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Deliverable 6.2

Standard minimal dataset of clinical gait analysis outcome measures and associated context parameters needed for data exchange and modelling

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Abbreviations

CGA	Clinical Gait Analysis
CMC	Coefficient of Multiple Correlation
DLT	direct linear transformation
EMG	Electromyography
FP	Force Platform

FS	Foot-switch sensors
HBM	Human Body Model
KUL	KU Leuven
MPP	marker placement protocols
OPBG	Children's Hospital 'Bambino Gesù'
OPWF	operational protocols and workflow
OS	Optoelectronic system
PiG	PlugInGait marker set
RMSE	Root Mean Square Error
STA	soft tissue artifacts
TQA	technical quality assurance
URLS	University of Rome La Sapienza
VBS	video based stereophotogrammetric systems
VUA	VU Medisch Centrum
^{B}	Between laboratories
^{w}	Within laboratory

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Nature of this Deliverable

This Deliverable 6.2 provides a standard minimal dataset of clinical gait analysis outcome measures and associated context parameters needed for data exchange and modelling, for all data types and all patient categories in the NND area. The data is collected according to the protocols as presented in Deliverable 6.1. This comprises:

1. Presentation of the quality assurance (QA) data, according to the QA protocol (Task 6.1)
2. Presentation of the first gait data sets for patients with CP (Task 6.2)
3. Presentation of the first gait data sets for patients with DMD and CMT (Task 6.3)
4. Presentation of the first MRI data sets for CP, DMD and CMT (Task 6.4)

Short description

The aim of WP6 is to collect data from patients affected by Neurological and Neuromuscolar disease in order to provide the basics for the modelling partners to build patient specific models as part of the WP11, as well as to provide a large dataset of both retrospective and prospective data for probabilistic modelling in WP14. All the collected data within this WP will be stored in the digital repository.

In this deliverable, the first complete data sets are presented for CP, DMD and CMT patients, as well as for healthy subjects ahere needed. These data sets serve the following purposes:

- Demonstrate the TQA for the gait data, as described in Task 6.1. This concerns both the 'low level' TQA of the gait analysis equipment, and the 'high level' TQA of gait analysis measurements, including repeatability of marker placement.
- Provide input to the modeling partners in WP11, so that the entire pipeline from MRI + gait data to patient-specific models can be run and evaluated for the first patients.
- Provide input to the repository, so that the entire pipeline from data collection to storage in the repository can be developed and evaluated.

The deliverable decribes for each of the clinical centers how the data is collected, what issues were encountered and solved, and what the status of data collection is.

Task 6.1 - QA on data collection and clinical protocols

The task 6.1 started with a complete description of the protocols used in the clinical institutes, which is the base for a common descriptive format and its default values. Three levels have been considered:

1. Technical Quality Assurance (TQA) protocols in Gait analysis laboratories;
2. Marker Placement Protocols (MPP) in 3D Optoelectronic Clinical Gait Analysis (CGA);
3. Operational Protocols and Workflow (OPWF) used in clinical practice.

In Deliverable 6.1, this Consensus Proposal for EU CGA gait labs was drawn up for all three levels, and will not be further dicussed here.

For the TQA, the clinical partners performed reliability measures of the protocols, to ensure quantitative levels of reliability. The outcomes of these data have been used as input for sensitivity analysis and reliability estimates of model outputs, as described below. The experimental protocol of the TQA have been already included in D6.1, and are also reported in order to enhance the document readability.

Task 6.1.1 Technical Quality Assurance (TQA)

Two levels of protocols are considered:

i. the technical quality assurance of the performance of the equipment in the three laboratories (also called “low level”), as well as

ii. the overall performace of the repeatability of measurements in the lab on actual subjects (“high level”).

For both levels URLS, who is the responsible for the Technical Quality Assurance, has developed the protocols and performed measurements to assess the quality of the measurements conducted in the involved labs. The CGA centers involved in the experimental protocol are:

i. KU Leuven (KUL);
ii. VU Medisch Centrum (VUA);
iii. Children’s Hospital ‘Bambino Gesù’ (OPBG).

The protocol, breafly described in the following sections, is aimed to provide the overall inter-laboratory/rater repeatability of gait analysis data.

The centers provided the technical characteristics of their own instruments to measure marker positions, ground reactions and EMG signals during the gait data collection. The characteristics are listed in the table below.

Table 1 - Technical characteristics of instruments for each center.

		KUL	VUA	OPBG
Optoelectronic system	*Model*	Vicon MX	Grail - Bonita	Vicon MX
	Sample frequency	100 Hz	100 Hz	200 Hz
	Resolution	1.3 MP	1.0 MP	2.0 MP
	Marker size/type	Spherical 12.5 mm	Spherical 13 mm	Spherical 12.5 mm
	Marker protocol	PiG (SACR + KAD)	HBM	PiG
Force Platform	*Model*	AMTI	R-MILL	AMTI OR6-6 1000
	Output channel	6 components (Fx, Fy, Fz, Mx, My, Mz)	6 components (Fx, Fy, Fz, Mx, My, Mz) – Dual Belt	6 components (Fx, Fy, Fz, Mx, My, Mz)
	Sample frequency	1.5 kHz	100 Hz	1 kHz
	FSO	2,225 N (Fx, Fy) 4,450 N (Fz) 1,100 Nm (Mx) 1,000 Nm (My) 600 Nm (Mz)	5,000 N (Fx, Fy) 10,000 N (Fz) *missing data* (Mx, My, Mz)	2,225 N (Fx, Fy) 4,450 N (Fz) 1,100 Nm (Mx) 1,000 Nm (My) 600 Nm (Mz)
EMG system	*Model*	Cometa Zero Wire	Cometa Zero Wire	Cometa Zero Wire
	Output channel	16 channels	16 channels	16 channels
	Output type	Analog	Analog	Analog
	Sample frequency	1.5 kHz	1 kHz	1 kHz
	Sensor placement protocol	SENIAM	SENIAM	SENIAM

Task 6.1.1.1 Technical Quality assurance of CGA equipment (low level)

The accuracy[1] and repeatability[2] of gait analysis data depends on the accuracy of the raw data acquired by the selected measurement systems. The experimental protocol of the low-level validation for each measurement system is reported in the following.

Optoelectronic System Validation (OS-validation)

A spot check of the functionality/accuracy of the Optoelectronic Systems were performed by means of a fixed length wand equipped with reflective markers, one of the methods cited by Cappozzo *et al* [1]. An effective example of this wand can be the calibration wand itself, which is equipped with 5 active/passive markers at a known distance between each other (Figure 1).

The OS-validation protocol consisted in moving the wand for 10 seconds inside the measurement volume. From the acquired positions of the markers, distances ($\overline{21}$, $\overline{23}$, $\overline{24}$, $\overline{25}$) and angles ($\angle 125$ and $\angle 325$) among

[1] Accuracy: closeness of agreement between a measured quantity value and a true quantity value of a measurand. Vocabulaire international de métrologie – Concepts fondamentaux et généraux et termes associés (VIM).

[2] Repeatability: condition of measurement, out of a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time. Vocabulaire international de métrologie – Concepts fondamentaux et généraux et termes associés (VIM).

markers were evaluated. The values were then compared with the actual distances and angles, which were computed with the wand placed on the origin of optoelectronic system for 5 seconds during a static acquisition.

The repeatability of parameters was evaluated as root mean square error (RMSE) between actual and measured values for each parameter. The comparison between parameters permitted to evaluate the optoelectronic system accuracy in the dynamic 3D reconstruction. The dynamic trial were repeated three times for each center.

Figure 1 - Passive (a) and active (b) wand.

Force Platform validation (FP-validation)

In order to check the functionality of the force platforms a similar methodology proposed by *Collins at al.* [2] was performed for the FP-validation. Specifically, a pointer (LC-P) equipped with a 6-component load cell (GAMMA SI-130-10, ATI Industrial Automation, USA - Figure 2) has been developed (Figure 3).

SI-130-10	Full Scale	Resolution
F_x,F_y	130 N	1/40 N
F_z	400 N	1/20 N
T_x,T_y, T_z	10 Nm	1/800 Nm

Figure 2 – 6-component loadcell GAMMA SI-130-10.

LC-P was equipped with reflective markers to allow OS to track the position and orientation of LC-P reference system respect to the OS one. The end of the LC-P is also equipped with a fully rotational ferrule (Flexyfoot, http://www.flexyfoot.com/) which permits to tilt the LC-P in several directions, manteining the ferrule attached to the ground (Figure 4). LC-P is assumed as the gold standard to test and to compare the outputs of force platforms, in terms of force components and moment components.

Figure 3 - The device developed to test the force platform.

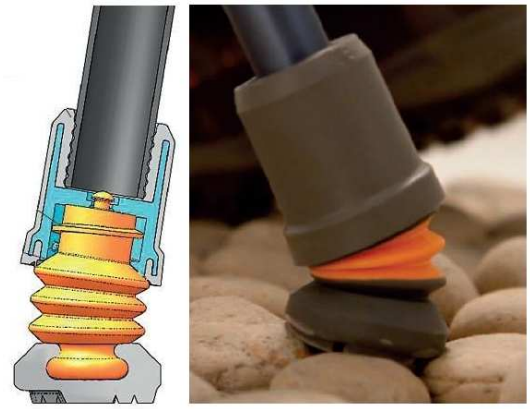


Figure 4 - Fully rotational ferrule.

The FP-validation procedure consisted in:

i. Application of arbitrary forces to each force platform pushing on it with the LC-P. We selected seventeen points on each square platform: nine points in the middle part and eight points near the edge of platform (Figure 5.a). As regards the rectangular platforms which are implemented in the Grail system at VUA, we selected fifteen points: five in the middle part and ten along the edge of platform (Figure 5.b).

ii. The trial was repeated three times in function of the orientation of LC-P. Specifically, the LC-P was oriented along the vertical axis (Figure 6.a), tilted of approximately 30° around both the x (Figure 6.b) and the y (Figure 6.c) axes of the FP reference system.

iii. For each acquisition trial, the forces and moments measured with LC-P ($\mathbf{F}^{LC-P}$ and $\mathbf{M}^{LC-P}$) were projected onto the OS reference system knowing the position and orientation of LC-P reference system by means of OS. Contributions from weights of each mechanical component of LC-P were taken account of the evaluation of $\mathbf{F}^{LC-P}$ and $\mathbf{M}^{LC-P}$. We did not include inertial components of forces and moments from dynamicsof the LC-P considering it in quasi-static positions.

iv. The forces and moments measured with FP ($\mathbf{F}^{FP}$ and $\mathbf{M}^{FP}$) were projected onto the OS reference system.

v. $\mathbf{F}^{LC-P}$ and $\mathbf{M}^{LC-P}$ were compared with $\mathbf{F}^{FP}$ and $\mathbf{M}^{FP}$ evaluating the RMSEs for each pushed point considering only values higher than 1% of Full Scale of FP outputs.

vi. Statistical analysis were conducted in order to find statistical differences between FPs and between points on the edge and on the middle part of platforms.

