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EXECUTIVE SUMMARY OF THE THESIS

Cerebral Palsy treated with botulinum toxin: OpenSim to obtain a biomechanical model

TESI MAGISTRALE IN BIOMEDICAL ENGINEERING

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ACADEMIC YEAR: 2022-2023

1. Introduction

Cerebral Palsy (CP) is a permanent disorder of the motor function [1]. CP presents multiple gait deviations, including jump gait, crouch gait, and true equinus. Hence, the activity of gastrocnemius and tibialis anterior muscles in children with Cerebral Palsy may be compromised due to the brain injury, resulting in muscle activations that differ from the typical physiological patterns. This thesis focuses on botulinum toxin, a pharmacological approach, useful to reduce muscle spasticity. This type of treatment offers several advantages, such as safety, which is guaranteed when the maximum total dose is appropriately defined, reduced muscle stiffness, improved muscle contraction in both upper and lower limbs, better passive mobility and prevention of skeletal deformities. There are multiple studies in literature in which musculoskeletal modeling has been used to derive muscular activations and kinematics. Regarding the experimental data acquisition, the Davis marker set protocol [2] appears to be the most widely used protocol in the clinical environment, flanked by the Plug-In Gait marker set [3]. The aim of this study is to validate a biomechanical model in OpenSim, starting from the Davis marker protocol used in clinical practice. In this sense, data present from repository were used. The dataset included movement acquisitions of 28 children with CP treated with botulinum toxin injections. Kinematic curves and muscle activation patterns were obtained by analyzing patients' gait before and after the treatment.

2. Materials and Methods: the Biomechanical model

During the acquisitions performed at IRCCS San Raffaele (Rome), two force platforms were used to record the ground reaction forces (GRF) and the Davis protocol was applied for the subject's markers placement. The clinical protocol involves 22 markers placed on:

- Trunk: right and left acromion, and C7 vertebra;
- Pelvis: left and right anterior-superior iliac spines (ASIS) and sacrum;
- Thigh: greater trochanter, lateral femoral epicondyle and at 1/3 of the length of the thigh, bilaterally;
- Leg: lateral malleolus, head of the fibula and 1/3 of the leg, bilaterally;
- Foot: fifth metatarsal head and heel, bilaterally.

During standing acquisition three markers were kept at the foot, while during the walking trials the heel marker was removed.

1. Elite System

All standing and walking acquisitions were examined through the BTS Bioengineering SpA software (Garbagnate Milanese, MI, Italy): SMART Analyzer, TDF inspector, and SMART Tracker. Once markers and force vectors were labeled, the files were exported in .osim format.

2. Model Scaling

OpenSim is an open-source platform implemented by a group of Stanford researchers used for modeling, simulation and analysis of the neuro-musculoskeletal system. Model segments' dimensions were resized to match the distances between virtual markers of the standard Gait2392 in OpenSim with the experimental ones, which were placed on bony prominences of the patients during the analysis according to Davis protocol. Four virtual markers were added to the 22 Davis model markers on the femoral condyles and medial malleoli to obtain a more accurate scaling at the lower limb level. The generic Gait2392.osim was input to the software, as well as the file .trc including experimental markers' positions and the marker set .xml. Therefore, it was possible to obtain subject-specific models, adjusted to the anthropometric measurements of the patients, maintaining RMS and Maximum Marker Error values below 2 cm and 3 cm, respectively [4]. For example, for patient 23 we obtained:

- RMS error pre-toxin = 0.0179903
- RMS error post-toxin = 0.0147302
- Max Marker error pre-toxin = 0.0231496
- Max Marker error post-toxin = 0.0244231

3. Inverse Kinematics (IK)

The scaled model and file .trc containing the experimental markers trajectories were input in the software. By IK tool, the knee and ankle joints kinematics of each individual was estimated, starting from the experimental trajectory of the markers [5].

4. Static Optimization (SO)

Through the SO tool [6], muscular activation patterns were estimated. The IK file .mot and the file related to the experimental ground reaction forces applied on the heels were input in the model. The main point of this study was to estimate the temporal activation patterns of the medial and lateral gastrocnemius muscles. Due to the motor deficit, the children suffer from anomalous activations compared to healthy subjects; in fact, as will be demonstrated later, in most cases, subjects with PCI show temporal muscle activations of the medial and lateral gastrocnemii often not in the normal range (between 20% and 50% of the gait cycle).

