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Article

Kinematic Analysis of Patients with Charcot–Marie–Tooth Disease Using OpenSim

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Featured Application

The aim of this study is to develop patient-specific biomechanical models for individuals with Charcot–Marie–Tooth disease within the OpenSim environment in order to perform computational simulations that support the design of active gait assistance devices.

Abstract

This study proposes a methodology for conducting computational simulations of pathological gait. The literature shows a consensus that biomechanical models for gait analysis should be formulated as control problems. To achieve this, it is common practice to guide the solution using kinematic or kinetic data to prevent temporal instability. The aim of this study is to implement a biomechanical model of the Charcot–Marie–Tooth disease in OpenSim software that enables more comprehensive simulations, which may in future involve the musculoskeletal system of patient and predictive studies. In this way, it will be possible to design specific active assistive devices tailored to each patient. Experimental gait data from six Charcot–Marie–Tooth patients were used. The dataset comprises three-dimensional trajectories of reflective markers placed according to the Davis-Heel protocol. The acquired data allowed a patient-specific adjustment of the biomechanical model. The inverse kinematic was solved, and the results were validated by comparing them with those obtained using the commercial BTS Bioengineering® software. The results show a strong alignment in ankle kinematics between the OpenSim model and the data generated by BTS Bioengineering®. Additionally, the kinematic results have been compared with normative curves, allowing the identification of potential areas for intervention using active assistive devices aimed at improving movement patterns of patients.

Keywords: Charcot–Marie–Tooth; OpenSim; gait analysis; instability; ankle kinematics

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1. Introduction

Charcot–Marie–Tooth disease (CMT) is a hereditary and progressive peripheral neuropathy, characterised by the degeneration of motor and sensory nerve fibres. This condition leads to muscle atrophy and weakness, beginning its manifestation in the distal third of the lower limb, especially in the muscles controlling the ankle and foot, resulting in structural deformities such as pes cavus and varus, as well as joint biomechanical alterations [1,2]. From a genetic and pathophysiological perspective, CMT is primarily classified into types 1 (demyelinating), 2 (axonal), and X (X-linked), with subtype 1A being the most prevalent [3–5]. Functionally, patients exhibit significant gait abnormalities, including so-called “foot drop”, weakness of the dorsiflexors and evertors muscles, Achilles tendon stiffness, and both kinematic and kinetic dysfunctions during the stance and propulsion phases of the gait cycle [6].

Several studies have documented the impact of CMT on lower-limb biomechanics, particularly in paediatric populations [1,2,7–10]. In children and young adults, a reduction in ankle dorsiflexion during the swing phase and decreased dorsiflexor moment generation during the loading response have been observed, accompanied by a compensatory gait pattern with increased knee and hip flexion, commonly referred to as “steppage gait” [7]. Comparatively, in patients with CMT type 2, greater weakness in dorsiflexion and plantarflexion, increased dorsiflexion during the terminal stance phase, and reduced ankle power generation have been reported relative to type 1, suggesting more pronounced proximal compensatory patterns [8].

From a therapeutic perspective, the management of CMT currently focuses on alleviating symptoms and preserving function, as no curative treatment exists. Commonly employed strategies include physiotherapy, aimed at maintaining muscle strength and flexibility; the use of passive orthoses, such as ankle braces or insoles; and, in cases of severe deformities, orthopaedic surgery. Additionally, pharmacological agents for neuropathic pain complement symptomatic management. In recent years, studies [9–14] have demonstrated that the use of active gait-assistive devices, such as active orthoses, exoskeletons, or exosuits, can reduce metabolic cost and improve lower-limb mobility in individuals with neuromuscular disorders.

The effective development of these active devices requires precise characterisation of ankle and foot kinematics, the structures primarily affected by CMT. Among the most representative studies is that of Õunpuu et al. [1], who evaluated 63 paediatric patients using a Vicon motion capture system (Vicon Motion Analysis Inc., Oxford, UK) with the Plug-in-Gait protocol, classifying subjects according to maximum dorsiflexion during terminal stance. They concluded that there was a generalised reduction in ankle joint power and moments, with significant differences depending on the phenotype. In a subsequent study [2], the same authors identified three distinct phenotypes (reduced, typical, and excessive dorsiflexion) in 25 young individuals with CMT1, emphasising the need to tailor therapeutic interventions to each specific kinematics of patient. Kennedy et al. [7], also using Vicon Nexus and the Plug-in-Gait protocol in a sample of 60 children and adolescents, stratified participants according to functional severity (CMTPedS scale), observing early alterations in ankle dorsiflexion and compensatory adaptations in the hip and knee. Similarly, Beckmann et al. [15] employed a high-resolution multisegment foot model (HFMM) to analyse 80 feet with CMT compared with controls, demonstrating that not all patients exhibit equinus, thereby reinforcing the need to avoid assuming generalised biomechanical patterns in this condition. Finally, Wegener et al. [16] used a wand-type marker protocol on the hindfoot, midfoot, and forefoot in eight adult patients, finding that the use of sensorimotor orthoses increased hindfoot eversion during the stance phase, improving both stability and perceived comfort during gait.