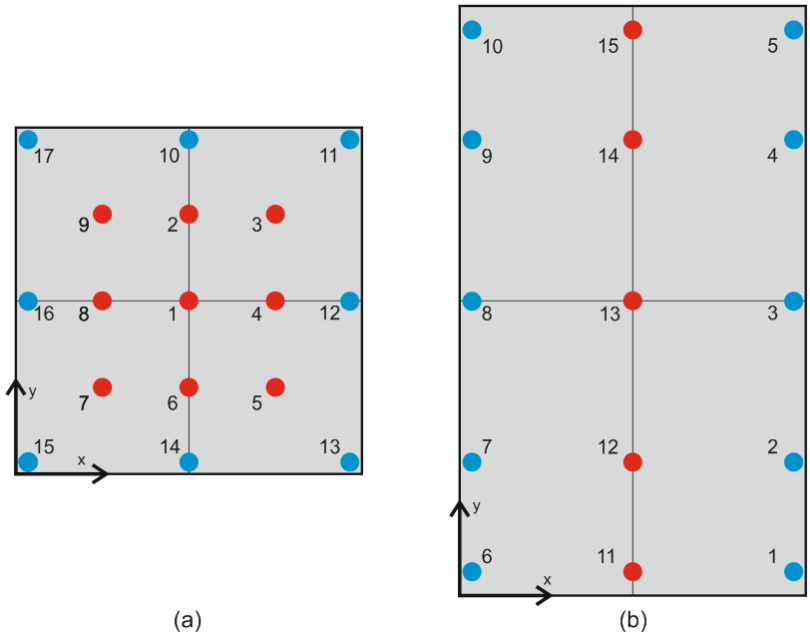


Figure 5 - Square (a) and rectangular (b) force platforms; Circles are the tested points at the middle part (red) and edge (blue) of platforms.

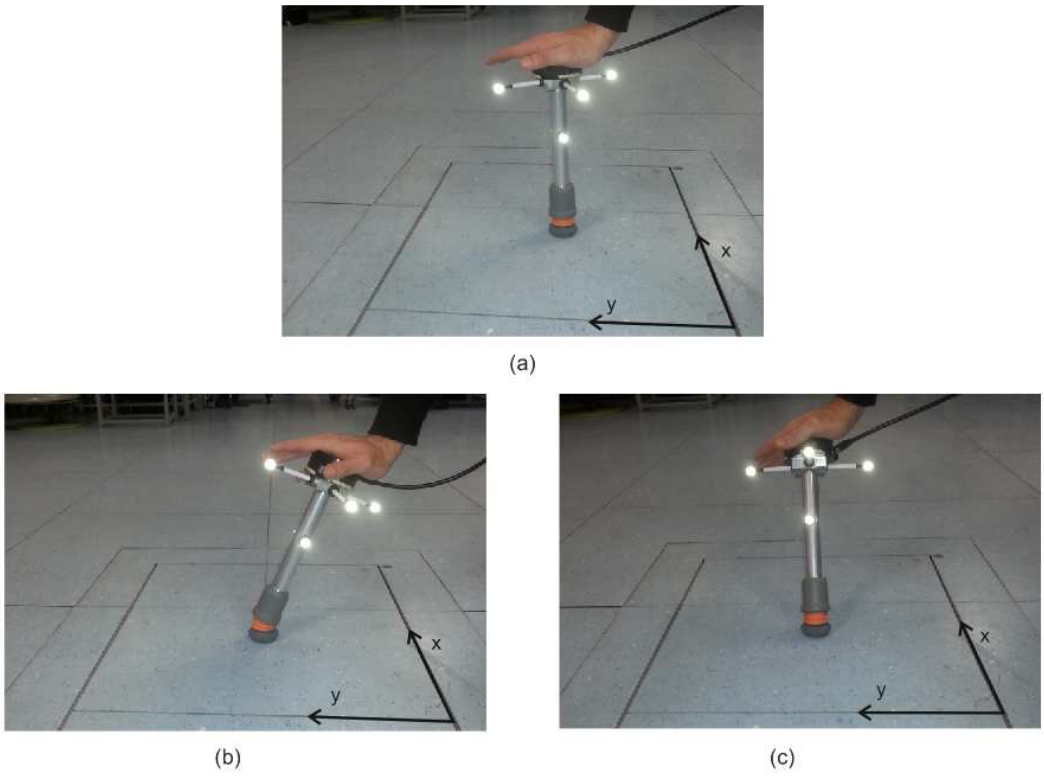


Figure 6 - Experimental procedure of FP-validation

The applied vertical forces are checked to be less than 400 N that is the full scale of LC and higher than the 1% of full scale of vertical components of force platforms (100 N for FP installed at VUA, 45 N for FP at OPBG and KUL). Taking into account children's weights, the selected force range allows us to validate the metrological performances of FP when gait analyses are performed by children until 11 years old [3], see Figure 7.

It is whorthy to note that the FP-validation methodology here described implies two relevant improvements respect to the methodology proposed by *Collins et al.*:

i. the use of a 6-component load cell instead of a uni-axial one permits to measure moments and shear forces that are ignored in the cited paper,

ii. the presence of the rotational ferrule permits to tilt LC-P with angles higher than 20° which is the maximum value used by *Collins et al.*; it allows us to impose higher values of shear forces to force platforms close to the oned recorded in CGA.

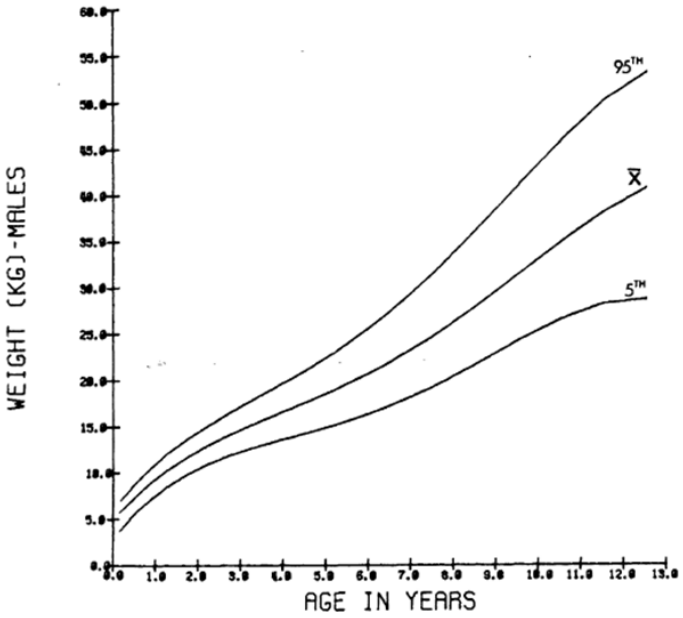


Figure 7 - Height vs. weight of healthy children [3].

Signal synchronization (S-synchro)

The signal synchronization between the force platform and the EMG system has been tested. It is worthy to note that the EMG Cometa system is provided with Foot-switch sensors (FS) which are acquired synchronously with EMG. The S-synchro protocol consisted in the following procedure (Figure 8):

i. A Foot-Switch FS was put on each force platform;
ii. A pointer was used to apply a pressure on the Foot-Switch;
iii. The signals force platform (FP) and EMG system were registered;
iv. Two signals were selected:
    a. the z component of the force (F_z) acquired by FP;
    b. the output of the FP gathered by EMG system;
v. The time delay between EMG and FP (T_{EMG-FP}) was selected when both signals were equal to zero.

Figure 8 - Pointer, foot-switch and force platform.

Results

1. OS-validation

An example of the wand displacement recorder at KUL center is reported in Figure 9. The RMSE values for each parameter are reported in Table 2. The values measured at VUA were slightly higher than the ones obtained at OPBG and KUL. it is due to the optoelectronic system, i.e. Bonita (VICON), integrated in the Grail system. In fact, Bonita system is characterized by the lowest value of resolution (1.0 MP) and it is considered the entry level model of the optoelectronic systems manufactured by VICON. However, the RMSEs were always lower than 1 mm and 0.5° for distances and angles, respectively.

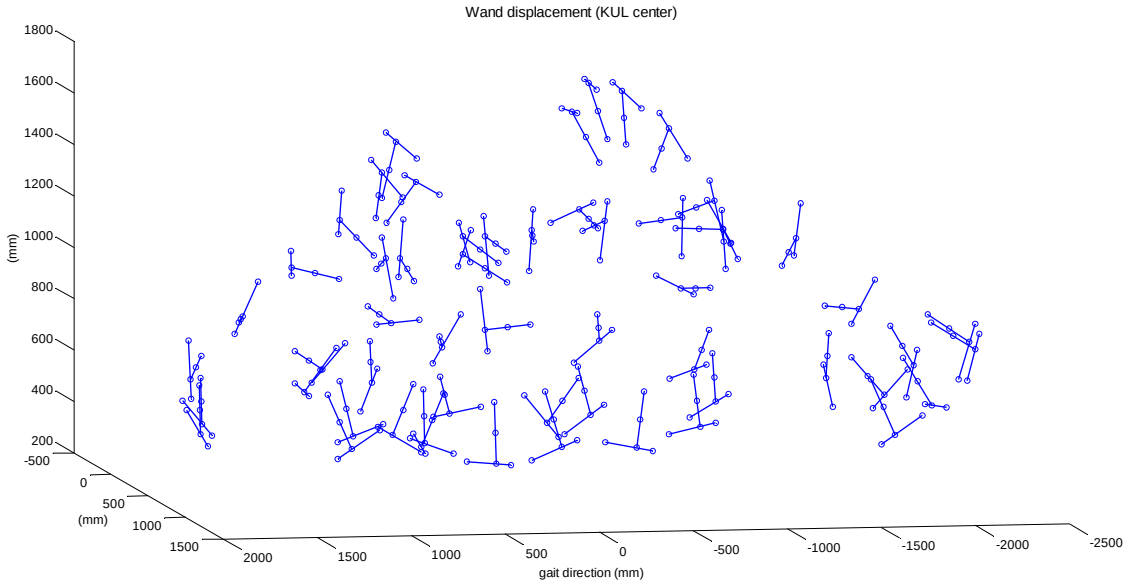


Figure 9 - Wand displacement gathered at KUL.

Table 2 - RMSE values for distances and angles for each center

Parameters	Centers		
	OPBG	VUA	KUL
$\overline{12}$ [mm]	0.3	0.8	0.4
$\overline{23}$ [mm]	0.3	0.9	0.4
$\overline{24}$ [mm]	0.3	0.6	0.5
$\overline{25}$ [mm]	0.4	0.5	0.5
$\angle 125$ [°]	0.2	0.5	0.3
$\angle 325$ [°]	0.3	0.3	0.2

2. FP-validation

Examples of FP-Validation performed at OPBG, KUL and VUA are reported in Figure 10, Figure 11, and Figure 12, respectively. Forces and Moments measured with FP were comparable with the same parameters evaluated by means of LC-P. Differences between curves were observable only at VUA for F_x and F_y.

In order to have a quantitative evaluation of performance of FPs at each centers, the RMSE values are reported in Table 4. Significant differences between measured points on edge and middle part of platform were observed only for F_y and F_x at OPBG and VUA, respectively. Only in these cases, the performance of force measurements got worse from the center to the edge of platform. For the other parameters, the platforms did not show different behaviors due to the position of the tested points. As regards the OPBG center, the lower values of RMSE were obtained in the validation of the shear forces of the first platform. From a comparison between FPs, the first one showed better performance in the moment measurements but worse one in the evaluation of forces. As regards the KUL center, the behavior of FPs was comparable in the measurement of shear forces and flexion moments but there were statistical differences in the measurements of F_z and M_z. As regards the VUA center, shear forces showed significant differences comparing the two FPs.From an overall analysis, RMSEs were higher at VUA than at OPBG and KUL. It can be due to the higher values of full scale of FPs installed at VUA as reported in Table 1. Moerover, all RMSE values were lower than the 1% of Full Scale of each platform.

