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SENSITIVITY OF MODEL-PREDICTED MUSCLE FORCES OF PATIENTS WITH CEREBRAL PALSY TO VARIATIONS IN MUSCLE-TENDON PARAMETERS

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Computational musculoskeletal modeling and simulation platforms are efficient tools to gain insight into the muscular coordination of patients with motor disabilities such as cerebral palsy (CP). Muscle force predictions from simulation programs are influenced by the architectural and contractile properties of muscle-tendon units. In this study, we aimed to evaluate the sensitivity of major lower limb muscle forces in patients with CP to changes in muscle-tendon parameters. Open-access datasets of children with CP ($n = 8$) and healthy children ($n = 8$) were considered. Monte Carlo analysis was executed to specify how sensitive the muscle forces to perturbations between +10% and −10% of the nominal value of the maximum isometric muscle force, optimal muscle fiber length, muscle pennation angle, tendon slack length, and maximum contraction velocity of muscle. The sensitivity analysis revealed that muscle forces of CP patients and healthy individuals were most sensitive to perturbations in the tendon slack length ($p < 0.05$), while forces of CP patients were more sensitive to tendon slack length when compared to the healthy group ($p < 0.05$). Muscle forces of patients and healthy individuals were insensitive to the other four parameters ($p > 0.05$), except for the gracilis and sartorius muscles in which the proportion of optimal muscle fiber length to tendon slack length is higher than 1; forces of these two muscles were also sensitive to the optimal muscle fiber length. The results of this study are expected to contribute to our understanding of which parameters should be personalized when conducting musculoskeletal modeling and simulation of patients with CP.

Keywords: Cerebral palsy; musculoskeletal modeling and simulation; Monte Carlo sensitivity analysis; subject-specific model; muscle-tendon parameters.

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1. Introduction

Cerebral palsy (CP) is a neurological disease that causes several deformities in the musculoskeletal system.[1] These developing musculoskeletal impairments cause several gait pathologies such as crouch gait and stiff knee gait.[2–4] Prevalent interventions approved for the treatment of CP focused on the joint contractures and muscle functions.[5] Motion analysis is a frequently preferred method for making-decision in the treatment of patients with CP.[6,7] Even though gait analysis provides satisfactory information regarding joint kinetics and kinematics, there are still limitations in the estimation of muscle force. Prediction of the muscle forces of patients with CP would provide a valuable aspect for the treatment and monitoring procedures.

Computational musculoskeletal modeling and simulation platforms are efficient tools for the prediction of muscle forces.[8–12] Such platforms are based on a skeletal system represented by rigid bodies, interconnected by joints, and actuated by Hill-type muscle-tendon units.[8,9] The prediction performance of model simulations is mainly affected by the musculotendon parameters introduced to the muscle-tendon unit.[13–16] Major parameters that are introduced to a Hill-type muscle model are maximum isometric muscle force, optimal muscle fiber length, tendon slack length, pennation angle, and maximum contraction velocity,[13] which rely on the neuromuscular and physiological conditions of individuals.[17]

In simulation platforms, generic models are generally utilized for the characterization of the musculoskeletal systems of healthy individuals and patients. The generic musculoskeletal models are created based on cadaveric studies.[18] Even though model calibrations are carried out to construct a reliable musculoskeletal model, muscle-tendon parameters are unique for each individual and this makes it challenging to characterize the specific force generation capacity of each muscle.[16,19–21] Scaled-generic musculoskeletal models based on static marker data recorded during the static pose of the individuals can be utilized to describe an individual's musculoskeletal geometry. But such models would not reflect the specific and accurate representation of the contractile and architectural muscle-tendon parameters.[22]

Personalization of a musculoskeletal model has likely substantial importance,[16,23] especially in patients with CP, since these patients often have various musculoskeletal deformities such as hip flexor, knee extensor or plantar flexor muscle weakness, hamstring contracture, shorter or longer Achilles tendon, reduced muscle cross-sectional area, increased or reduced tibial torsion or femoral anteversion.[7] The major challenge is to adjust muscle-tendon parameters used in musculoskeletal models for patients with CP. Because these patients have very heterogeneous musculotendinous characteristics that directly affect the properties of muscle-tendon parameters. In the literature, various approaches were proposed to introduce patient- or subject-specific characteristics to muscle-tendon unit models. For example, van der Krogt *et al.* created an OpenSim knee model by scaling

maximum isometric muscle forces according to the subject's mass.[24] Correa and Pandy developed a scaling method including individual mass and muscle-tendon lengths.[25] Handsfield *et al.* calculated muscles' volumes using magnetic resonance imaging (MRI) data and obtained maximum isometric muscle forces proportional to these values.[26] Kainz *et al.* and Hegarty *et al.* modified the maximum isometric muscle force by scaling based on hand-dynamometer measurements.[27,28] Hainisch *et al.* developed a method to determine the muscle-tendon parameters by calculating the muscle volume, extracting the muscle paths, and specifying the locations of muscle attachment points using MRI data.[29] Veerkamp *et al.* modified muscle-tendon parameters by utilizing the Calibrated Electromyography-Informed Neuromusculoskeletal Modeling that regulated muscle-tendon parameters to minimize the difference between joint moments obtained from inverse dynamics and electromyography-driven musculoskeletal model.[30]