Beyond traditional kinematic analysis, computational simulations incorporating kinetics provide an effective tool for assessing gait and developing personalised assistive devices. Such simulations allow the estimation of the effect an assistive device may have on kinematics of each patient, which is particularly relevant given the phenotypic heterogeneity observed in CMT patients [2]. The open-access software OpenSim [17,18] facilitates this type of advanced biomechanical simulation. However, implementing this methodology requires the development of a realistic biomechanical model of the patient. One of the most common procedures for this preliminary step involves solving an inverse problem and comparing the results with those provided by the commercial software used for motion capture. Nevertheless, according to the literature review conducted, no studies have analysed real CMT patient data using biomechanical models in OpenSim. Related work includes the study by Ong et al. [19], which developed a musculoskeletal model focused on patients with plantarflexor muscle weakness, and that of Arones et al. [20], which employed OpenSim to simulate gait in two post-stroke patients.

Considering this context, the primary objective of the present study is to analyse ankle and foot kinematics in patients with CMT disease using musculoskeletal simulations based on real patient data, employing the OpenSim software. This approach will not only allow for a more precise characterisation of specific gait cycle alterations in this population but also enable the identification of phases in which an active intervention may be most effective. To this end, a methodology is proposed to adapt OpenSim biomechanical models to patients with peripheral neuropathies using the Davis–Heel marker protocol [21]. To the best knowledge of the authors, this is the first study to apply OpenSim with real CMT patient data, representing an innovative and potentially transformative contribution to the design of personalised assistive devices for this condition.

2. Materials and Methods

2.1. Patients

A total of six patients with CMT neuropathy were analysed. Tables 1 and 2 show clinical and demographic characteristics of the patients enrolled. All patients had been genetically diagnosed of CMT, with a disease course between 3 and 22 years.

All included patients exhibited predominant distal muscular weakness, being dorsiflexors and eversors muscles more affected. Strength in proximal muscles in lower limbs was 4+ or 5 in Medical Research Council Scale. Participation in the study was voluntary. To be eligible for this study, patients had to meet the following inclusion and exclusion criteria:

Inclusion criteria:

(a) Individuals aged between 18 and 50 years. This age range was defined to control for potential selection bias given the demographic characteristics of CMT patients.
(b) A confirmed diagnosis of CMT.
(c) Consent to participate in the study.

Exclusion criteria:

(a) Any neurological disorder other than CMT.
(b) Presence of musculoskeletal injuries or pain in the lower limbs.
(c) Orthopaedic deformities in the lower limbs.
(d) Any prior surgical intervention in the lower limbs within six months before inclusion in the study.

All patients provided written informed consent approved by the Ethics Committee of the Andalusian Biomedical Research Ethics Platform (approval number 20151012181252).

Table 1. Clinical and demographic characteristics of patients.

Patients	Gender	CMT Type/ Genetics	Age/Time Since Diagnosis (Years)	Neuropathy Type	Main Foot Deformity
P1	M	1A (PMP22)	29/20	Demyelinating	Pes cavus
P2	M	2A (MFN2)	34/13	Axonal	Pes cavus
P3	M	2A (MFN2)	51/3	Axonal	Drop foot
P4	M	1A (PMP22)	50/22	Demyelinating	Drop foot
P5	F	2A (MFN2)	19/15	Axonal	Drop foot
P6	M	X LINKED (GJB1)	29/11	Axonal	Drop foot + Achilles tendon retraction

Abbreviations: P1: Patient 1. P2: Patient 2. P3: Patient 3. P4: Patient 4. P5: Patient 5. P6: Patient 6. M: Male. F: Female. PMP22: Peripheral Myelin Protein 22—this duplication is the most common cause of CMT disease type 1A (CMT1A). MFN2: Mitofusin 2—these mutations cause the axonal subtype CMT2A. GJB1: Gap Junction Beta-1 (connexin 32); X-linked mutations lead to CMTX1.

Table 2. Muscular strength in distal muscles of lower limbs Medical Research Council scale (MRC scale).

Patients	Manual Muscle Strength Testing (MRC Scale)					
	Dorsiflexors		Peroneus		Plantarflexors	
	Right	Left	Right	Left	Right	Left
P1	3	2	2	2	3	4
P2	2	2	0	0	4	4
P3	2	2	5	5	4	4
P4	0	0	0	0	1	1
P5	0	0	0	0	0	0
P6	1	1	0	0	4	4

Notes: Grade 5: normal gait and full range of motion; Grade 4: movement against gravity and resistance; Grade 3: movement against gravity over (almost) the full range; Grade 2: movement of the limb but not against gravity; Grade 1: visible contraction without movement of the limb; Grade 0: no visible contraction.

2.2. Test Conditions and Instrumentation

To perform the kinematic analysis, the Davis–Heel marker protocol [21] was employed. This marker protocol is specific and used by default by the technicians at Hospital Virgen del Rocío, where the data collection took place, due to its ease to don and doff, especially in disabled subjects. This marker protocol comprises 22 reflective markers (Figure 1).

