. Eng.*, vol. 135, no. 2, p. 021015, Feb. 2013, doi: 10.1115/1.4023388.

[26] H. J. Lundberg, K. C. Foucher, and M. A. Wimmer, "A parametric approach to numerical modeling of TKR contact forces," *J. Biomech.*, vol. 42, no. 4, pp. 541–545, Mar. 2009, doi: 10.1016/j.jbiomech.2008.11.030.

[27] S. Martelli, F. Taddei, A. Cappello, S. van Sint Jan, A. Leardini, and M. Viceconti, "Effect of sub-optimal neuromotor control on the hip joint load during level walking," *J. Biomech.*, vol. 44, no. 9, pp. 1716–1721, Jun. 2011, doi: 10.1016/j.jbiomech.2011.03.039.

[28] S. Martelli, D. Calvetti, E. Somersalo, M. Viceconti, and F. Taddei, "Computational tools for calculating alternative muscle force patterns during motion: A comparison of possible solutions," *J. Biomech.*, vol. 46, no. 12, pp. 2097–2100, 2013, doi: 10.1016/j.jbiomech.2013.05.023.

[29] B. van Veen, E. Montefiori, L. Modenese, C. Mazzà, and M. Viceconti, "Muscle recruitment strategies can reduce joint loading during level walking," *J. Biomech.*, vol. 97, p. 109368, Dec. 2019, doi: 10.1016/j.jbiomech.2019.109368.

[30] B. Kirking, J. Krevolin, C. Townsend, C. W. Colwell, and D. D. D'Lima, "A multiaxial force-sensing implantable tibial prosthesis," *J. Biomech.*, vol. 39, no. 9, pp. 1744–1751, Jan. 2006, doi: 10.1016/j.jbiomech.2005.05.023.

[31] J. Heino, D. Calvetti, and E. Somersalo, "Metabolica: A statistical research tool for analyzing metabolic networks," *Comput. Methods Programs Biomed.*, vol. 97, no. 2, pp. 151–167, 2010, doi: 10.1016/j.cmpb.2009.07.007.

[32] S. Martelli, D. Calvetti, E. Somersalo, and M. Viceconti, "Stochastic modelling of muscle recruitment during activity," *Interface Focus*, vol. 5, no. 2, p. 20140094, Apr. 2015, doi: 10.1098/rsfs.2014.0094.