In conclusion, all the platforms showed limited values of RMSEs assuring the data comparability among centers. RMSE values will have to be considered to estimate the contribution of FP to the overall uncertainty of the kinetic variables measured during gait analyses.

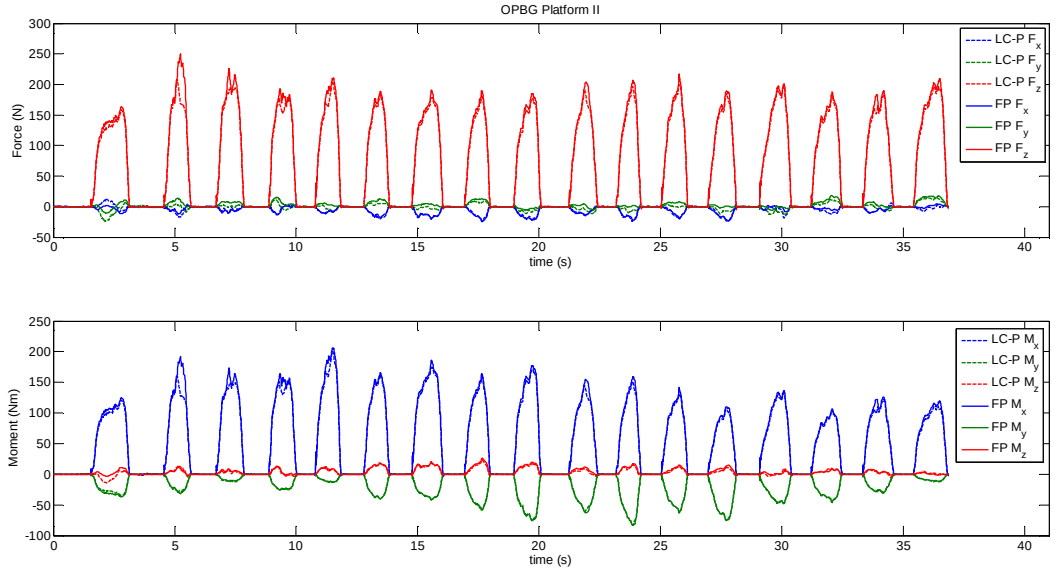


Figure 10 - Example of FP-validation performed at the OPBG lab.

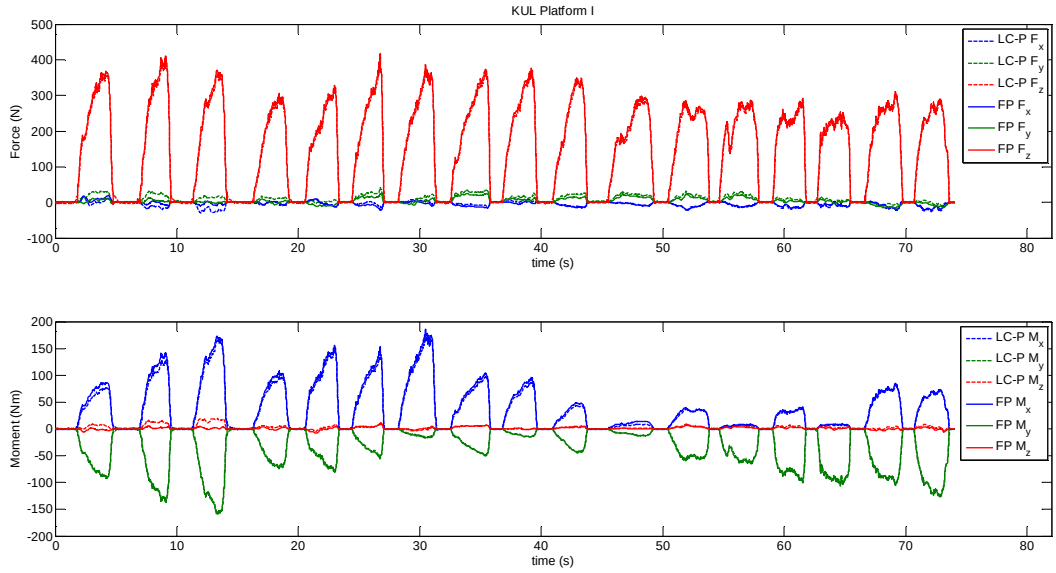


Figure 11 - Example of FP-validation performed at the KUL lab.

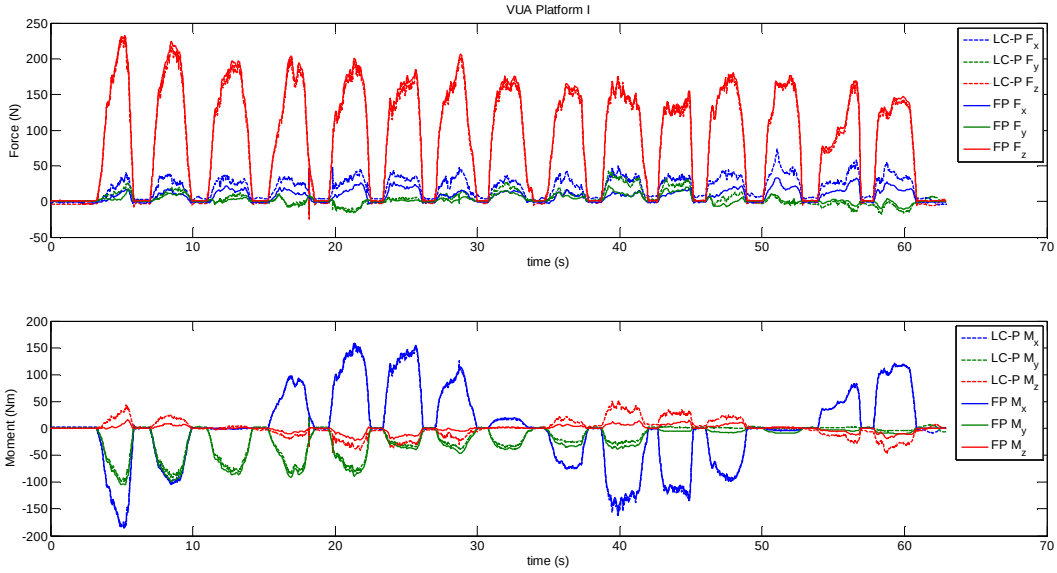


Figure 12 - Example of FP-validation performed at the VUA lab.

Table 3 - Mean and standard deviation of RMSEs between FP and LC-P measured at OPBG, KUL and VUA. Asterix reports statistical differences both between FPs and between points on edge and middle part of platforms.

Center	FP	Points	RMSE F_x [N]		RMSE F_y [N]		RMSE F_z [N]		RMSE M_x [Nm]		RMSE M_y [Nm]		RMSE M_z [Nm]	
OPBG	I	*Middle*	9.2 (4.9)	*	14.7 (9.6)	*	5.3 (2.7)		2.8 (1.2)	*	2.2 (1.8)		2.0 (0.6)	*
		Edge	6.1 (3.7)		10.3 (5.7)		5.7 (3.9)		2.8 (1.3)		2.5 (1.5)		2.5 (2.6)	
	II	*Middle*	4.2 (2.1)	*	2.7 (1.9)*	*	6.3 (2.7)		4.6 (1.0)	*	1.6 (0.8)		3.4 (1.1)	*
		Edge	4.4 (1.5)		4.4 (2.9)*		7.0 (2.5)		5.2 (2.0)		2.0 (1.2)		4.2 (2.0)	
KUL	I	*Middle*	5.7 (3.3)		4.5 (2.3)		7.7 (1.7)	*	4.3 (2.7)		3.1 (1.7)		1.8 (1.7)	*
		Edge	6.1 (3.3)		3.5 (1.5)		7.7 (1.5)		4.2 (2.5)		3.3 (2.0)		2.0 (1.9)	
	II	*Middle*	5.9 (1.4)		3.5 (2.6)		4.5 (1.5)	*	3.1 (2.7)		3.2 (1.2)		4.4 (0.6)	*
		Edge	4.7 (1.6)		3.0 (2.0)		4.7 (1.9)		2.8 (2.4)		3.3 (1.5)		4.1 (1.8)	
VUA	I	*Middle*	6.9 (3.2)	*	6.6 (0.9)	*	7.2 (3.8)		5.2 (2.4)		4.5 (1.8)		6.9 (5.3)	
		Edge	5.5 (3.3)		7.4 (3.6)		5.8 (2.2)		4.3 (2.2)		4.0 (2.2)		6.0 (3.3)	
	II	*Middle*	10.2 (3.3)*	*	1.4 (0.4)	*	8.5 (2.8)		4.7 (2.5)		5.3 (1.7)		9.3 (4.4)	
		Edge	16.1 (1.9)*		2.7 (1.6)		7.2 (1.6)		3.1 (1.5)		6.1 (1.3)		9.9 (5.5)	

3. S-synchro

The plot of F_z and FP normalized to their maximum values are reported in Figure 13. The time delays between EMG and FP (T_{EMG-FP}) are reported in Table 4. The highest value of the selected parameter was recorded at KUL. Each center has to consider that values as uncertainty when the EMG is used to evaluate the activation time of muscles during gait analyses.

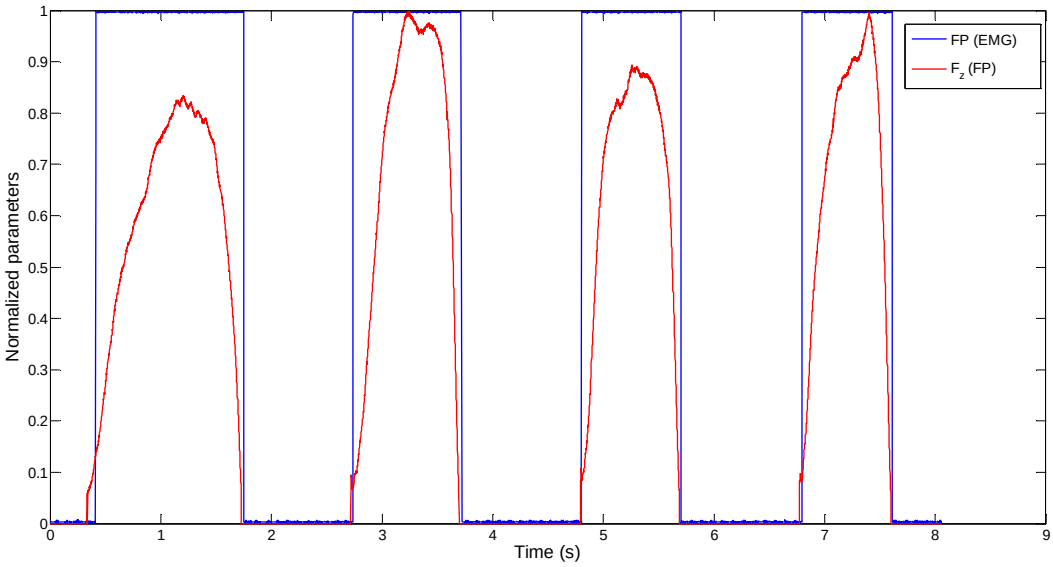


Figure 13 - Syncronization between EMG and FP.