Marker trajectories were captured using the Elite SMART D system (BTS Bioengineering S.p.A., Garbagnate Milanese (MI), Italia), which comprises six infrared cameras and two conventional video cameras. The infrared cameras operated at a sampling frequency of 100 Hz, while the force platform recorded at 1000 Hz. This equipment was installed in the Motion Analysis Laboratory in University Hospital Virgen del Rocío in Seville.

Each patient underwent between five and eight dynamic trials, as well as one static trial. The static trial required the patient to adopt a posture as close as possible to the anatomical position: standing upright, looking forward, with arms and legs extended. In this case, the patient was able to assume the anatomical position without difficulty. For the dynamic trials, gait velocity was self-selected, allowing the patient to walk at a comfortable pace. The kinematic data obtained with the BTS Bioengineering® system were used to validate the results produced by the biomechanical model implemented in this study.

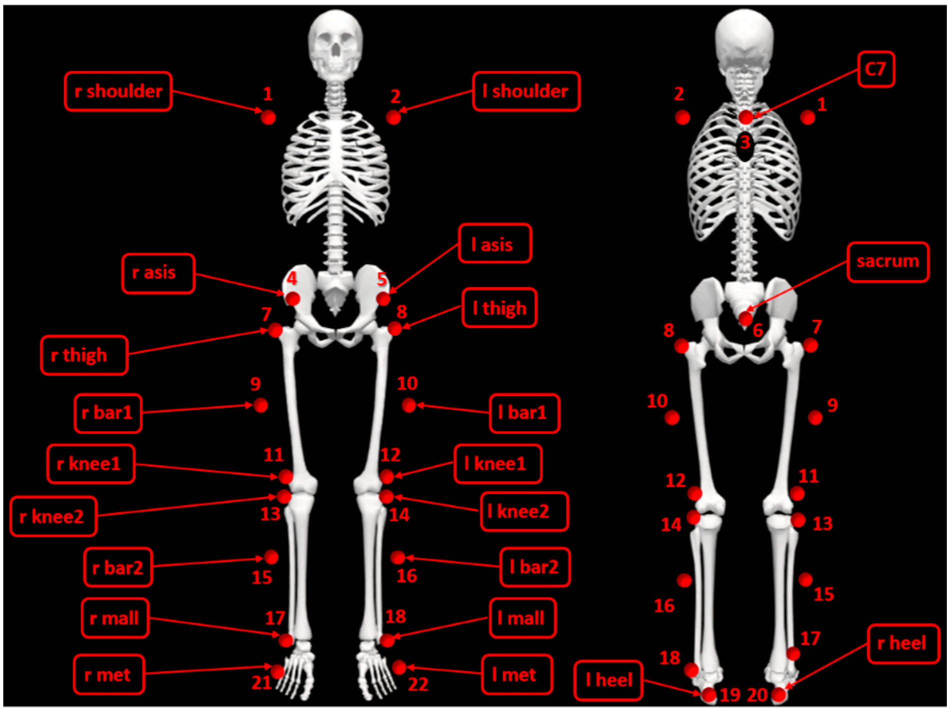

Figure 1. Marker placement for the Davis Heel protocol [21].

2.3. Data Analysis

In addition to solving the kinematic problem using the proprietary software provided by BTS Bioengineering® (GAITLAB SMART-Suite/SMART-Clinic), the same gait cycles were also analysed using the open-access software OpenSim 4.5 [17,18]. The biomechanical model implemented in BTS Bioengineering® included three degrees of freedom for each hip, three degrees of freedom for each knee, and two degrees of freedom for the ankle. To ensure consistency between the biomechanical models in both software platforms, the gait2392 model was selected in OpenSim and subjected to several modifications. The degrees of freedom for the knees and ankles in this model were augmented, resulting in three rotational degrees of freedom for each knee and two rotational degrees of freedom for each ankle, corresponding to ankle dorsiflexion and foot progression. Since BTS Bioengineering® did not include any degree of freedom for the foot, in OpenSim the foot was modelled as a rigid body.

Alongside the previously described modifications to the biomechanical model, the scaling parameters in OpenSim were adjusted to ensure a more accurate anatomical reconstruction by imposing the internal rotation angles for the hip, knee, and ankle, as well as the pelvis tilt, obtained from the static trial in the BTS Bioengineering® software. This approach was adopted due to the high sensitivity of transverse-plane results to small errors in the definition of the local coordinates of the virtual markers.

Finally, due to high-frequency noise in the data and based on residual analysis [22], the data were filtered with a low-pass filter (6 Hz, 4th order Butterworth filter) by a custom-made routine using Matlab R2024a (The MathWorks, Inc., Natick, MA, USA).

3. Results

Figure 2 presents, for the six analysed patients, a comparison of the mean values of all trials for right ankle dorsiflexion obtained in OpenSim and those obtained using BTS Bioengineering®. Similarly, Figure 3 shows a comparison between the mean values of left ankle dorsiflexion obtained in OpenSim and the corresponding values obtained with BTS Bioengineering®. Note that patient 5, who has severe paresis in all muscular groups, shows greater differences.