Due to ethical concerns and technical inadequacy, direct measurement of muscle-tendon parameters remains challenging, and their values available in the literature differ considerably.[26,31] Therefore, analysis of the sensitivity of model estimation to variations in muscle-tendon parameters, especially for patients with CP, is essential. Ackland *et al.* revealed that muscle forces obtained from a three-dimensional Hill-type muscle-actuated model of healthy individuals were most sensitive to changes in tendon slack length during self-selected walking.[32] Bujalski *et al.* performed an extended sensitivity analysis of healthy individuals during running by taking into account the 11 muscle-tendon parameters of the Hill-type muscle model.[33] They showed that muscle forces were substantially sensitive to changes in muscle-tendon parameters. Rezgui *et al.* carried out a sensitivity analysis of musculoskeletal parameters of patients with CP using a multibody dynamics simulation software (ADAMS, MSC Software Newport Beach, CA).[34] However, it was not clear in that study which parameters were changed for the sensitivity analysis and how the results were affected by these modifications.

In this study, we aimed to evaluate the sensitivity of calculated muscle forces in patients with CP to changes in muscle-tendon parameters used in OpenSim, a widely used computational musculoskeletal modeling and simulation software. Open-access datasets recorded from children with CP and healthy age-matched children were considered. Monte Carlo analysis was executed to specify how sensitive the predicted muscle forces to perturbations between +10% and −10% of the nominal value of the maximum isometric muscle force, optimal muscle fiber length, tendon slack length, pennation angle, and maximum contraction velocity of the muscle.

2. Materials and Methods

2.1. *Experimental protocol*

In this study, an open-access dataset released by Steele *et al.* was used.[35] Eight children with spastic diplegic CP (age: 8.3 ± 1.6, height: 1.21 ± 0.11 m, mass:

26.9 ± 9.2 kg) were included. Inclusion criteria were (i) having mild crouch during walking (minimum knee flexion angle was between 15° and 40° during stance phase), (ii) reaching a minimum 0° dorsiflexion angle during the physical exam (no equinus), (iii) having no previous surgeries, and (iv) having tibial torsion and femoral anteversion less than 30°.

Gait data were collected with a 12-camera motion capture system (Vicon Motion Systems, Lake Forest, CA). Thirteen reflective markers were attached to respective anatomical regions of the children according to a standard marker protocol.[36] Ground reaction force data were recorded using four force platforms (AMTI, Watertown, MA). Patients walked at self-selected walking speed (0.91 ± 0.14 m/s). Additionally, gait data of eight healthy age-matched children (age 9.5 ± 2.1, height: 1.28 ± 0.19 m, mass: 31.5 ± 7.9 kg) published by Lencioni *et al.* were used to obtain normative gait data.[37]

2.2. *Modeling and simulation of the musculoskeletal system*

Simulation of the musculoskeletal models of patients with CP was performed in OpenSim.[9] The full-body musculoskeletal model developed by Rajagopal *et al.*, which is freely available in OpenSim library, was used.[38] The 39 degree-of-freedom model was formed from 22 rigid body segments and 80 Hill-type muscle-tendon units. The contractile and physiological properties of the muscle-tendon units were based on the cadaver study by Ward *et al.*[39] and magnetic resonance imaging study on muscle volume by Handsfield *et al.*[40] Using the scaling tool in OpenSim, the model was scaled to each patient's anthropometry by matching the virtual marker positions of the model to experimentally recorded marker positions during the static pose of the subjects. Following the scaling process, the inverse kinematics was executed to calculate the joint angles during walking by minimizing the error between the virtual and experimental markers. The analysis was completed so that the maximum marker error was less than 0.05.[21]

Joint moments were calculated using inverse dynamics. Afterward, joint moments and ground reaction force were introduced to OpenSim to calculate muscle forces by using static optimization.[41] The biceps femoris muscle force was calculated as the mean value of the forces of the biceps femoris long head and biceps femoris short head. The gastrocnemius muscle force was calculated as the mean value of the forces generated by the medial gastrocnemius and lateral gastrocnemius.