Table 4 - Mean and standard deviation of time delay between EMG and FP

Parameters	Centers		
	OPBG	VUA	KUL
T_{EMG-FP} [ms]	18 (2)	58 (2)	65 (4)

Task 6.1.1.2. Technical Quality assurance of measurements (high level)

The Figure 14 shows the considered procedure to evaluate the uncertainty interval that affects the measures. The protocol incudes the following features:

i. Two healthy children, age-matched with the range considered in the project, have been recruited;
ii. Data collection was performed on these subjects in all the involved centers (KUL, VUA and OPBG);
iii. Two therapists per center performed the marker placement on each subject (those therapists were the ones who usually performed gait analysis in the centers);
iv. Five walking trials were collected.

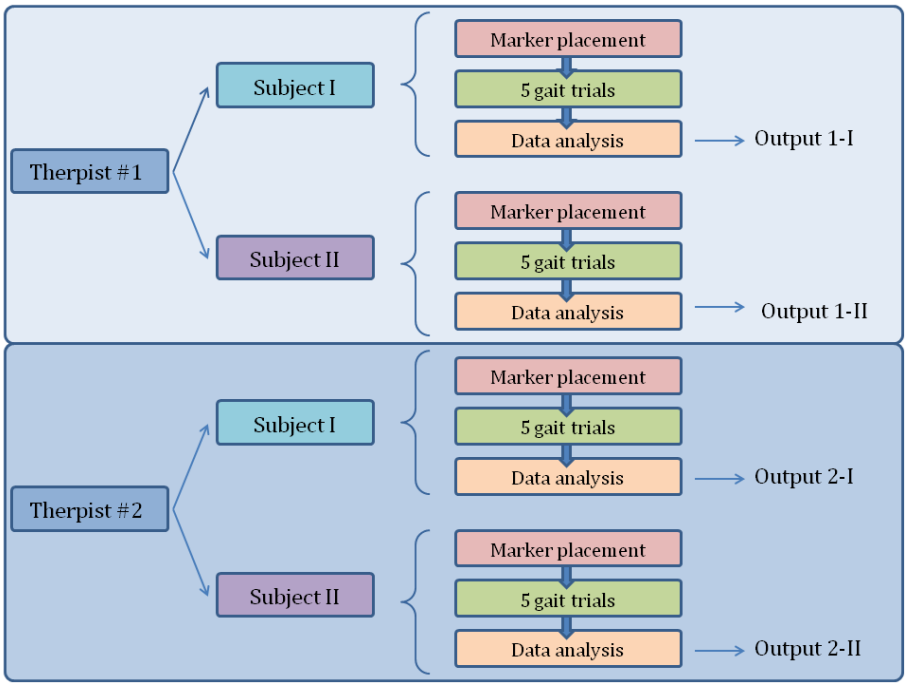


Figure 14 - Flow-chart of the experimental protocol for the high-level validation of the TQA.

Following the protocol, the collected data were processed with the typical pipelines of each center, including:

i. Filtering;
ii. Gap filling;
iii. Labeling;
iv. Static and Dynamic Kinematics, and Kinetics pipelines.

The considered variables are:

i. Joint angles (Kinematics);
ii. Joint moments (Kinetics);
iii. Timing on EMG signal activation.

As the filtering and the daily pipelines can be different between the centers, URLS also asked the gait centres to provide the raw-data (see the graph in Figure 15).

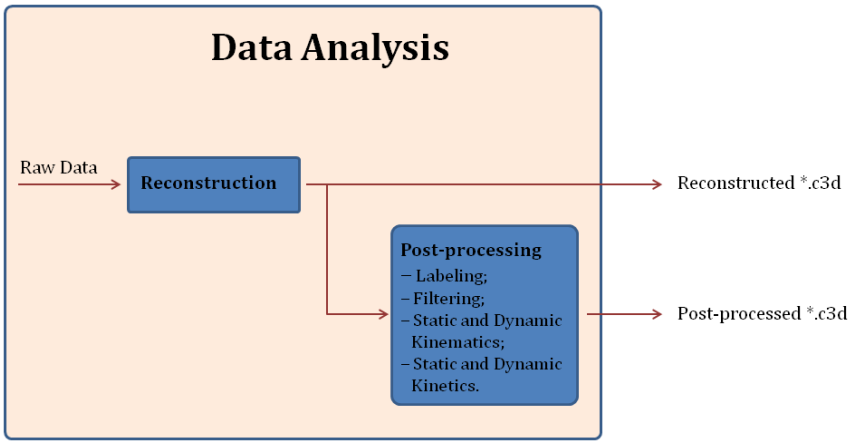


Figure 15 - Flow-chart of data analysis.

Kinematic and kinetic data were partitioned into individual gait cycles. Moreover, the data were analyzed according to the markers placement protocol adopted in each center: PiG in OPBG and KUL, HBM in VUA.

For each subject and each operator the following spatio-temporal parameters were calculated:

- Cadence (step/min);
- Walking speed (m/s);
- Swing to stance ratio (%);
- Stride length (m).

As regards the EMG signal, in order to reduce the noise, the collected data was, firstly, treated, in accordance to Hershler and Milner [4], with a fifth order high-pass Butterworth filter with 20 Hz cut-off frequency, rectified and smoothed with a 20 ms moving window average. Then, the signals were partitioned into gait cycles. After the normalization, the time of activation was calculated, in accordance to Knaflitz and Bonato [5], as the time interval during which the signal exceeds a threshold for almost 5 ms with respect to the total duration of the test; the threshold value is set as the standard deviation of the EMG baseline multiplied by a factor two.

The kinematic and kinetic variables, extracted by means of the above described protocol, were tested and compared with the evaluation of similarity indices. Kadaba and colleagues [6] state that the statistic tests are not sufficient to describe the variability between the waveforms of kinematic and kinetic parameters, expressed as a function of gait cycle. Hence, the Authors introduced the adjusted Coefficient Of Multiple Determination (R_a^2). According to Kadaba *et al.,* URLS computed the adjusted Coefficient of Multiple Determination (R_a^2) and the Coefficient of Multiple Correlation (CMC) in order to evaluate the repeatability of waveforms *within-laboratory*, that represents the between-operators variability, as follows:

$$R_a^2 = 1 - \frac{\dfrac{\sum_{l=1}^{L}\sum_{k=1}^{M}\sum_{j=1}^{N}\sum_{i=1}^{T}\left(x_{ijkl} - \bar{x}_{li}\right)}{LT(MN-1)}}{\dfrac{\sum_{l=1}^{L}\sum_{k=1}^{M}\sum_{j=1}^{N}\sum_{i=1}^{T}\left(x_{ijkl} - \bar{x}_{l}\right)}{L(TMN-1)}} \qquad (1)$$

Where:

L is the number of involved laboratories,

M is the number of operators,

N is the number of collected strides,

T is the number of time samples,

x_{ijkl} is the observed data at *i*th time, *j*th stride, *k*th operator and *l*th laboratory.

In addition the $\overline{x}_{li}$ and $\overline{x}_{l}$ are evaluated as follows:

$$\overline{x}_{l} = \frac{1}{MNT}\sum_{k=1}^{M}\sum_{j=1}^{N}\sum_{i=1}^{T} x_{ijkl}$$

$$\overline{x}_{li} = \frac{1}{MN}\sum_{k=1}^{M}\sum_{j=1}^{N} x_{ijkl}$$

The *between-laboratories* variability is assessed with the following equation:

$$R_a^2 = 1 - \frac{\dfrac{\sum_{l=1}^{L}\sum_{k=1}^{M}\sum_{j=1}^{N}\sum_{i=1}^{T}\left(x_{ijkl} - \overline{x}_{i}\right)}{T(LMN-1)}}{\dfrac{\sum_{l=1}^{L}\sum_{k=1}^{M}\sum_{j=1}^{N}\sum_{i=1}^{T}\left(x_{ijkl} - \overline{x}\right)}{LMNT-1}} \qquad (2)$$

Where:

$$\overline{x}_{i} = \frac{1}{MNL}\sum_{l=1}^{L}\sum_{k=1}^{M}\sum_{j=1}^{N} x_{ijkl}$$

$$\overline{x} = \frac{1}{MNLT}\sum_{l=1}^{L}\sum_{k=1}^{M}\sum_{j=1}^{N}\sum_{i=1}^{T} x_{ijkl}$$

Moreover, the Coefficient of Multiple Correlation, CMC, is calculated as the positive square root of R_a^2.

Three paired-sample t-test were performed in order to find significant differences between the operators of the same laboratory for both spatiotemporal parameters and muscle activation time. Statistical differences was set at 0.05. Whether significant differences between operators were not found, the one-way ANOVA was performed between laboratories data. When significant differences were found, a Bonferroni's test for multiple comparisons was performed.

Results

Reproducibility within laboratory

Firstly URLS examined the reproducibility *within laboratory*, thus CMC between operators in OPBG, KULeuven and VUA laboratory were calculated (CMC^{w}_{OPBG}, CMC^{w}_{KUL} and CMC^{w}_{VUA}) for each joint angle and for each joint moment of the two subjects. The results are shown in the following tables:

Table 5 – CMC *within laboratory* for kinematic variables of subject 1.

Joint Angle Subject #1	CMC^{w}_{OPBG}		CMC^{w}_{KUL}		CMC^{w}_{VUA}	
	Right	**Left**	**Right**	**Left**	**Right**	**Left**
Hip flexion/extension	0.99	0.98	0.99	0.98	0.98	0.98
Hip abduction/adduction	0.89	0.80	0.94	0.96	0.75	0.72
Hip rotation	0.85	0.88	0.80	0.84	0.20	0.21
Knee flexion/extension	0.99	0.98	0.99	0.99	0.97	0.93
Ankle dorsiflexion/plantar	0.94	0.91	0.97	0.95	0.70	0.85
Ankle abduction/adduction	0.83	0.92	0.94	0.96	na[3]	na
Ankle rotation	0.77	0.93	0.94	0.94	na	na

Table 6 - CMC *within laboratory* for kinetic variables of subject 1.

Moment Subject #1	CMC^{w}_{OPBG}		CMC^{w}_{KUL}		CMC^{w}_{VUA}	
	Right	**Left**	**Right**	**Left**	**Right**	**Left**
Hip flexion/extension	0.83	0.89	0.96	0.94	0.80	0.90
Knee flexion/extension	0.90	0.90	0.97	0.95	0.60	0.77
Ankle dorsiflexion/plantar	0.92	0.96	0.99	0.99	0.99	0.94

Table 7 - CMC *within laboratory* for kinematic variables of subject 2.

Joint angle Subject #2	CMC^{w}_{OPBG}		CMC^{w}_{KUL}		CMC^{w}_{VUA}	
	Right	**Left**	**Right**	**Left**	**Right**	**Left**
Hip flexion/extension	0.98	0.97	0.96	0.97	0.98	0.98
Hip abduction/adduction	0.9	0.81	0.85	0.83	0.95	0.9
Hip rotation	0.73	0.8	0.77	0.8	0.78	0.83
Knee flexion/extension	0.98	0.96	0.97	0.97	0.97	0.97
Ankle dorsiflexion/plantar	0.93	0.87	0.9	0.91	0.92	0.91
Ankle abduction/adduction	0.87	0.9	0.9	0.82	na[3]	na
Ankle rotation	0.84	0.9	0.91	0.85	na	na

[3] Missing data from HBM model of VUA

Table 8 - CMC *within laboratory* for kinetic variables of subject 2.