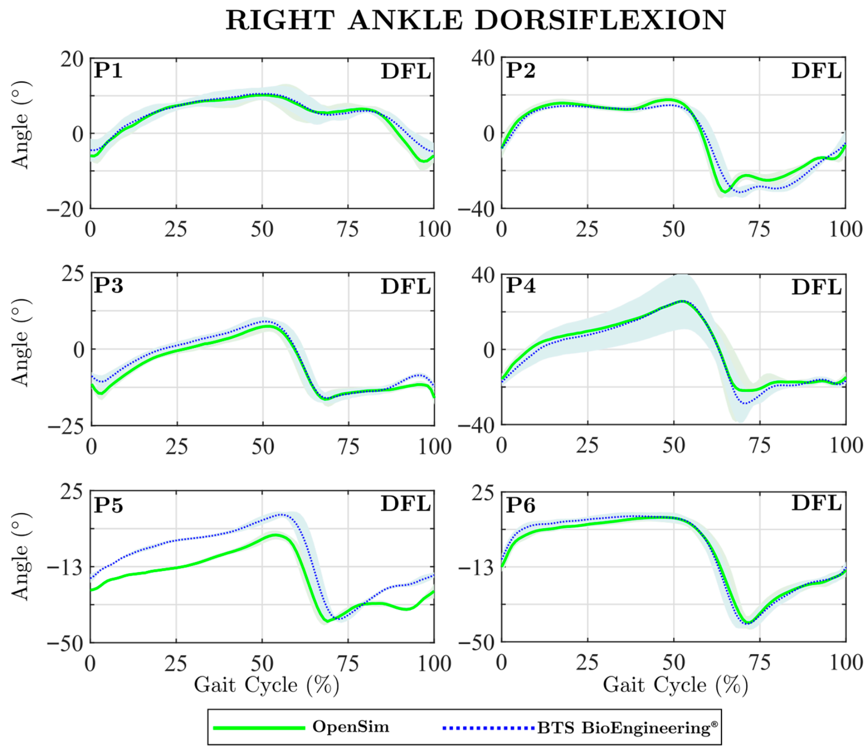

Figure 2. Comparison for each patient of the mean and standard deviation of the right ankle dorsiflexion values obtained in OpenSim and those obtained using BTS Bioengineering®. Abbreviations: P1: Patient 1. P2: Patient 2. P3: Patient 3. P4: Patient 4. P5: Patient 5. P6: Patient 6. DFL: Dorsiflexion angle.

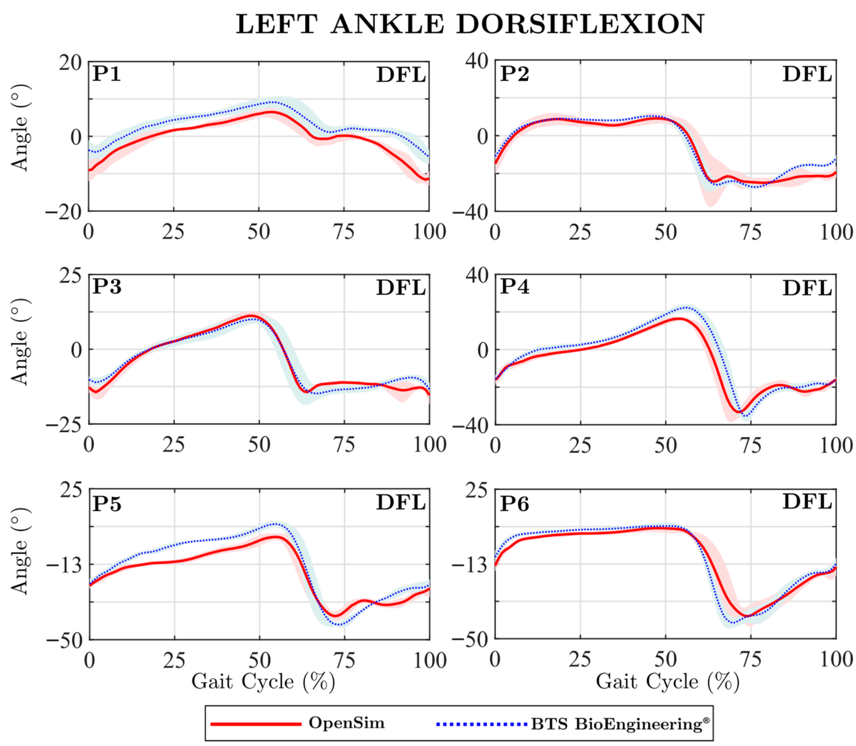

Figure 3. Comparison for each patient of the average value and standard deviation of left ankle dorsiflexion obtained in OpenSim and those obtained using BTS Bioengineering®.

Figure 4 shows a comparison of the average value of the right foot progression angle obtained in OpenSim with the value of the same variable obtained in BTS Bioengineering® for the six patients analysed. Similarly, Figure 5 shows the comparison for the left side of the same variables.