2.3. *Model sensitivity analysis*

Monte Carlo analysis was performed to evaluate the sensitivity of calculated muscle forces to variations in individual and combined five contractile and architectural parameters of muscle-tendon unit: maximum isometric muscle force, optimal muscle fiber length, tendon slack length, muscle pennation angle, and maximum contraction velocity of muscle.[42] Seven major lower limb muscles, namely the biceps femoris, gastrocnemius, gracilis, rectus femoris, sartorius, semimembranosus, and

tibialis anterior were considered in the study. Muscle forces acquired from the generic model were considered as the nominal forces. Static optimization was executed by randomly changing each model parameter between +10% and −10% of its nominal value. Root mean square difference (RMSD) and Pearson cross-correlation coefficient (PCC) were calculated to quantify the magnitude differences and pattern similarities between the nominal muscle force and muscle forces obtained from the Monte Carlo analysis, respectively. As an example, an RMSD value of 0.02 corresponds to a 2% difference, and a PCC value of 0.90 corresponds to a 90% similarity. A convergence criterion was assigned as a stopping rule for each Monte Carlo analysis. This criterion was finalizing the Monte Carlo analysis when the mean and standard deviation for the final 10% of the simulations were within 2% of the overall mean and standard deviation.[32] Monte Carlo analysis was performed for both patients and healthy individuals.

2.4. *Data analysis*

Calculated RMSD and PCC values for patients and healthy individuals were statistically analyzed. Statistical analysis was conducted using the SPSS program (Version 21.0; SPSS; Chicago, IL; USA). The statistical significance level was assigned at 0.05. The normality of the data was investigated by using the Shapiro-Wilk test. Since the data were not normally distributed, a non-parametric Mann–Whitney U test was used.

3. Results

The variations in muscle forces in the presence of perturbations in tendon slack length and optimal muscle fiber length over a gait cycle obtained from Monte Carlo analyses for patients with CP and healthy individuals were given in Figs. 1 and 2, respectively (please see Appendix for the figures depicting the variations in muscle forces in response to perturbations in maximum isometric muscle force, muscle pennation angle, and maximum contraction velocity of muscle). Magnitudes of muscle forces were normalized to body-weight (BW) of each subject.

The sensitivity analysis revealed that all muscle forces of CP patients and healthy individuals were most sensitive to perturbations in tendon slack length ($p < 0.05$), while forces of CP patients were more sensitive to tendon slack length when compared to the healthy group ($p < 0.05$). Muscle forces of patients and healthy individuals were insensitive to the other four parameters ($p > 0.05$), except for the gracilis and sartorius muscles in which the proportion of optimal muscle fiber length to tendon slack length is higher than 1; forces of these two muscles were also sensitive to optimal muscle fiber length ($p < 0.05$). The simultaneous perturbation of all five parameters resulted in similar muscle forces to those calculated by perturbing only tendon slack length, indicating that tendon slack length is the most dominant among the five parameters in the calculation of the muscle forces.