3. Results: Kinematic comparison OpenSim vs gold standard

In the following section the kinematic curves of the knee flexion-extension and ankle dorsi-plantar flexion are depicted. To validate the outcomes, the kinematic curves obtained from OpenSim were compared with the data given by the marker-based optoelectronic system, which is the gold standard for movement analysis. To accomplish this, it was needed to consider just the experimental acquisitions having both a valid quantification of ground reaction forces and markers fully visible by the cameras. Thus, if the kinematic curves generated by OpenSim included more than one gait cycle, the plots obtained from the optoelectronic software contained only one cycle. Hence, in order to have a graphical comparison, the same gait cycle as the gold standard was chosen by reducing the trials to the most significant frames. In the depicted graphs, 0% and 100% mark the first and second-foot contacts with the ground, while the 60% point of the gait cycle represents the toe-off event.

The gastrocnemius' activity (Figure 1) in healthy children is reduced during foot-ground contact to facilitate the action of the tibialis anterior muscle, which controls foot landing on the ground, performed with a slight dorsiflexion of the ankle.

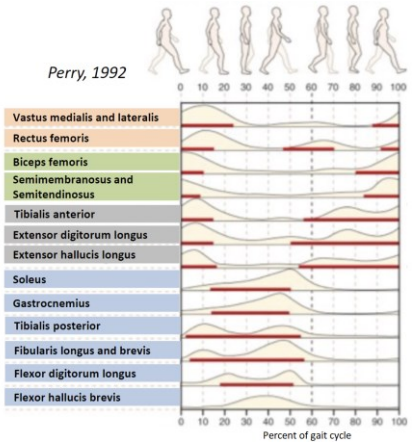

Figure 1 Muscular physiological activations during the gait cycle.

During the push off phase, as the foot lifts off the ground, the activity of the gastrocnemius muscle gradually increases, reaching its peak during propulsion when the muscle is highly recruited to plantarflex the ankle and prepare the limb for the swing phase. Then, the gastrocnemius' activity decreases promptly, allowing the effective action of the tibialis anterior, which contracts to dorsiflex the ankle, preventing the foot from swinging during the swing phase.

The figures below show the results of patient 23: Figure 2 depicts the knee flexion-extension curves obtained from OpenSim, which were compared with the gold standard represented in Figure 3, before the injection of BoNT. Data relative to the post treatment conditions are depicted in Figure 4 and Figure 5.

Due to equinus gait, at the initial contact the patient exhibited a larger knee flexion than the physiological norm (10°) for both limbs. The results obtained by OpenSim were almost similar to the data coming from the optoelectronic system for knee flexion-extension between 50% and 100% of the gait cycle. However, some differences in the first half of the gait cycle were evident. In fact, in OpenSim the left knee flexion at the initial contact had an amplitude smaller of 5° than the one predicted by the gold standard; in addition, in the load acceptance phase there was an extension of the both right and left knee in OpenSim, while data coming from the gold standard showed a slight knee flexion after the initial contact.

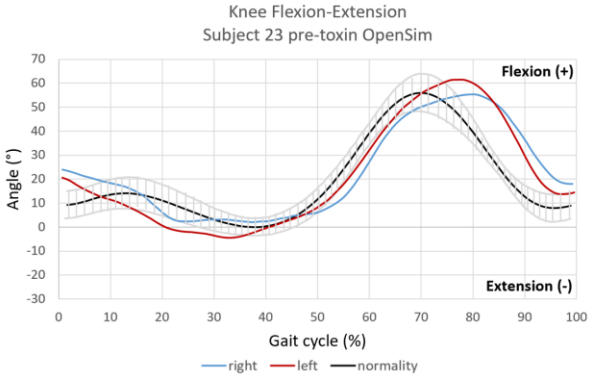

Figure 2 Knee Flexion-Extension pre-toxin OpenSim.