Moment Subject #2	CMC^{w}_{OPBG}		CMC^{w}_{KUL}		CMC^{w}_{VUA}	
	Right	**Left**	**Right**	**Left**	**Right**	**Left**
Hip flexion/extension	0.93	0.93	0.93	0.94	0.95	0.89
Knee flexion/extension	0.94	0.92	0.94	0.95	0.76	0.73
Ankle dorsiflexion/plantar	0.97	0.97	0.98	0.97	0.95	0.90

Reproducibility between laboratories

Moreover, CMC were calculated between each laboratories that used PiG model (CMC^{B}_{PiG}), i.e OPBG and KUL, and CMC between the three laboratories that used different models, $CMC^{B}_{PiG-HBM}$. The following tables show the CMC *between laboratories* values related to kinematic and kinetic variables of both subjects.

Table 9 – CMC *between laboratories* for kinematic variables of subject 1.

Joint angle Subject #1	CMC^{B}_{PiG}		$CMC^{B}_{PiG-HBM}$	
	Right	**Left**	**Right**	**Left**
Hip flexion/extension	0.97	0.98	0.95	0.97
Hip abduction/adduction	0.87	0.81	0.74	0.72
Hip rotation	0.77	0.84	0.33	0.43
Knee flexion/extension	0.98	0.98	0.97	0.96
Ankle dorsiflexion/plantar	0.94	0.96	0.75	0.90

Table 10 - CMC *between laboratories* for kinetic variables of subject 1.

Moment Subject #1	CMC^{B}_{PiG}		$CMC^{B}_{PiG-HBM}$	
	Right	**Left**	**Right**	**Left**
Hip flexion/extension	0.86	0.87	0.83	0.82
Knee flexion/extension	0.90	0.89	0.79	0.75
Ankle flexion/extension	0.95	0.97	0.81	0.94

Table 11 - CMC *between laboratories* for kinematic variables of subject 2.

Joint angle Subject #2	CMC^{B}_{PiG}		$CMC^{B}_{PiG-HBM}$	
	Right	**Left**	**Right**	**Left**
Hip flexion/extension	0.94	0.93	0.95	0.94
Hip abduction/adduction	0.71	0.80	0.77	0.77
Hip rotation	0.70	0.76	0.57	0.67
Knee flexion/extension	0.96	0.96	0.96	0.96
Ankle dorsiflexion/plantar	0.83	0.88	0.81	0.81

Table 12 - CMC *between laboratories* for kinetic variables of subject 2.

Moment Subject #2	CMC^{B}_{PiG}		$CMC^{B}_{PiG-HBM}$	
	Right	**Left**	**Right**	**Left**
Hip flexion/extension	0.91	0.93	0.85	0.82
Knee flexion/extension	0.90	0.93	0.79	0.75
Ankle flexion/extension	0.95	0.96	0.81	0.93

Kinematic variables

From an overall exam of the previously reported tables it emerges that in the sagittal plane, the repeatability of joint angle motion at the hip, knee and ankle were good (CMC>0.7) in the *within laboratory* comparison (see Table 5, Table 6, Table 7, and

Table 8) as well as in the *between laboratories* comparison (see Table 9, Table 10, Table 11 and

Table 12).

Furthermore, in the frontal and transverse plane the results show a good repeatability, with the exception of the hip rotation in VUA laboratory for the subject 1 (CMC=0.2), see Table 5. This result implies that, in the transverse plane, repeatability between the three laboratories is lower than the repeatability between the laboratories of OPBG and KULeuven. This finding could be due to variability in the alignment of markers in pelvis and shank between the three laboratories.

Kinetic variables

As regards joint moment, the repeatability in VUA of the moment at knee was lower (CMC ~ 0.7) than ankle and hip moment (CMC ~0.8-0.9), see Table 6 and

Table 8. The repeatability between the three centers was lower than the repeatability between OPBG and KULeuven, however always in the range of a good repeatability.

The CMC values offer a quantitative information of repeatability of kinematic and kinetic measurements. For a qualitative analysis see the figures in the Appendix.

Spatio-temporal parameters

The following tables show the results of paired-sample t-tests, means and standard deviations of spatio-temporal parameters between operators within the three centers (OPBG, KUL and VUA) for both subjects. Please notice that the two operators per center are selected among the therapists or phisicians operating at the laboratory.

Table 13 – Means and standard deviations of spatio-temporal patameters of subject 1. * indicates significant differences.

Subject 1	OPBG		KUL		VUA	
Spatio/temporal parameter	Operator 1	Operator 2	Operator 1	Operator 2	Operator 1	Operator 2
Cadence (steps/min)	130.9 (4.6)	125.7 (3.2)	121.8 (4.0)	122.1 (0.9)	122.1 (4.2)	125.7 (3.5)
Walking speed (m/s)	1.32* (0.08)	1.18* (0.01)	1.13 (0.04)	1.27 (0.09)	1.07* (0.04)	1.34*(0.03)
Swing to stance ratio (%)	37.6 (3.4)	36.4 (1.6)	42.4 (1.4)	40.1 (1.9)	35.4 (1.5)	36.6 (1.3)
Stride length (m)	1.22* (0.04)	1.13* (0.05)	1.29 (0.01)	1.25 (0.05)	1.03*(0.02)	1.37* (0.02)

Table 14 - Mean and standard deviations of spatio-temporal patameters of subject 2. * indicates significant differences.

Subject 2	OPBG		KUL		VUA	
Spatio/temporal parameter	Operator 1	Operator 2	Operator 1	Operator 2	Operator 1	Operator 2
Cadence (steps/min)	127.1 (5.9)	125.1 (6.5)	125.6 (2.8)	125.3(3.1)	127.1 (5.9)	125.3 (3.1)
Walking speed (m/s)	1.14* (0.09)	1.23* (0.1)	1.13* (0.07)	1.27*(0.09)	1.22* (0.03)	1.42* (0.06)
Swing to stance ratio (%)	38.2 (2.5)	38.6 (2.1)	37.4 (1.3)	38.1 (1.5)	36.2(0.4)	36.6(1.3)
Stride length (m)	1.08* (0.09)	1.18* (0.9)	1.23* (0.05)	1.17* (0.05)	1.28* (0.03)	1.34* (0.03)

Hence, the cadence and swing to stance ratio were not influenced by the performance of the different operators in both subjects. Therefore, two one-way ANOVAs and Bonferroni *post-hoc* tests were performed *between laboratories*. The results are reported in the following tables where the apex indicates with which laboratories statistically differences were found.

Table 15 –Mean and standard deviations of spatio-temporal parameters of subject 1. Apex indicates with which laboratories statistically differences were found according to Bonferroni test.

ANOVA Subject 1				
Spatio/temporal parameter	OPBG	KUL	VUA	p-value
Cadence (steps/min)	128.3 (4.7)^{KUL}	121.9 (3.9)^{OPBG}	123.9 (4.0)	0.007
Swing to stance ratio	37.0 (2.6)^{KUL}	41.5 (1.7)$^{OPBG-KUL}$	36.0 (1.2)^{KUL}	<0.001

Table 16 - Mean and standard deviations of spatio-temporal parameters of subject2. Apex indicates with which laboratories statistically differences were found according to Bonferroni test.

ANOVA Subject 2

Spatio/temporal parameter	OPBG	KUL	VUA	p-value
Cadence (steps/min)	126.1 (5.9)	125.4 (2.8)	126.2 (4.5)	0.928
Swing to stance ratio	38.4 (2.2)^{VUA}	37.7 (1.4)	36.4 (0.9)^{OPBG}	0.032

From the results of statistical test emerges the repeatability lack in spatio-temporal parameters. This finding may be ascribed to:

i. the variability of the gait performed by normally developed children;

ii. a different post-processing of gait phase recognition.

EMG signals

As regard EMG, the activation time of 8 muscles (4 agonist and 4 antagonist) of one lower limb was calculated. Then, paired-sample t-tests were performed *within laboratory* (see the following tables).

Table 17 - Mean and standard deviations of muscle activation time of subject 1. * indicates the significant difference found.

Subject 1	OPBG		KUL		VUA	
Muscle attivation time (%)	Operator 1	Operator 2	Operator 1	Operator 2	Operator 1	Operator 2
Rectus Femoris	14.2 (1.1)	13.6 (0.9)	12.8 (1.7)	12.4 (1.5)	13.4 (1.3)	12.2 (1.7)
Medial Hamstring	17.4 (2.1)	17.1 (0.7)	17.4 (1.3)	16.4 (0.5)	18.2 (1.9)	16.8 (0.9)
Anterior Tibialis	19.1* (1.2)	16.8* (1.6)	15.0 (1.4)	16.3 (2.2)	15.6 (2.3)	18.2 (3.3)
Gastrocnemius	18.2 (5.2)	13.1 (2.3)	18.6 (3.3)	16.4 (1.9)	16.8* (1.6)	20.2* (1.6)
Vastus Lateralis	16.1 (1.2)	15.8 (1.3)	16.2 (1.6)	15.6 (0.6)	15.7 (0.5)	16.6 (1.5)
Biceps Femoris	18.4 (4.4)	16.6 (1.6)	16.4 (1.3)	15.8 (1.1)	17.1 (2.2)	18.4 (2.1)
Soleus	15.6 (4.1)	21.0 (5.3)	18.2 (6.2)	18.8 (4.0)	17.6 (4.1)	15.2 (1.6)
Gluteus Medius	9.1 (2.1)	8.8 (1.9)	8.2 (0.8)	7.2 (0.8)	13.8 (2.2)	10.6 (3.6)

Table 18 - Mean and standard deviations of muscle activation time of subject 2. * indicates the significant difference found.

Subject 2	OPBG		KUL		VUA	
Muscle attivation time (%)	Operator 1	Operator 2	Operator 1	Operator 2	Operator 1	Operator 2
Rectus Femoris	11.8 (2.3)	12.1 (1.2)	12.4 (1.6)	12.1 (1.6)	11.8 (1.3)	13.2 (1.1)
Medial Hamstring	15.4 (0.5)	16.2 (1.0)	16.6 (1.5)	14.8 (2.3)	16.4 (1.1)	17.4 (2.1)
Anterior Tibialis	16.6(2.3)	18.0 (3.4)	18.2 (1.4)	18.6 (2.7)	15.1 (0.7)	14.8 (1.1)
Gastrocnemius	20.0 (1.6)	18.2 (2.8)	18.8* (2.2)	15.6* (0.9)	15.2 (0.8)	16.2 (1.6)
Vastus Lateralis	13.8 (1.3)	13.0 (1.6)	13.2 (1.3)	13.4 (1.6)	12.6 (1.8)	13.8 (1.3)
Biceps Femoris	19.3 (3.3)	17.8 (2.7)	19.2 (2.3)	18.8 (1.5)	15.8 (1.8)	18.4 (2.2)
Soleus	17.6 (4.1)	15.2 (1.6)	19.1 (3.6)	20.6 (3.2)	17.6 (2.6)	18.2 (3.7)
Gluteus Medius	17.8 (3.0)	16.6 (3.2)	19.2 (1.9)	21.6 (2.8)	11.8 (0.8)	11.1 (3.2)

The attivation time of Rectus femoris, medial Hamstring, anterior tibialis (only for subject 2), vastus lateralis, biceps femoris, soleus and gluteus medius were not influenced by the performance of the different operators in both subjects. Therefore, two one-way ANOVAs and Bonferroni *post-hoc* tests were performed *between laboratories*. The results are reported in the following tables where the apex indicates with which laboratories statistically differences were found.