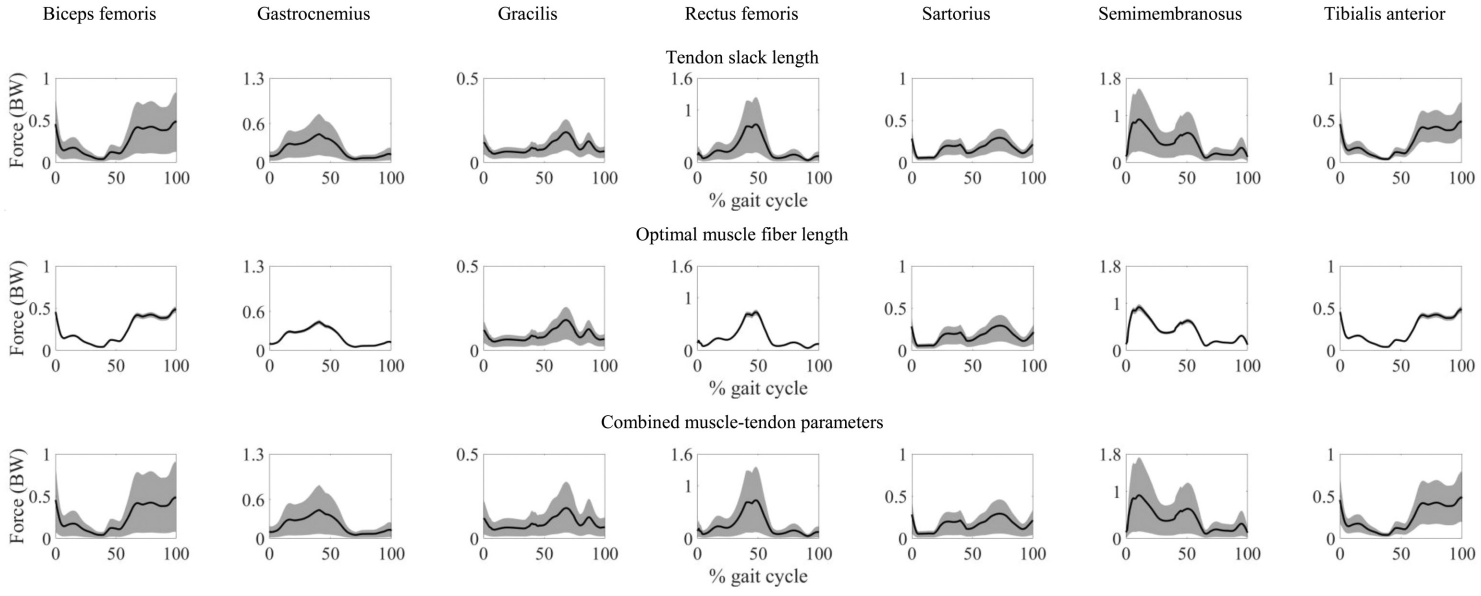

Fig. 1. Variations in muscle forces obtained from Monte Carlo analyses by perturbing tendon slack length, optimal fiber length, and the combination of five muscle-tendon unit parameters for patients with CP. Gray shaded regions indicate the range of the muscle force values, while black solid lines indicate the nominal muscle force values.

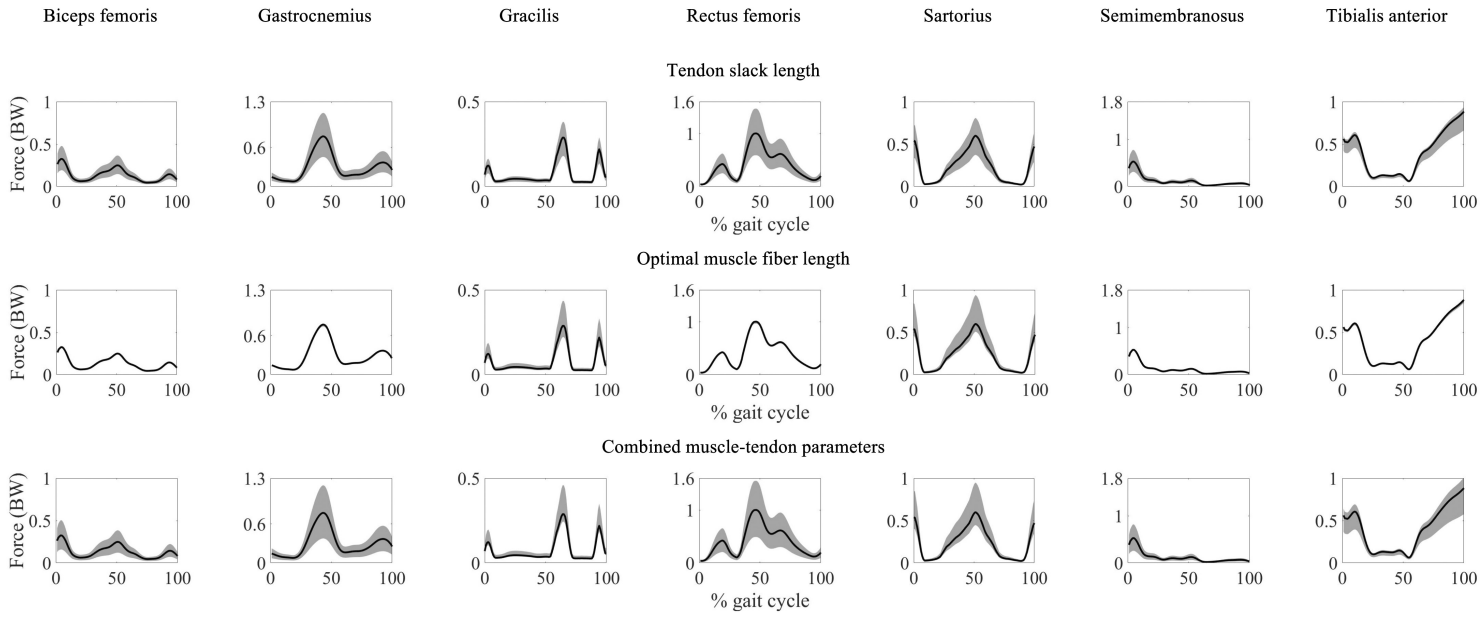

Fig. 2. Variations in muscle forces obtained from Monte Carlo analyses by perturbing tendon slack length, optimal fiber length, and the combination of five muscle-tendon parameters for healthy individuals. Gray shaded regions indicate the range of the muscle force values, while black solid lines indicate the nominal muscle force values.

Table 1. Average RMSD values representing the level of differences between the nominal and perturbing muscle forces obtained from Monte Carlo simulations. Significant differences were marked bold.