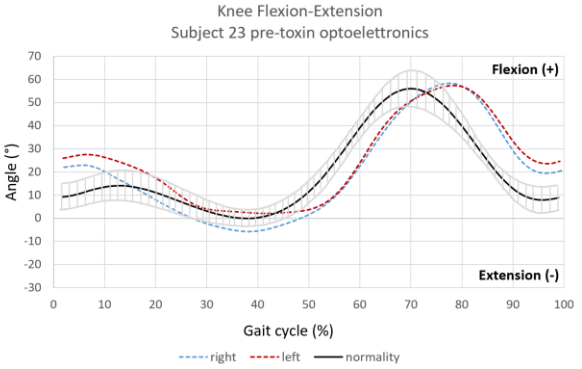

Figure 3 Knee flexion-extension pre-toxin optoelectronics.

After the injection of botulinum toxin at the level of the lateral gastrocnemius, regarding the right limb, the toxin had a hyper-corrective effect: a hyperextension of the knee was visible between 30% and 50% in both results obtained by OpenSim (Figure 4) and the gold standard (Figure 5).

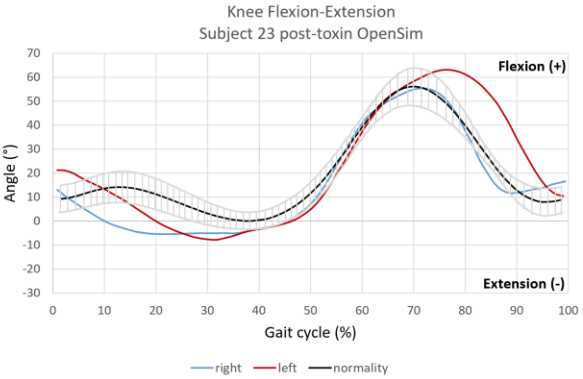

Figure 4 Knee flexion-extension post-toxin OpenSim.

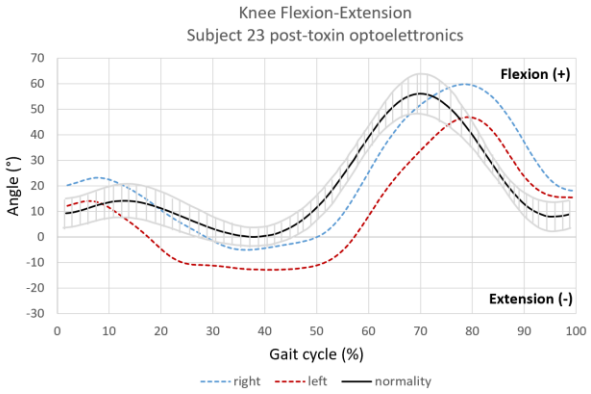

Figure 5 Knee Flexion-Extension post-toxin optoelectronics.

Analysing the ankle plantarflexion-dorsiflexion graphs, there was no plantarflexion throughout the gait cycle: the ankle appeared dorsiflexed with a difference of about 8° between the results obtained in OpenSim (Figure 6) and the optoelectronic system (Figure 7).

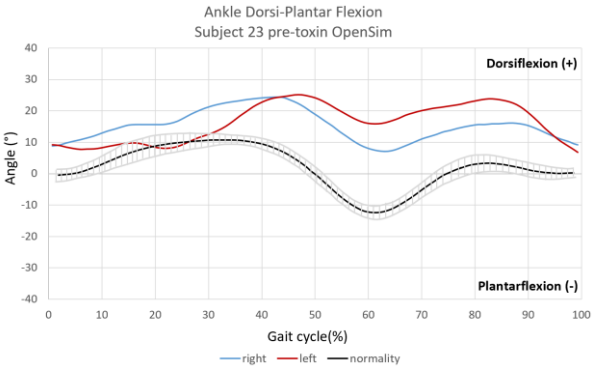

Figure 6 Ankle Dorsi-Plantarflexion pre-toxin OpenSim.