Table 19 - Mean and standard deviation of muscle activation time of subject1. Apex indicates with which laboratories statistically differences were found.

ANOVA Subject 1				
Muscle attivation Time (%)	OPBG	KUL	VUA	p-value
Rectus Femoris	13.9 (0.9)	12.6 (1.5)	12.8 (1.6)	0.072
Medial Hamstring	17.2 (1.4)	16.9 (1.1)	17.3 (1.7)	0.814
Vastus Lateralis	15.9 (1.2)	15.8 (1.2)	16.1(1.2)	0.918
Biceps Femoris	17.5 (3.3)	16.1 (1.2)	17.7 (2.1)	0.271
Soleus	18.3 (5.3)	18.4 (4.9)	17.6 (2.8)	0.915
Gluteus Medius	8.9 (1.9)^{VUA}	7.7 (0.9)^{VUA}	12.2 (3.2)$^{OPBG-KUL}$	<0.001

Table 20 - Mean and standard deviations of muscle activation time of subject2. Apex indicates with which laboratories statistically differences were found.

ANOVA Subject 2				
Muscle attivation Time (%)	**OPBG**	**KUL**	**VUA**	**p-value**
Rectus Femoris	11.9 (1.7)	12.2 (1.5)	12.5 (1.3)	0.691
Medial Hamstring	15.7 (0.8)	15.6 (2.0)	16.9 (1.6)	0.177
Anterior Tibialis	17.3 (2.8)^{VUA}	18.4 (2.1)^{VUA}	14.9 (0.8)$^{OPBG-KUL}$	<0.001
Vastus Lateralis	13.4 (1.4)	13.3 (1.4)	13.2 (1.6)	0.952
Biceps Femoris	18.5 (2.9)	19.0 (1.8)	17.1 (2.3)	0.213
Soleus	16.4 (3.2)	19.8 (3.3)	17.9 (3.0)	0.072
Gluteus Medius	17.2 (3.4)$^{KUL-VUA}$	20.4 (2.6)$^{OPBG-VUA}$	11.4 (2.1)$^{OPBG-KUL}$	<0.001

The EMG signals, although is not simple the exact repositioning of the electrodes especially in pediatric subjects, presented a good repeatability both *within laboratory* as well as *between laboratories*, except for anterior tibialis in subject 1 in OPBG and gastrocnemius in VUA for subject 1 and in KUL for subject 2. Moreover, statistical differences *between laboratories* were found for gluteus medius in both subjects and in anterior tibialis in subject 2.

Task 6.2 Gait analysis collection for CP

Overview

Task 6.2 is the collection of gait analysis data for CP patients, to be provided to the work packages that are involved in biophysical and probabilistic modelling.

A complete dataset related to clinical gait analysis consists of:

1. A standardised anamnesis
2. Standard clinical testing: Physical Examinations and Tests; Questionnaires
3. Xrays if applicable
4. From gait analysis:
    i. Kinematic data;
    ii. Kinetic data;
    iii. EMG Data;
    iv. O2 Data.
5. Contextual data, like treatments received

The above items were further specified in the Consensus Protocol for clinical gait analysis as delivered in Deliverable 6.1.

For retrospective data, in total, KULeuven will provide 400 sets of data from its current database. OPBG will provide 200 sets of data (kinematics, kinetics, and electromyography) from its current database. As many datasets as possible are combinations of one pre- and one post-treatment dataset. Data quality checks will be performed for each subject.

Criteria for selection are based on children with CP that are routinely measured in the gait lab: classified as GMFCS 1-3; diplegic or hemiplegic; sufficient cognitive skills; without relevant visual deficit; and older than 6 years.

For prospective data, the following will be collected in total:

1. Complete data sets of 10 CP patients for each clinical center (VUA, OPBG, KULeuven) will be provided for biophysical modelling.

2. For the probabilistic modeling, datasets from the (adapted) clinical workflow will be included, based on the clinical load, the aim is to include 50 (with a minimum of 30) datasets per center (VUA, OPBG, KULeuven) before month 36. As many datasets as possible are combinations of one pre- and one post-treatment dataset.

In this task description, we present the current status of data collection, showing the first complete data sets to serve as input for biophysical and probabilistic modelling work packages. For each type of data, we describe per partner the issues encountered, if and how they were solved, and the current status. The precise status of data collection (what type of data is collected for which patient, status of data processing and uploading to the database, etc) is recoreded in an excel table, which is bi-weekly updated. A printscreen of the current version of the table is presented as Appendix 2.

Retrospective data collection

OPBG**:** at OPBG, a systematic review of the all our gait analysis database has been conducted. From the first overview, 200 suitable datasets heve been recognized. The selection of the first 39 retrospective datasets has been completed and it's now ready to be uploaded. In order to put reliable and valid data on the digital repository, the OPBG group is also carrying out a specific work of analysis and double check of the data to verify their consistency. A manual search about a longitundinal data is also being perfomed, with selection of pre- and post- evaluations of some treatment (orthosis, pharmacological- and/or surgery treatment) and/or a consecutive follow-up of natural history of the single patient.

The retrospective data collection has some limitations and there are pending issues to be discussed more deeply. First of all, retrospective data are suscettible to bias as there is a quote of missing or not reliable data. About Physycal Examination (PE) data, OPBG has not retrospective data quickly avaible as the PE files were not stored in the gait lab but in the medical records. Moreover, OPBG used a different protocol of examination from that collected by Lueven. Consequently, it was decided to unify the PE data using a minimum common dataset.

OPBG and KULeuven share the plug-in-gait model based on Vicon system, that is, the marker labels (anatomical repere and virtual markers as joints centre) are the same except for the muscles selection that is user dependent. Main OPBG's retrospective data have been collected recording 8 muscles s_EMG , 4 for each lower limb and will be uploaded in such format. The Infostrusture is in charge of uniform data format and to extract the selected biomarkers.

KUL: Although KUL experienced a slow start, it's currently collecting the retrospective data in a steady manner and have 111 gait analyses (55 pre and 56 post) ready to be uploaded. Hopefully, the collection of the dataset of 400 gait analyses should be completed by the end of 2015.

One of the reasons for the slow start, was that collecting the data takes more time than we anticipated, since each trial needs to be checked for quality of sEMG, kinematics and kinetics. This process will be speeded up by recruiting a colleague that will solely focus on retrospective data collection from the half of 2015 on. Another reason for the delay is that it was (and still is to some extend) unclear how the data will be uploaded in the database. This depends on the data type (C3D, MOX, PDF etc), parameter labels (as mentioned previously by OPBG) and how to store the data. Currently, a lab-specific data processing suite (DPS) is being developed by the infostructure group to synchronize the data of all the three participating labs. We already defined a list of parameter labels, which will be finalized during the meeting on 23-24th of February in Amsterdam.

Prospective (extended) data collection

Patient recruitment

OPBG: 8 patients with CP (3 Left hemiplegic, 2 right hemiplegic, 3 diplegic) for prospective collection and 6 CP (2 Left hemiplegic, 3 right hemiplegic, 1 diplegic) for extended prospective data have been recruited, included also MRI, and EE. All the families of the children involved in the study have given their informed consent.

KU Leuven: Currently, two CP children with the standard protocol (both barefoot and with orthoses) have been included and ten are scheduled from now until the end of March 2015.

Recruitment of children for the extended protocol has started, but currently no participants have been found. Therefore, the experiences described below are only applicable for the standard protocol.

VUmc: 5 CP patients were recruited for the standard prospective data collection, and these performed all measurements. As these patients were also part of a different study on the effect of functional gait training, these data sets are all pre-treatment evaluations. The post-treatment evaluation is foreseen in the beginning of May. As 3D gait analyses are not performed on a daily basis in our lab and only performed routinely for orthopedic patients, we needed to increase the number of 3D gait analyss in order to reach the numbers required. We are in the process of changing the clinical logistics, in order to include a set of patients pre- and post-botox treatment as part of their clinical routine. Vumc also filed and got approved an amendment to the medical ethics approval, that allows the inclusion of 1) patients that receive 3D gait analysis as part of a different research study; or 2) patient that are clinically referred for a 2D (video) gait analysis, but approve to receive a 3D gait analysis (accoriding to the MD-Paedigree protocol, so including PE and anamnesis) instead.

Furthermore, one patient for the extended data collection has been recruited. The MRI and gait analysis have been performed on the same day. The second part of the measurements (O2, HHD, anamnesis, PE) is planned in the coming week.

Anamnesis

OPBG: anamnesis have been collected according to the new protocol for all patient recruited.

KU Leuven: The anamnesis/patient history is very similar to the one used in UZ Leuven. In order to save time, a questionnaire with the additional questions for the parents to fill in has been drafted. This works quite well, although the parents are not always able to answer all questions.

VUmc: The anamnesis has been translated into Dutch and a questionnaire for parents to fill out is being prepared. VUmc is trying to find as much of the information as possible from our patients' paper and electronic records.

Clinical examination

OPBG: Clinical examination is quite long but it works for the major part of the subjects. Data coming from items that required the active participation of the subjects are considered with a lower degree of confidence. The evaluation of selectivity for example could be affected by bias that concerned the capacity of the subject to understand the task and to effectively perform it.

KU Leuven: The additional measurements in the clinical exam, compared to the standard clinical exam done at UZ Leuven, are described on a plastized 'cheat chart' (table 1; in Dutch). The additional measurements

will take some time to get used to and for some of the measurements it is helpful to have an extra pair of hands.

Anamnese	Vragenlijst in te vullen door ouders
Antropometrie	Bovenbeen-, onderbeen- en voet omvang + voetlengte. Inter ASIS afstand
sEMG	Mediale gastrocnemius
Markers	Extra markers naast standaard PiG
Gait analysis	Drie stapsnelheden met kinematica, kinetica en sEMG
Klinisch onderzoek	Functionele meting PROM: alle hoeken moeten gemeten worden PROM: heup extensie in buiklig als extra meting PROM: enkel varus, valgus, pronatie en supinatie als extra metingen Spasticiteit: Duidelijk aangeven of er een catch en release aanwezig is

Table 1.

VUmc: The clinical examination is similar to the one already performed in our lab, so this does not cause any issues.

3D gait analysis

OPBG: The new protocol for data acquisition seems to work efficiently. Marker protocol and electrodes positioning for s_EMG do not present any difficulties and data acquisition flowed without any particular difficulties. In order to take complete advantage from new marker protocol, it is needed the development of an ad-hoc dynamic model to integrate, for example, the two markers on the heads of the 1st and 5th metatarsal, or the functional calibration of the hip and the knee. From an overview of the acquired data running the plug-in-gait standard model, gait data appeare quite distinctive of different gait pattern and able to differenziate pathologies. Diplegic CP are characterized by lower limb flexion, hemiplegic CP by partial asymmetry, with specific peculiarity for the right side affected respect to the left side.