		Biceps femoris			Gastrocnemius			Gracilis			Rectus femoris			Sartorius			Semimembranosus			Tibialis anterior		
		Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p
Max. isometric muscle force	Mean	0.05	0.03	0.55	0.04	0.02	0.65	0.03	0.02	0.71	0.06	0.02	0.45	0.03	0.01	0.51	0.07	0.02	0.68	0.03	0.01	0.58
	Max	0.09	0.04		0.07	0.03		0.05	0.03		0.10	0.04		0.06	0.03		0.11	0.03		0.05	0.02	
	Min	0.01	0.0		0.0	0.0		0.01	0.0		0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.0	
Tendon slack length	Mean	0.5	0.27	**0.03**	0.44	0.31	**0.04**	0.43	0.30	**0.04**	0.47	0.31	**0.04**	0.45	0.29	**0.04**	0.49	0.21	**0.03**	0.36	0.24	**0.04**
	Max	0.88	0.48		0.81	0.51		0.79	0.64		0.85	0.53		0.82	0.52		0.91	0.41		0.65	0.45	
	Min	0.0	0.0		0.0	0.0		0.0	0.01		0.01	0.0		0.01	0.0		0.0	0.0		0.0	0.0	
Optimal fiber length	Mean	0.03	0.01	0.51	0.03	0.01	0.52	0.46	0.33	**0.04**	0.04	0.01	0.87	0.48	0.25	**0.03**	0.03	0.01	0.49	0.02	0.01	0.67
	Max	0.06	0.02		0.05	0.02		0.81	0.68		0.06	0.01		0.85	0.51		0.05	0.02		0.03	0.02	
	Min	0.0	0.0		0.0	0.0		0.01	0.0		0.0	0.01		0.0	0.01		0.0	0.0		0.0	0.0	
Pennation angle	Mean	0.02	0.01	0.52	0.01	0.01	0.71	0.01	0.01	0.75	0.02	0.01	0.73	0.01	0.01	0.79	0.02	0.01	0.79	0.01	0.02	0.97
	Max	0.04	0.01		0.02	0.01		0.01	0.01		0.03	0.02		0.02	0.01		0.03	0.02		0.02	0.01	
	Min	0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.01		0.0	0.0		0.0	0.0	
Max contraction velocity	Mean	0.01	0.01	0.94	0.01	0.01	0.86	0.01	0.01	0.93	0.01	0.01	0.91	0.01	0.01	0.84	0.02	0.01	0.79	0.01	0.01	0.95
	Max	0.02	0.01		0.02	0.01		0.01	0.01		0.02	0.02		0.01	0.01		0.03	0.02		0.01	0.01	
	Min	0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.0	
Combination of the parameters	Mean	0.55	0.36	**0.03**	0.5	0.35	**0.04**	0.51	0.35	**0.04**	0.52	0.37	**0.04**	0.52	0.32	**0.03**	0.54	0.28	**0.02**	0.38	0.30	**0.03**
	Max	1.01	0.62		0.96	0.67		0.93	0.75		0.98	0.71		0.89	0.67		1.05	0.51		0.71	0.57	
	Min	0.0	0.0		0.0	0.0		0.01	0.0		0.0	0.0		0.01	0.01		0.0	0.0		0.01	0.0	

Notes: p: level of statistical significance between compared pairs. Max and Min represent the maximum and minimum RMSD values, respectively.

Table 2. Average PCC values representing the level of similarities between the nominal and perturbing muscle forces obtained from Monte Carlo simulations.

		Biceps femoris			Gastrocnemius			Gracilis			Rectus femoris			Sartorius			Semimembranosus			Tibialis anterior		
		Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p	Patient	Healthy	p
Max. isometric muscle force	Mean	0.91	0.92	0.68	0.87	0.91	0.52	0.89	0.92	0.67	0.88	0.92	0.52	0.88	0.92	0.69	0.90	0.91	0.73	0.88	0.93	0.41
	Max	0.95	0.97		0.89	0.95		0.91	0.94		0.92	0.94		0.91	0.94		0.94	0.94		0.91	0.96	
	Min	0.84	0.86		0.83	0.87		0.84	0.89		0.85	0.89		0.86	0.89		0.85	0.87		0.85	0.89	
Tendon slack length	Mean	0.84	0.83	0.71	0.85	0.88	0.59	0.83	0.87	0.73	0.83	0.85	0.67	0.84	0.85	0.71	0.81	0.83	0.66	0.85	0.86	0.69
	Max	0.88	0.89		0.88	0.91		0.86	0.90		0.86	0.89		0.87	0.89		0.85	0.87		0.88	0.90	
	Min	0.78	0.76		0.80	0.84		0.78	0.83		0.79	0.79		0.81	0.82		0.76	0.79		0.81	0.81	
Optimal fiber length	Mean	0.89	0.89	0.97	0.87	0.88	0.72	0.88	0.91	0.79	0.90	0.93	0.61	0.91	0.92	0.74	0.92	0.92	0.92	0.91	0.92	0.71
	Max	0.91	0.92		0.89	0.91		0.90	0.93		0.92	0.95		0.93	0.94		0.94	0.96		0.93	0.95	
	Min	0.87	0.85		0.84	0.85		0.85	0.88		0.88	0.89		0.87	0.88		0.88	0.87		0.87	0.87	
Pennation angle	Mean	0.89	0.90	0.71	0.91	0.92	0.69	0.88	0.90	0.71	0.88	0.91	0.66	0.89	0.89	0.79	0.91	0.92	0.71	0.92	0.91	0.69
	Max	0.94	0.94		0.95	0.96		0.92	0.92		0.91	0.95		0.92	0.91		0.93	0.94		0.95	0.94	
	Min	0.83	0.85		0.86	0.89		0.85	0.87		0.84	0.87		0.85	0.87		0.87	0.87		0.87	0.89	
Max contraction velocity	Mean	0.89	0.91	0.65	0.89	0.94	0.44	0.87	0.92	0.68	0.90	0.92	0.68	0.88	0.91	0.62	0.86	0.91	0.47	0.87	0.92	0.43
	Max	0.92	0.94		0.93	0.96		0.92	0.95		0.92	0.93		0.90	0.93		0.90	0.93		0.91	0.94	
	Min	0.84	0.86		0.86	0.91		0.83	0.88		0.87	0.89		0.85	0.88		0.81	0.87		0.81	0.88	
Combination of the parameters	Mean	0.81	0.83	0.63	0.82	0.84	0.64	0.82	0.82	0.89	0.81	0.83	0.68	0.82	0.83	0.72	0.79	0.82	0.53	0.83	0.83	0.94
	Max	0.86	0.87		0.85	0.89		0.84	0.85		0.84	0.86		0.85	0.85		0.83	0.85		0.86	0.87	
	Min	0.74	0.78		0.79	0.78		0.79	0.79		0.77	0.79		0.77	0.80		0.73	0.78		0.78	0.79	