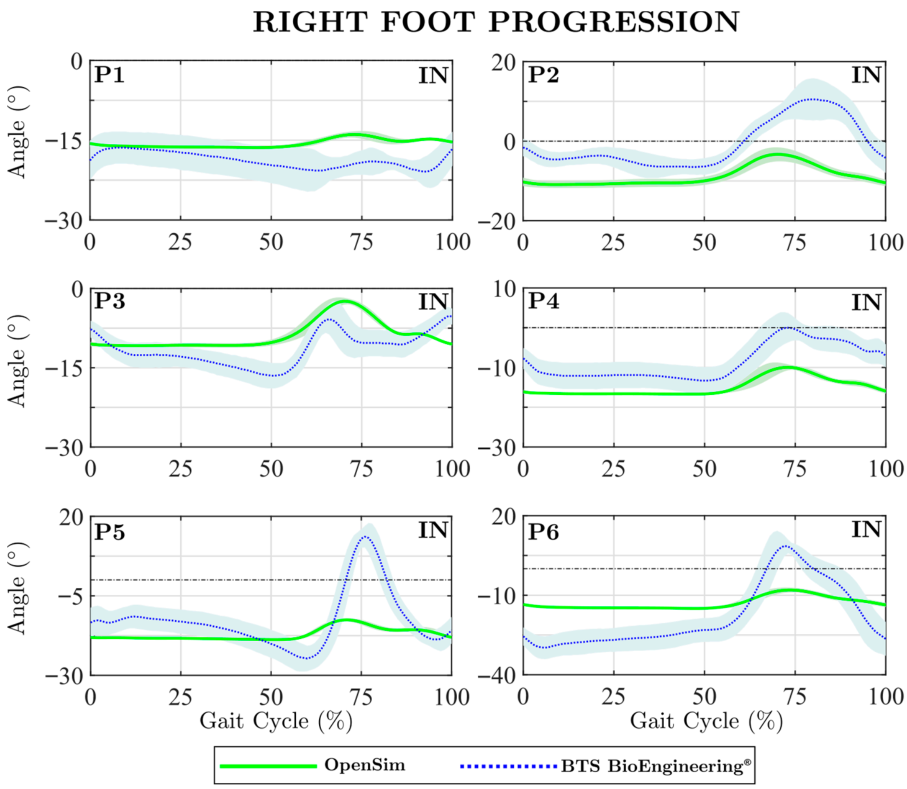

Figure 4. Comparison for each patient of the mean and standard deviation of the right foot progression angle values obtained in OpenSim and those obtained using BTS Bioengineering®. Thin black line with a dot and a dash refers to a value of 0. IN: Toe-In angle.

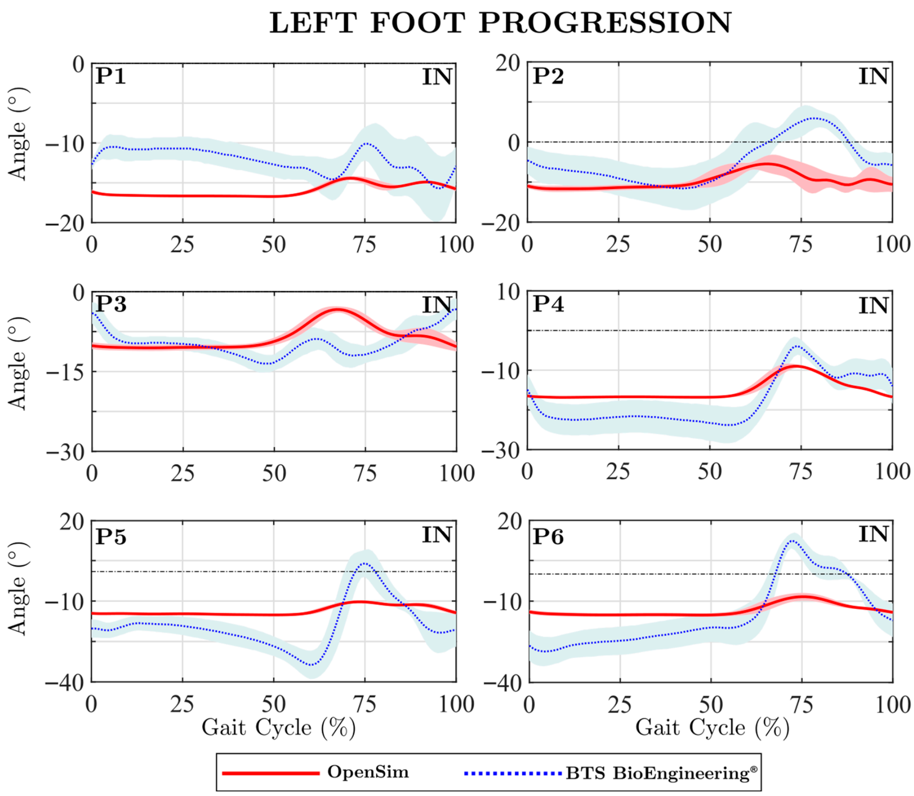

Figure 5. Comparison for each patient of the mean and standard deviation of the left foot progression angle values obtained in OpenSim and those obtained using BTS Bioengineering®. Thin black line with a dot and a dash refers to a value of 0.