KU Leuven: Similar to the anamnesis/patient history, the gait analysis is comparable to the one done in UZ Leuven with exception of the marker protocol. As a reminder we made plastized 'cheat charts' for the clinicians on which the new marker protocol is plotted (figure 1).

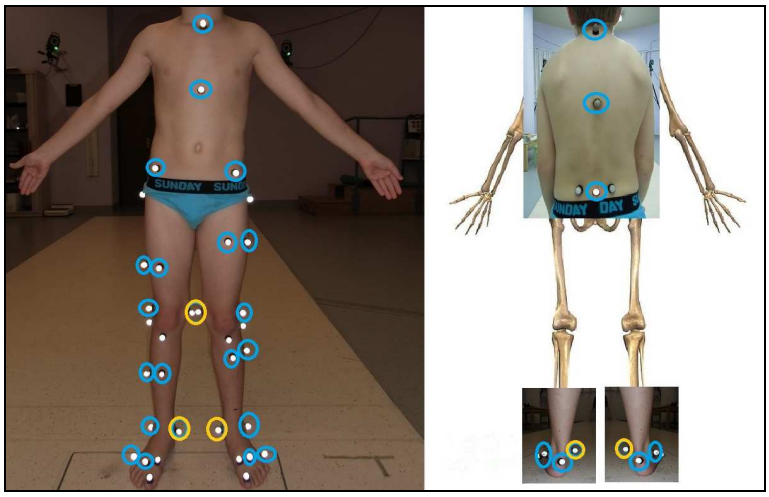


Figure 1.

VUmc: As different motion capture system is available in VUmc's lab (Optotrak) compared with OPBG/KUL (Vicon), but the process of switching to Vicon is currently ongoing, it has been decided to wait with the

inclusion of 3D gait data until the new system is installed and working. Unfortunately this took longer than foreseen, especially since new acquisition software had to be developed by Motek Medical (to allow for both 3D and only 2D/video gait analysis with the same system). The system is now almost ready for use, and we expect to include the first patients in the gait lab in March. As stated above, we also needed to change the clinical logistics in order to be able to include more 3D gait analyses than before.

In the meanwhile, it has been decided to include several patients that received a 3D gait analysis in the VUmc's Virtual Reality lab, a treadmill-based system surrounded by a large screen (GRAIL, Motek Medical BV, The Netherlands), see Figure. It was already foreseen to perform the extended measurements on this system, and we now filed an amendment and received ethical approval to also perform the standard data collection on this system. Previous study (van der Krogt et al. 2014) has shown that the kinematics are very similar between both labs. This allowed VUmc to include data of 5 pre-treatment gait analyses. Furthermore, the first measurement for the extended protocol has been performed.

With regard to technical issues, some problems with the visibility of the 42 markers required (40 of the MD-Paedigree protocol + 2 extra required by the GRAIL software) were encountered, especially in small children. The data could be analysed, but this took a long time. VUmc is currently committed in checking the camera and software settings to improve the visibility.

Another issue encountered is that it is not feasible (unconfortable and prone to injury) to walk barefoot on the treadmill. In order to create a situation as close as possible to walking barefoot, it has been decided to have subjects walking on very simple gymnastic shoes, which fit the feet tightly.

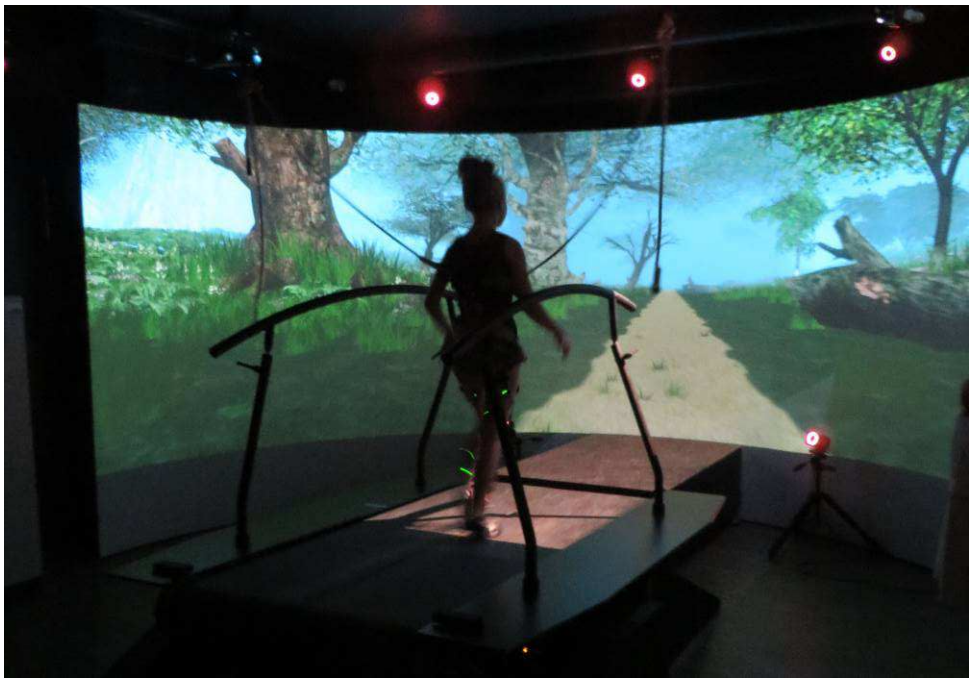


Figure: One of the CP patients walking in our treadmill-based gait lab.

Hand-held dynamometry

OPBG: the HHD manual was used, without using the specific software; subsequently, the single value of recorded force have been manually written down. The children with CP have some difficulty in understanding the task and in performing the muscle contraction with only tested muscle. Often they apply a generalized contraction/and co-contraction, including also other muscles. The task is being perfomed

holding the child in place manually; this reduces the problem but does not solve it. For this reason, OPBG group is not very confident with the data acquired because of:

- difficulty of the subject to perform a selective control on the requested movement;
- poor repeatability of the force measurements;
- inability to produce force at the selected angles, i.e. some subjects are able to produce a flexion of the hip at 40° but not at 90°.

KUL: KU Leuven is familiar with using the HHD for strength measurements, but a different test position is used. Therefore, several test sessions were performed to get familiar with the test positions described in the consensus protocol.
VUmc: several test sessions were performed, including one a healthy child, to figure out the best way to fixate the child and hold the dynamometer. The first patient measurement for the extended protocol is planned in the coming weeks (March 2015).

Energy expenditure

OPBG: Energy expenditure is well tollerated by the subject and not many difficulties have been found, except for one subject that was very active, with a tendency to talk and to remove the wire connection of the apparatus.

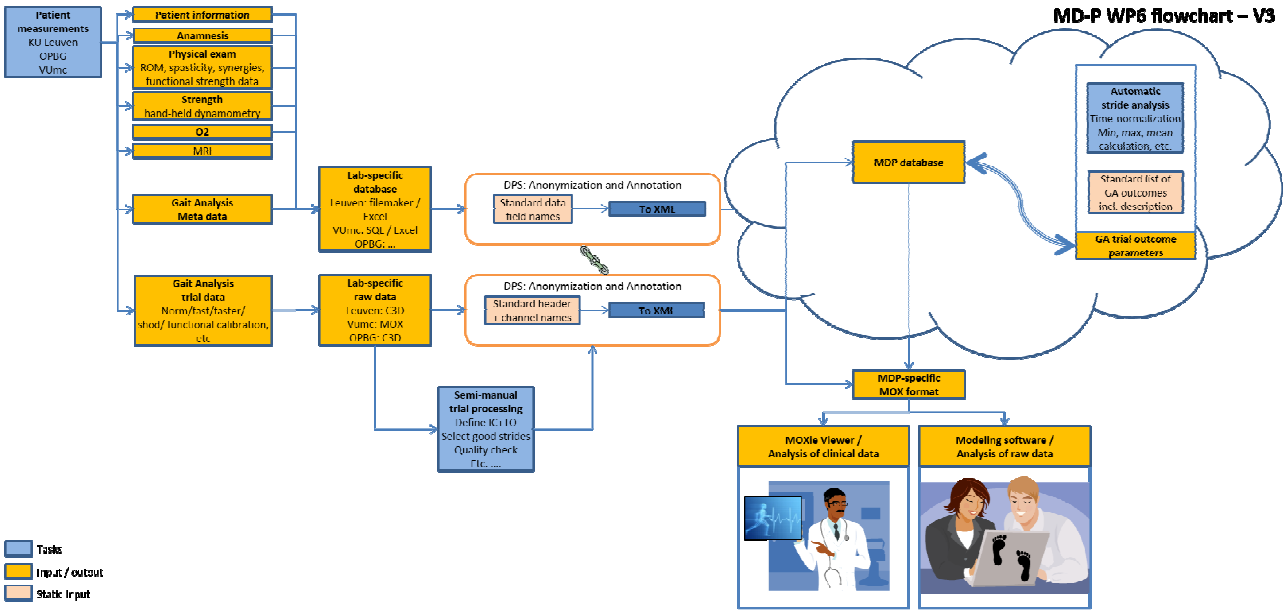
KU Leuven: This protocol is familiar in UZ Leuven and will not cause any difficulaties.

VUmc: This protocol is performed quite routinely in our center, also on CP patients, so it does not cause any issues.

Data processing and storage

All centers have uploaded the data sets for the TQA (same 2 healthy subjects in all centers; each measured twice; see task 6.1.1.2) on the Gnubila website. This was done using a standard folder structure, and only 3D gait data (C3D and MOX files) were uploaded.

In order to upload all data to the MD-PAEDIGREE repository, the data structure needs to be standardized. This is not a trivial task, as large data sets with many different parameters of different forms are collected for each patient. A flowchart for this process is shown below.



Two types of data are considered:

1) the clinical data, as stored in lab-specific databases (all information about anamnesis, physical exam, strength, O2 and MRI and gait descriptive 'meta' data
2) the gait analysis time series, i.e. 'lab-specific raw data', i.e. marker data, kinematics, kinetics and emg data

For 1) we developed a large excel table with all outcome parameters. Most but not all of this was also specified in the Consensus Protocol. The list contains over 500 parameters, as collected during the extensive protocol. For each parameter we specify the ID (name), a description, the data type (string, number, etc) and if needed a list of possible drop down items. This list of parameters is used by the infostructure work packages to develop a Data Processing Suite (DPS, see figure), that allows for the lab-specific conversion from the local database fields to the standardized outcome parameters. Next, all parameters are stored in an .xml file per data set and then loaded in the repository. At this point we are ready to collaborate with the infostructure group and upload the first data through the DPS.

For 2) each center needs to pre-process the data to check for data quality, identify initial contacts and select good strides, etc. Currently this has been done already by each center for all data using their own standards. We are also considering to use a standardized Vicon subject and marker template, as well as processing pipeline, to further standardize the data. Next, we agreed to convert all gait traces to a standardized format, i.e. a specified motion-xml (.mox) format. As the original .mox format as developed by VUmc was not suitable for 3D gait data, we developed a new .mox schema. This format was developed in collaboration between VUmc, KUL, OPBG, University of Sheffield (infostructure group), and Motek Medical. It will be adopted both by Motek Medical in WP11 for their Human Body Model outcomes, and by the infostructure group, and is attended to serve as a new standard for the gait community. It contains a

standard list of parameter names (i.e. marker names, joint angle names, emg names, etc.). We are currently finalizing some technical details of this new mox format in order to prepare the DPS for data upload.