Notes: p: level of statistical significance between compared pairs. Max and Min represent the maximum and minimum PCC values, respectively.

In terms of RMSD results, model-predicted muscle forces of CP patients were more sensitive to tendon slack length when compared to the healthy group ($p < 0.05$) (Table 1). Maximum mean RMSD values were 0.50 (biceps femoris) for patients and 0.31 (gastrocnemius and rectus femoris) for healthy individuals for the case in which the tendon slack length was changed. Although perturbation of optimal fiber length in CP patients led to higher RMSD values than those in the healthy group, these differences were not significant ($p > 0.05$), except for the gracilis and sartorius muscles ($p < 0.05$). Gracilis and sartorius forces in patients showed higher sensitivity to optimal muscle fiber length than those in healthy individuals ($p < 0.05$). Muscle force estimates were not sensitive to changes in maximum isometric muscle force, muscle pennation angle, and maximum contraction velocity of muscle ($p > 0.05$). When all muscle-tendon parameters were perturbed at the same time, maximum mean RMSD values in patients were significantly higher than those in healthy individuals for all muscles ($p < 0.05$).

PCC values calculated for patients with CP were slightly lower than those for healthy individuals ($p > 0.05$) (Table 2). Although it is not statistically significant, the lowest PCC values were obtained from perturbations in tendon slack length among five musculotendinous parameters in both patient and healthy groups ($p > 0.05$).

4. Discussion

Accurate prediction of muscle forces would provide critical insight into treatment decision-making in patients with CP. Therefore, investigation on how the variations in muscle-tendon parameters would affect muscle force estimations in patients with CP should be one of the steps in the muscle force prediction process. In this study, we aimed to reveal the sensitivity of model-predicted muscle forces of patients with CP to changes in maximum isometric muscle force, optimal muscle fiber length, tendon slack length, muscle pennation angle, and maximum muscle contraction velocity. We found that all calculated muscle forces were most sensitive to changes in tendon slack length and insensitive to maximum isometric muscle force, muscle pennation angle, and maximum muscle contraction velocity (Figs. A1 and A2). Only the gracilis and sartorius forces showed sensitivity to optimal muscle fiber length. The effect of tendon slack length on muscle forces alone was similar to that obtained from simultaneous changes of all five muscle-tendon unit parameters. This indicated that tendon slack length is a major determinant in the calculation of muscle forces in Hill-type muscle models. Ackland *et al.* reported similar results for healthy subjects.[32] Another major finding of our study is that magnitude of muscle forces of patients with CP was found more sensitive to changes in tendon slack length (and optimal fiber length only for gracilis and sartorius muscles) than those obtained from healthy individuals (Table 1). This indicated that specifying subject-specific musculotendinous parameters of patients with CP is of high importance for the accurate determination of the muscle forces.

The maximum isometric muscle force is calculated by the multiplication of the physiological cross-sectional area (PCSA) and specific muscle tension.[43] In the musculoskeletal model we used,[38] this value was calculated to be precisely correlated with the PCSA which was based on the total muscle volume adopted from Handsfield *et al.*[26] It was shown that muscle volumes of patients with CP were 20% lower than that of healthy individuals on average by utilizing MRI data.[26] Even though patients with CP would have lower maximum isometric muscle forces than healthy individuals, sensitivity analysis of our study revealed that variations in maximum isometric muscle force between +10% and −10% of its nominal value would not significantly affect the muscle force predictions. Bolsterlee *et al.* evaluated the effect of personalizing PCSA by using magnetic resonance images in a large-scale musculoskeletal model of the upper extremity.[44] They found that PCSA scaling only marginally influenced muscle force predictions for submaximal exertions.