To complement these figures, Table 3 presents the root mean square error (RMSE) obtained when comparing the average values of the ankle dorsiflexion and foot progression angles for both right and left legs measured in OpenSim and in BTS Bioengineering®. Patients 5 and 6 showed higher RMSE values, due to and increased variability among trials, mainly due to their severe paresis as previously stated.

Table 3. RMSE values between the data obtained in OpenSim and BTS Bioengineering® for the six patients.

Patients	RMSE (°)			
	Dorsiflexion Angle		Progression Angle	
	Right	Left	Right	Left
P1	1.154	3.555	3.674	4.306
P2	3.724	2.898	9.088	6.706
P3	1.867	1.708	3.849	3.688
P4	2.299	4.986	6.772	4.925
P5	10.136	5.299	9.041	9.664
P6	2.071	3.602	10.773	10.101

Figure 6 shows the comparison between the time evolution of ankle dorsiflexion in healthy subjects and the average dorsiflexion curves obtained in the OpenSim software for both ankles. Except patient 1 (who had relative strength preservation in dorsiflexor muscles) all of them showed plantarflexion in swing phase. Similarly, Figure 7 shows the same comparison of variables but in this case focused on the foot progression angle. All the patients walked with some degree of external foot progression angle, but patients 4, 5 and 6, more severely affected, showed greater values.

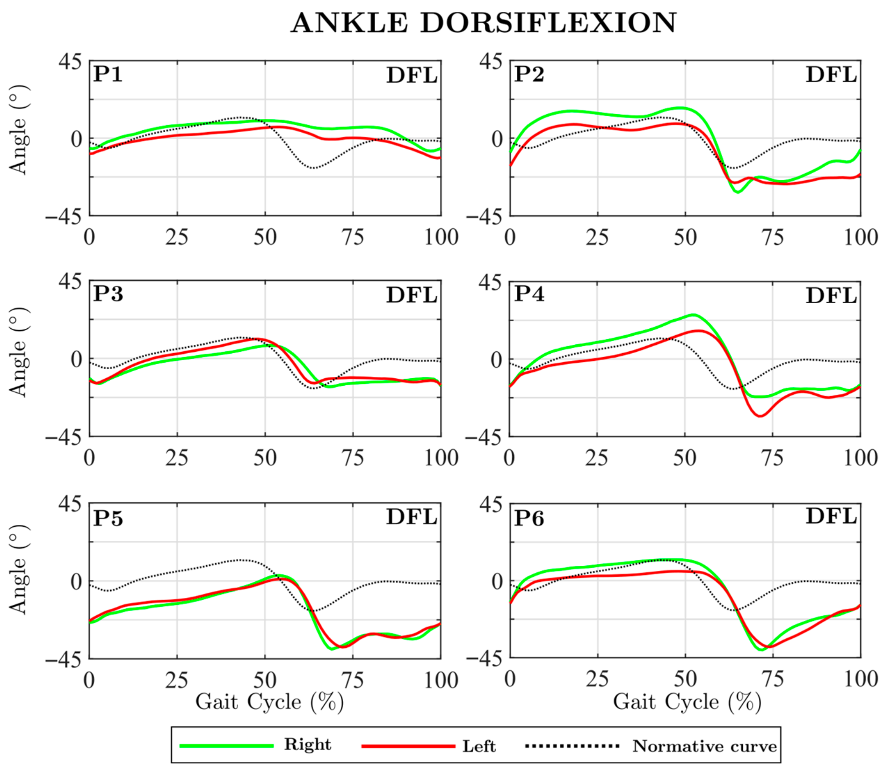

Figure 6. Comparison for each patient of the average ankle dorsiflexion values for the right ankle and left ankle obtained in OpenSim with the time evolution of dorsiflexion in healthy subjects.