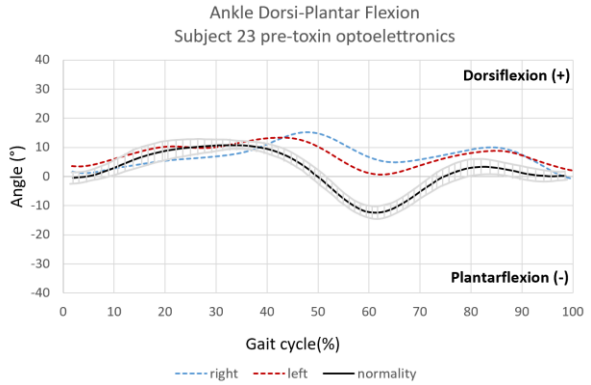

Figure 7 Ankle Dorsi-Plantar Flexion pre-toxin optoelectronics.

After the treatment, due to excessive toxin correction, in OpenSim (Figure 8) the right ankle goes into plantarflexion between 0% and 20% of the gait cycle. This was confirmed by the gold standard data, showing a plantarflexion of right and left ankles in both the load acceptance phase and swing phase (Figure 9).

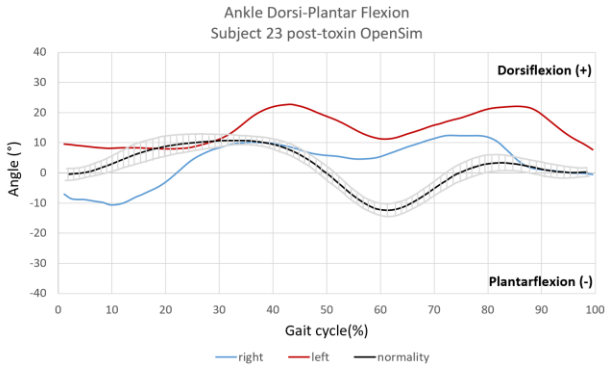

Figure 8 Ankle Dorsi-Plantar Flexion post-toxin OpenSim.

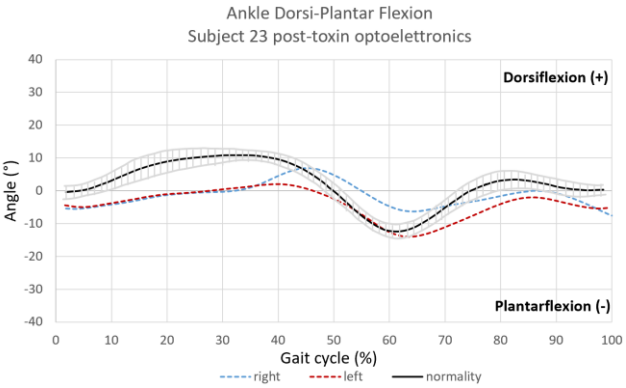

Figure 9 Ankle Dorsi-Plantar Flexion post-toxin optoelectronics.

4. Muscle activation results

Because of the presence of initial knee flexion noted by the optoelectronic report, doctors decided to perform a bilateral injection of toxin to the medial and lateral gastrocnemius muscles. The patient in the pre-toxin condition showed pre-activation of medial and lateral gastrocnemius compared with the physiological patterns. For the right limb (Figure 10) there was a single contraction from 10% to 65% of the gait cycle, so the activation is earlier than the physiological. For what concerns the left limb (Figure 11), the patient showed a double activation of medial and lateral muscles of gastrocnemius from 4% of the gait cycle to the 60%, and other two activations of small amplitude during the swing phase.

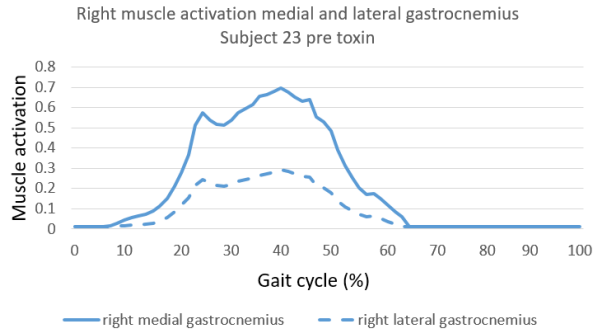

Figure 10 Right medial and lateral gastrocnemius muscle activations pre-toxin.