Direct determination of tendon slack length is challenging since the determination of the aponeurotic part of the tendon is problematic. Barber *et al.* reported that tendon slack length of the Achilles tendon of patients with CP was 10% longer than those obtained from healthy individuals.[45] In our study, the sensitivity of muscle forces to variations in tendon slack length was highest when compared to other muscle-tendon parameters. This finding is well-accepted in the literature for healthy subjects.[32,46] Variations in tendon slack length substantially influence the muscle operating length, hence the force generation capacity. Accordingly, our study revealed that tendon slack length would be a predominant parameter in the calculation of muscle forces using a subject-specific musculoskeletal model. Perturbation on tendon slack length resulted in significant differences between patients with CP and healthy individuals in terms of muscle force magnitude (Table 1), while muscle force profile did not differ significantly (Table 2). This finding may be interpreted as muscle functions of CP children do not differ significantly when compared to healthy individuals, but the amplitude of muscle forces differs.[35]

Unlike the gracilis and sartorius, predicted forces for the biceps femoris, gastrocnemius, rectus femoris, semimembranosus, and tibialis anterior were found to be insensitive to variations in optimal fiber length. Redl *et al.* showed that estimated muscle forces were more sensitive to alterations in optimal fiber length when the proportion of optimal muscle fiber length to tendon slack length was higher than 1.[46] In our study, tendon slack length values of the investigated five muscles (biceps femoris, gastrocnemius, rectus femoris, semimembranosus, and tibialis anterior) are 80% higher than their optimal fiber length values. On the other hand, the proportion of optimal muscle fiber length to tendon slack length is higher than 1 for the gracilis and sartorius. This may be an explanation for why the gracilis and sartorius forces were sensitive to changes in optimal fiber length. Also, the lowest RMSD values were calculated from the tibialis anterior which has the lowest proportion of tendon slack length to optimal fiber length (71%).

Some limitations should be considered when interpreting the results. First, we did not introduce any musculoskeletal deformities of CP children to the models that likely affect the muscle force predictions. Second, perturbations in muscle-tendon parameters were applied to only 7 (9 muscle-tendon units) out of 80 muscles of the musculoskeletal model. Even though these muscles are major contributors to walking, other muscles that we did not analyze have also important roles in gait. Third, the Monte Carlo analysis was performed during only self-selected walking. Ackland *et al.* reported that the sensitivity of muscle behavior to variations in muscle-tendon parameters was task-dependent even in healthy individuals.[32] For instance, Bujalski *et al.* revealed that muscle force estimations were sensitive to alterations in maximum isometric muscle force during running,[33] while Ackland *et al.* found that perturbations in maximum isometric muscle force did not affect the muscle force predictions during walking.[32]

5. Conclusion

We found that model-predicted muscle forces of patients with CP and healthy individuals were most sensitive to the perturbations in the tendon slack length, while forces of CP patients were more sensitive to tendon slack length when compared to the healthy group. Forces of the gracilis and sartorius in which the proportion of optimal muscle fiber length to tendon slack length is higher than 1 were also sensitive to the optimal muscle fiber length, while forces of these two muscles in patients were more sensitive when compared to the healthy group. Other muscle-tendon parameters were relatively less effective on muscle force estimations. The results of our study are expected to contribute to our understanding of which parameters should be personalized when conducting musculoskeletal modeling and simulation to calculate reliable muscle forces of patients with CP.