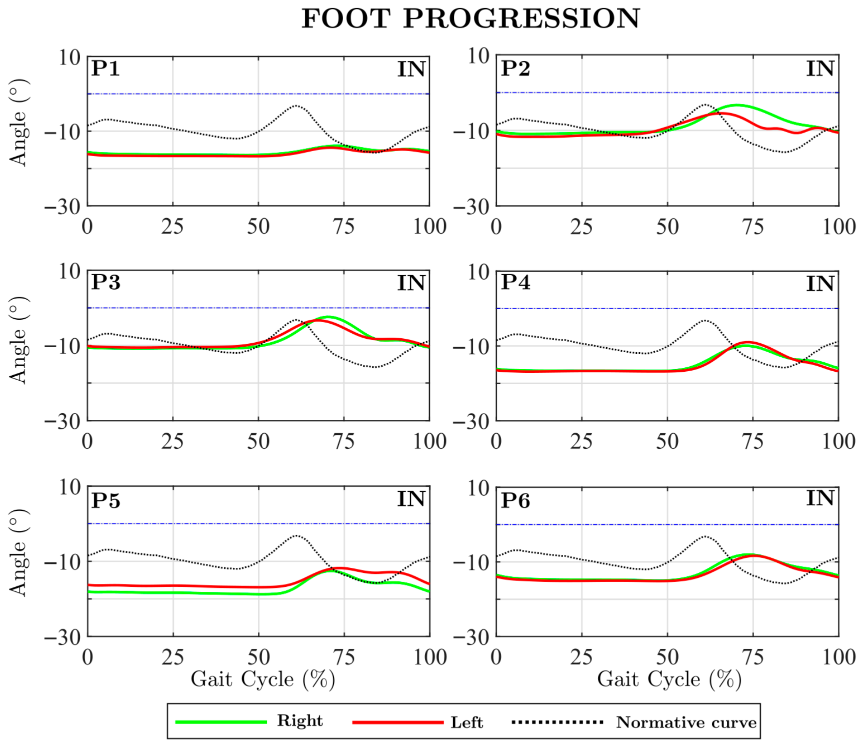

Figure 7. Comparison for each patient of the average foot progression angle values for the right ankle and left ankle obtained in OpenSim with the time evolution of foot progression angle in healthy subjects. Thin blue line with a dot and a dash refers to a value of 0.

4. Discussion

The goal of developing a biomechanical model in OpenSim that represents the kinematic behaviour of a patient with CMT disease is to enable computational simulations aimed at designing active assistive devices that help improve gait quality in these patients. To this end, a comparison was conducted between the results obtained from the patients and the normative curves for two joint angles: ankle dorsiflexion and foot progression.

4.1. Validation of the Biomechanical Model

To validate the model, the results provided by the commercial BTS Bioengineering® software were used as a reference. In the case of the dorsiflexion angle, the temporal evolution of the joint variables is very similar between BTS Bioengineering® and OpenSim for the six patients analysed (see Figures 2 and 3), with the RMSE remaining below 5° in all cases except for patient 5, particularly in their right leg, where the RMSE exceeds 10° (see Table 3). Patient 5 exhibited a slightly different morphology compared to the rest of the patients due to the severe muscular weakness in all distal muscular groups of this patient. In consequence, the biomechanical model was more sensitive to the definition of the local coordinate systems of markers.

Regarding the foot progression angle, greater differences are observed between the OpenSim biomechanical model and the results obtained from BTS Bioengineering®. Although the temporal evolution pattern is similar in both cases, the joint range is smaller in OpenSim (see Figures 4 and 5). From a quantitative perspective, RMSE values are slightly higher than those observed for the dorsiflexion angle. The main reasons for this greater discrepancy in the transverse plane are primarily due to the lack of precision in the adjustment of the local coordinate systems of markers within the model. To the best of our knowledge, the standard procedure for fitting a marker protocol in an OpenSim model relies on estimation and trial-and-error methods. This approach is sufficiently effective for analysing sagittal plane movements, as shown in Figures 2 and 3 and Table 3. However, for movements outside this plane, where joint ranges are an order of magnitude smaller, the lack of adjustment becomes more significant. Additionally, in this study, a non-optimal pose estimator protocol [23] based on a minimal number of markers was implemented, which makes the results more sensitive to small discrepancies in the positioning of the virtual markers. From a clinical perspective, the lack of precision observed in the foot progression angle is acceptable. Firstly, because all patients exhibit an out-toeing gait pattern, as a compensation to reduce the risk of tripping during walking. Secondly, because the main impairments associated with CMT are found in the sagittal plane [1,2].

4.2. Pathological vs. Normal Pattern

Regarding the ankle dorsiflexion angle, no common pattern was observed across all patients. In this study, two distinct dorsiflexion patterns (DFP) were defined: DFP1 (Patient 1), and DFP2 (Patients 2, 3, 4, 5, and 6).

- DFP1. During the initial contact and loading response phase (0–10%), increased plantarflexion was observed in both ankles. This increase may be associated with weakness of the tibialis anterior muscle, a characteristic feature of the peripheral motor neuropathy that defines CMT. Such a deficit can compromise eccentric control during foot landing, favouring the appearance of foot drop and increasing the risk of tripping. In the mid-stance phase (10–50%), the curves of patient exhibited flatter and lower-amplitude kinematics, suggesting functional rigidity or a compensatory strategy to stabilise the ankle in response to muscular weakness. This alteration may reflect a reduced capacity of the foot–ankle complex to adapt to the mechanical demands of single-limb support, thereby affecting gait efficiency. During push-off (terminal stance and preswing phase, 50–62%), insufficient plantarflexion was evident in both ankles, particularly in the right one. This limitation may be due to weakness in the plantarflexor muscles, also present in some patients during the course of the disease. Additionally, the observed asymmetry between ankles suggests a non-homogeneous neuromuscular involvement, which is common in CMT due to the variable progression of the disease.
- DFP2. The two stance phases show a similar behaviour to the DFP1 pattern. However, during the push-off and swing phase, insufficient dorsiflexion was observed in both ankles, with a relatively mild difference between them. This limitation compromises forefoot clearance during the swing phase, potentially inducing compensatory gait patterns such as increased hip or knee flexion (steppage gait).