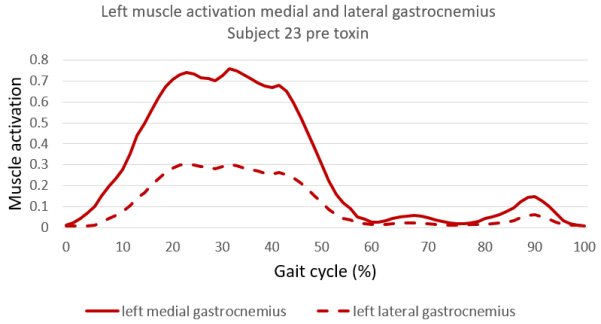

Figure 11 Left medial and lateral gastrocnemius muscle activations pre-toxin.

Regarding the right side (Figure 12), the toxin had a hypercorrective effect, in fact all activations of the lateral and medial gastrocnemii are inhibited. The prediction of these muscles' activations involved the outcomes of the inverse kinematics (joint kinematics estimated by OpenSim): plantarflexion of the ankle in both the early and swing phase and a hyperextension of the knees. After botulinum toxin injection at the level of the left lateral gastrocnemius, no significant changes in activation of the limb were evident (Figure 13).

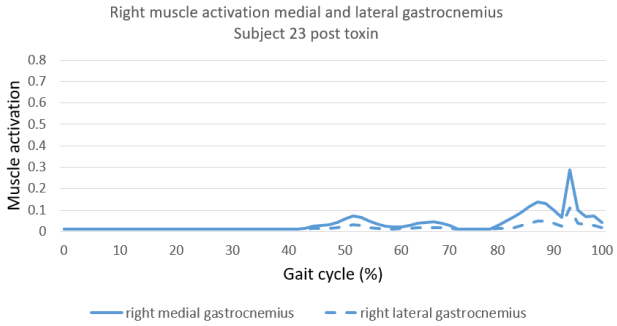

Figure 12 Right medial and lateral gastrocnemius muscle activations post-toxin.

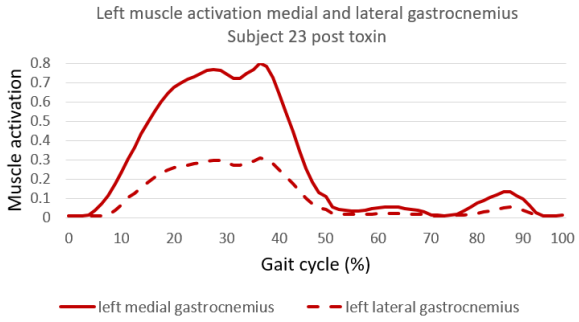

Figure 13 Left medial and lateral gastrocnemius muscle activations post-toxin.

5. Conclusions

The model was applied to children with spasticity resulting from cerebral palsy; it was able to predict the muscle activations of interest and to obtain knee kinematic almost consistent to the one from the marker-based optoelectronic system. The dataset was reduced due to the presence of noise during acquisitions. Regarding the estimation of kinematics, the Davis protocol appeared quite suitable for the estimation of the kinematics of the knee, but not for the ankle joint. This could be due to the heel markers removal during the dynamic gait acquisition, which led the software to estimate the ankle kinematics by only two markers' trajectories. Due to this insufficiency in terms of information in input to the model, the estimation of ankle kinematics and tibialis anterior muscle activation was unreliable. Consistently, the estimation of muscle activations, which received the obtained kinematics as input, was more accurate for biarticular muscles, which can rely not only on ankle kinematics, considered inaccurate, but also on knee kinematics, which proved to be more reliable. Therefore, for the estimation of monoarticular muscle activations, as muscles acting on the ankle joint, the Davis protocol involving the removal of heels' markers would appear to be not suitable. In fact, the knee kinematic estimates reported in this study deviated by only few degrees from the results of the gold standard, which cannot be said for the ankle. The muscle activations results showed consistently more intense activations of the medial gastrocnemius than the lateral one, both before and after toxin treatment [7]. The trend of muscle activations could allow to understand the type of rehabilitation that could be useful and to identify the muscular site that could benefit from a therapeutic approach.

Starting from experimental data obtained by gait analysis performed by the Davis protocol, typically used in clinics, with four markers added at the level of the femoral condyles and medial malleoli in OpenSim, it was possible to obtain adequate scaling, subject-specific patterns, with acceptable error values.

6. Bibliography

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