Appendix A

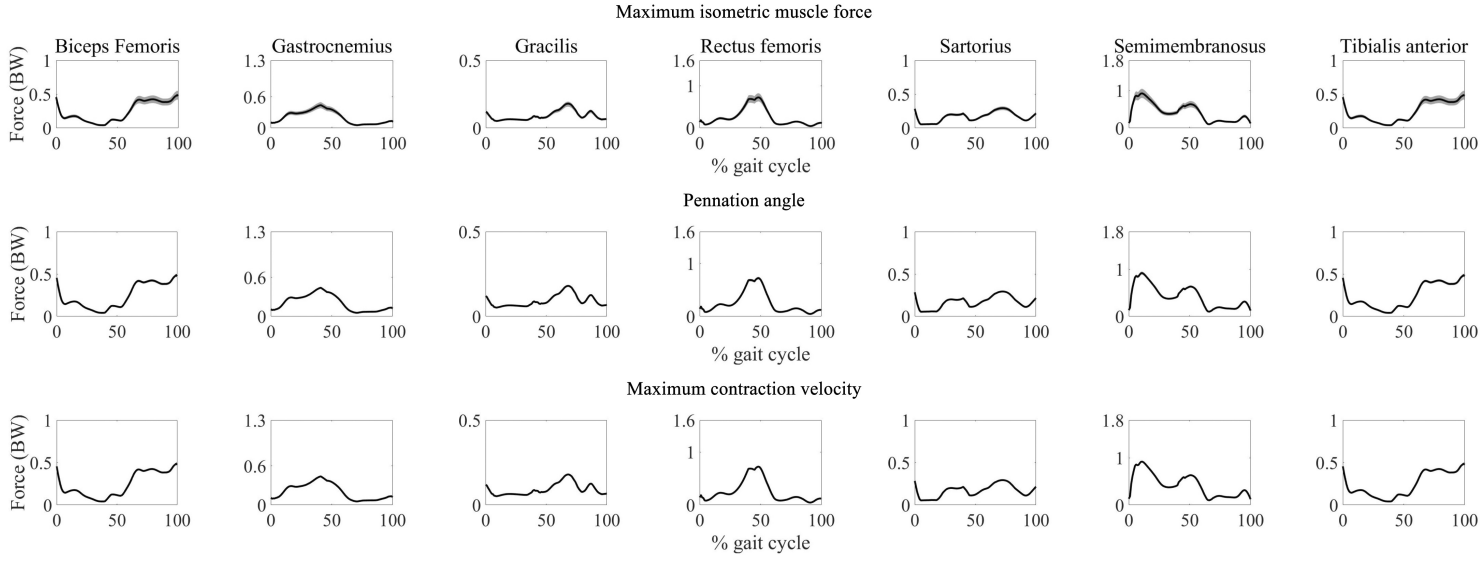

Fig. A1. Variations in muscle forces obtained from Monte Carlo analyses by perturbing maximum isometric muscle force, pennation angle, and maximum contraction velocity for patients with CP. Gray shaded regions indicate the range of the muscle force values, while black solid lines indicate the nominal muscle force values.

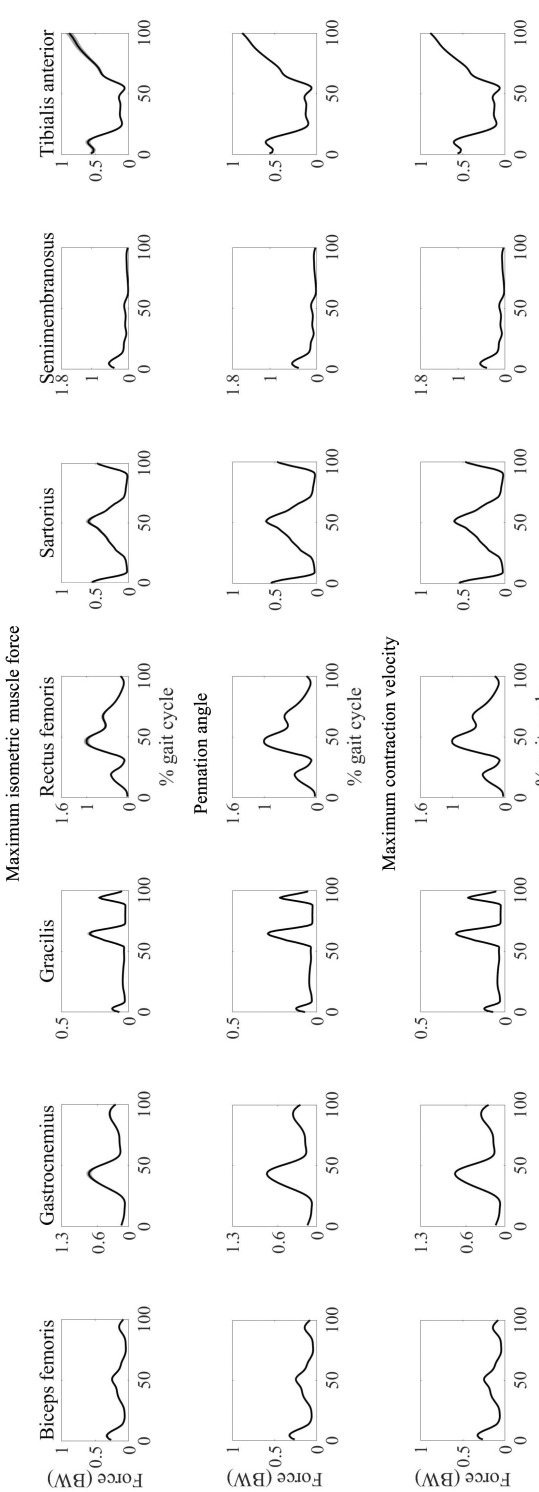

Fig. A2. Variations in muscle forces obtained from Monte Carlo analyses by perturbing maximum isometric muscle force, pennation angle, and maximum contraction velocity for healthy individuals. Gray shaded regions indicate the range of the muscle force values, while black solid lines indicate the nominal muscle force values.

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