Regarding the foot progression angle, all six patients exhibited a similar pattern. This pattern showed an almost flat evolution, indicating a loss of the physiological modulation that characterises healthy gait. This oscillation typically reflects the coordination among the pelvis, hip, tibia, and foot throughout the gait cycle. Its absence suggests a strategy of rigidity and postural fixation aimed at enhancing stability, which is typical in CMT disease. Throughout the entire cycle, the angle remains in negative values, indicating a constant toe-out position. This characteristic may be caused by compensatory adaptations in the hip and pelvis that favour toe-out. The coexistence of toe-out with foot drop, commonly observed in these patients, may serve as a compensatory mechanism to prevent tripping by externally orienting the foot and facilitating lateral clearance. This behaviour has several biomechanical implications:

- Excessive toe-out may alter the trajectory of the centre of pressure and increase the energetic cost of walking.
- Sustained external progression increases medial loading of the knee and the first ray of the foot, potentially contributing to femoropatellar pain and medial metatarsalgia.

4.3. Analysis of CMT Disease Within OpenSim Environment

The kinematic alterations observed in patients with CMT disease in ankle dorsiflexion and foot progression angle (FPA) provide critical insights for the development of biomechanical models and assistive devices within the OpenSim simulation environment.

The variability in dorsiflexion patterns highlights the need for personalised modelling approaches. The asymmetry between limbs suggests that bilateral device designs may require independent actuation profiles to accommodate differential neuromuscular impairments. Conversely, more uniform limitations support the feasibility of symmetric control strategies, albeit with careful calibration to address the overall reduction in range of motion and dorsiflexor strength.

The consistently flat and negative FPA curves across all patients indicate a persistent toe-out gait pattern, likely a compensation for foot drop in swing phase. This behaviour reflects a loss of physiological modulation and suggests a rigid postural strategy aimed at enhancing stability. From a modelling perspective, this implies that OpenSim simulations must incorporate constraints or stiffness parameters that replicate the reduced rotational control observed clinically.

These findings have direct implications for the design of active assistive devices: the presence of toe-out combined with foot drop necessitates mechanisms that not only support dorsiflexion during swing but also modulate transverse plane alignment to optimise foot clearance and reduce tripping risk. In addition, the increased medial loading associated with sustained external progression may inform the design of devices that redistribute plantar pressures or provide targeted support to the medial knee and forefoot. Finally, the observed rigidity in rotational control suggests that devices should allow for controlled flexibility in the frontal and transverse planes to facilitate directional changes and improve functional mobility.

4.4. Limitations and Future Work

The principal limitation of this study lies in the adjustment of the kinematic results obtained in the transverse plane. As previously discussed, this discrepancy may be attributed to the influence of error in movements involving a smaller range of motion. As a future line of work, it is proposed to refine the local coordinates of the virtual markers through optimisation techniques.

Another limitation is the definition of the foot as a rigid solid, which does not allow for the analysis of structural deformities typical of CMT, such as pes cavus, cavovarus, claw toes, and foot drop. As previously explained, the rigid foot model was employed because this study specifically focused on the analysis of foot drop syndrome, and in addition, it was necessary to develop a biomechanical model comparable to that used in BTS Bioengineering®. Therefore, in future work, a multisegment foot biomechanical model will be developed in OpenSim to enable a more comprehensive analysis of structural deformities typical of CMT patients.

A further limitation of this study relates to the marker protocol employed, which was based on a non-optimal pose approach. While this protocol minimised the number of markers to enhance patient comfort and improve laboratory efficiency, it may have compromised the accuracy of movements with a limited range of motion. Moreover, the protocol did not fully comply with the recommendations of the International Society of Biomechanics (ISB) [24]. Consequently, future work should aim to implement, in OpenSim, a marker protocol incorporating a greater number of markers, adopting a redundant approach (Least-Square Pose Estimator) [23], and adhering to ISB guidelines [24], in line with the recommendations set out in this article.

As future work, it is proposed to solve the extended inverse dynamics problem up to the level of muscular forces. Based on this, the aim is to adjust the muscle parameters that have been observed to exhibit pathological behaviour, to perform predictive simulations incorporating active assistive devices.

5. Conclusions

In this study, biomechanical models were developed within the OpenSim environment based on experimental data from patients with CMT. The kinematics of the foot–ankle complex were analysed, and the results were validated against those obtained using the commercial BTS Bioengineering® software. The kinematic outputs were compared with normative curves, enabling the identification of gait cycle phases and the establishment of intervention criteria for the design of assistive walking devices.

The integration of patient-specific kinematic profiles into OpenSim models enables the simulation of realistic gait dynamics and the evaluation of tailored intervention strategies. These models serve as a foundational tool for the iterative design and optimisation of assistive technologies aimed at restoring gait efficiency and safety in individuals with CMT.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. Data are not publicly available due to ethical reasons.

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Conflicts of Interest: The authors declare no conflicts of interest.

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