Current status of the work

Total retrospective data collected:	149	(final aim: 600)
Total prospective clinical data collected:	16	(final aim: 120)
Total prospective extended data collected:	7	(final aim: 30)

The detailed status of the patient acquisition for prospective and retrospective data can be found in the attached excel table (Appendix 2).

Planning of data collection

OPBG: Retrospective data collection: 200 datasets are already recognized in the retrospective database. Specific work is needed to clean the data before the upload in the digital repository. As mentioned in self-assessment of February 2015, at least 100 datasets will be ready for the upload within M36.

Prospective clinical data: OPBG is regularly recruiting patients for this pupose. The enrollment is quite on time and OPBG scheduled visits regularly in order to reach the number of at least 30 patients within M36.

Prospective extended data: OPBG collected already 6 patients and the remaining 4 patients will be recruited within M36.

KUL: Retrospective data collection: as mentioned previously, a colleague will be recruited and he/she will solely focus on retrospective data collection from the half of 2015 on. KUL is aiming to finish the data collection at the end of 2015 (M34).

Prospective clinical data: KUL is currently recruiting and collecting the data and is confident that with a steady recruitment of 5-10 patient per month, data collection will be finished by the end of 2015 (M34).

Prospective extended data: KUL is currently recruiting, but was not able to find a willing patient yet. With the help of the physicians and physical therapists in recruiting the CP children, KUL is aiming to finish the data collection between M36 and M40.

VUmc: Prospective clinical data: 5 post-treatment data collections have been planned for May 215 on the GRAIL. As described above, several steps have been taken to speed up data collection in the overground lab as well (ethical approval amendment to include patients from different studies or recruit extra patients on top of current clinical routine). Once the new lab has been taken into use, which is expected in April 2015, we plan to collect one pre- or post btx 3D gait analysis every two weeks, which is currently being implemented in clinical logistics. Furthermore, we plan to more routinely acquire 3D gait analysis in general, which should speed up the data collection and allow us to reach the goal of at least 30 data sets by M36.

Prospective extended data: VUmc is currently recruiting and the 2nd measurement is already planned. With a pace of 1-2 patients per month, we do not foresee any issues to finish the data collection by M36.

Task 6.3 Gait analysis collection for DMD and CMT

Overview

Most of the above described issues are similar between CP, DMD, and CMT. This paragraph describes the additional or deviating issues in the latter to diseases, as well as the status of data collection.

Although the problems in Duchenne Muscular Dystrophy (DMD) and Charcot Marie Tooth (CMT) are not so complex as in CP (e.g. no spasticity) , the protocols developed in T6.1 apply for these populations, to be used in conjunction with modeling, to demonstrate reusability. The clinical problems in DMD and CMT are to trace subtle changes in motor performance during walking, in order to monitor the effects of intervention very quickly.

Data will be collected by OPBG and KU Leuven from 20 ambulant patients in total with genetically confirmed CMT1A with manifestation of symptoms starting within the age of 10 years. Inclusion criteria will include ambulant patients with an age range 6-15 years.

All patients will receive a longitudinal full control evaluation at baseline (0) and after 12-18 month(1). Measurements:

1. Functional motor scales:
    - Charcot-Marie-Tooth disease pediatric scale (lower limb only)
    - 6 minutes walk test to measure strength and fatigue
    - O2 measurements if the patient is compliant,
    - hand held myometer (Microfet2) to measure strength in all main lower extremity muscle groups
2. Gait analysis according to protocols T6.1

Clinical data will be collected by OPBG, and KU Leuven from 20 ambulant genetically confirmed DMD patients treated with the same steroid regimen of daily deflazacort (around 0,75mg/kg/day)and with the most common mutations in the DYS gene.

Age range of patients will be between 5 to 11 years. In particular we will recruit 10 patients with age between 5-7 years, and additional 10 patients with age between 8-11 years. In this second group of DMD patients we will be able to observe longitudinally the progression of the disease in the time span of 4 years, because it is known from current natural history data that DMD patients start a downhill progression of function after age 7-8 years. All patients (10 by OPBG and 10 by KU Leuven) will receive a longitudinal full control evaluation at baseline (0), and after 12-18 month (1)

Measurements:

1. Functional motor scales:
    - the North Star Ambulatory Assessment (NSAA)
    - 6 minutes walk test (6MWT) to measure strength and fatigue,
    - hand held myometer (MicroFet2) to measure strength in all main lower extremity muscle groups
2. Gait analysis according to protocols identified in T6.1
3. In addition OPBG and KU Leuven will acquire electrocardiographic and echocardiographic data from all the 20 DMD patients

Data collection

OPBG: 8 DMD and 8 CMT patients have been recruited so far. All patient completed the entire protocol including MRI and EE (except 1 DMD and 2 CMT for technical problems with the device during the EE acquisition).

The protocol is quite long but children recruited so far have been compliant to all the procedures. There is a quote of fatigue in the final part of the examination. For this reason, it has been planned to conduct the protocol in 2-3 consecutive days.

From the overview of the gait data, DMD gait is characterized by the pelvis anteversion, relative trunk extension and a tendency to produce toe walking. CMT gait could be differentiated by the pelvis retroversion and relative trunk flexion.

KU Leuven: KUL is currently recruiting DMD and CMT1A and is starting the measurements at the end of March/ beginning if April. We hope to finish the measurements by the end of 2015.

Current status of the work

Total baseline data collected (DMD):	8	(final aim: 20)
Total baseline data collected (CMT):	8	(final aim: 20)
Total follow-up data collected (DMD + CMT):	0	(final aim: 40)

The detailed status of the patient acquisition for prospective and retrospective data can be found in the attached excel table (Appendix 2).

Planning of data collection

OPBG: Baseline data collection: as reported previously, OPBG is on time with recruitment of DMD and CMT patients.

The follow-up evaluations of the enrolled patients are yet scheduled. OPBG is confident to recruit the other 2 pending patients for each disease within M30.

KUL: Baseline data collection: KUL is currently recruiting (starting with DMD) and is aiming to start measuring by the end of March/ beginning of April 2015. A physical therapist, study nurse and medical secretary are assisting in patient recruitment and planning of the measurements. Baseline data collection of both DMD and CMT1A should be finished by the end of 2015/beginning of 2016 (M34-M36). Follow-up data collection will start at the beginning of 2016 and will be finished by the end of 2016 (M46)

Task 6.4 - Image acquisition

Overview

As an input to WP11, each clinical center will acquire at least 10 MRIs of CP patients (30 total) and OPBG and KU Leuven will each acquire 10 MRIs for DMD and 10 for CMT. All MRIs will include the markers that are needed for gait analysis. Volume of interest includes pelvis, femur, tibia, foot.

As input for the models as developed in WP11, OPBG will acquire 24 sets of MRI images from typically developing children with the same protocol as above, but without gait analysis markers.

MR data acquisition

OPBG: So far, MRI of the lower limbs of 8 CMT patients, 8 DMD patients, 6 CP (2 Left hemiplegic, 3 right hemiplegic, 1 diplegic) have been collected. MRI of the lower limbs of 24 healthy subjects have been collected as well. Currently T1w isotropic volumetric (3D) sequences (FLASH) have been collected. Also a VIBE DIXON CAIPIRINHA (**C**ontrolled **A**liasing **i**n **P**arallel **I**maging **R**esults in **H**igher **A**cceleration) were acquired, using our 3T Siemens MRI with dedicated lowel limb coil and adding a body coil depending on patient's size; this sequence provide a four contrast images; one of them is like the T1w FLASH; other contrast images can provide better muscular and tendinous definition improving the segmentation of the single structures.

Many images for each patient are obtained (4000-5000). This causes sometimes problems in the recontruction of the image (time required is 2-3 minute longer than the initial T1w acquisition). Healthy subjects are enrolled among patients who take MRI exam for another clinical reason not involving the lower limbs (i.e. wrist fractures).

KU Leuven: As mentioned previously, KUL started recruiting CP (extended protocol), DMD and CMT1A patients and hope to start measuring at the end of March 2015. A test scan is planned on March 9th 2015.

VUmc: two test scans (one adult, one child) have been collected, to test procedures and confirm the protocol and data quality with Siemens (WP11). Furthermore, the first extended CP patient has been collected (see figure).

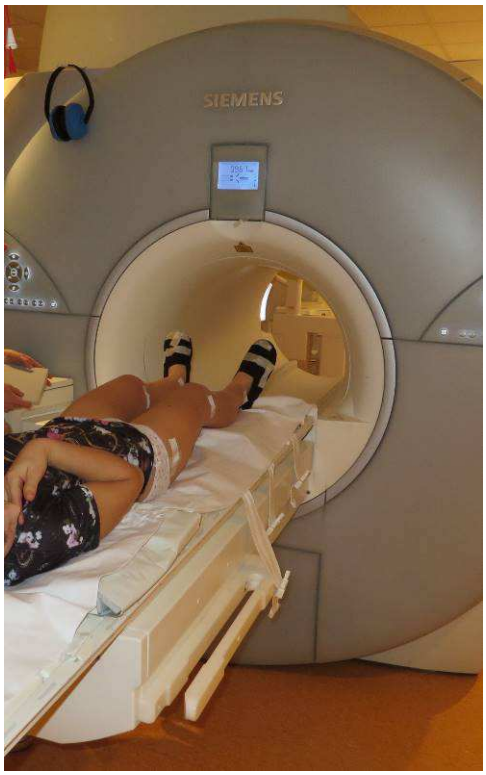


Figure: MRI set-up of the first CP patient. MR-visible markers (vitamin e pills) are taped to the locations of the skin where the gait markers are placed. The exact location is marked on the skin. Gymnastic shoes as used on the treadmill are worn to guearantee the same marker location.

MR data processing and storage

In order to acquire images of the full pelvis + legs, typically three stacks of data are taken. These are combined to one image by the software of the MRI machine. The data is then stored as Dicom images, zipped, and uploaded to the Gnubila server.

Current status of the work

Total CP images collected:	7	(final aim: 30)
Ttal DMD images collected:	8	(final aim: 20)
Total CMT1A images collected:	8	(final aim: 20)
Total healthy images collected:	24	(final aim: 24)

The detailed status of the patient acquisition for prospective and retrospective data can be found in the attached excel table (Appendix 2).

Planning data collection.

OPBG: the MRI collection is on time. The recruitment of healthy subjects for MRI is completed. For the extedend protocol, required for CP, DMD, CMT, OPBG will complete the MRI acquisition within M36.

KUL: As mentioned previously, KUL is currently recruiting CP, DMD and CMT1A children for the extended protocol (including the images) and is aiming to start measuring at the end of March/beginning of April 2015. Image collection is scheduled to be finished between M36 and M40.

References

1. Cappozzo, A.; Della Croce, U.; Catani, F.; Leardini, A.; Fioretti, S.; Maurizi, M. Stereometric system accuracy tests. In *Measurement and data processing methodology in clinical movement analysis-preliminary. CAMARC II Internal Report.*; 1993.

2. Collins, S. H.; Adamczyk, P. G.; Ferris, D. P.; Kuo, A. D. A simple method for calibrating force plates and force treadmills using an instrumented pole. *Gait Posture* **2009**, *29*, 59–64.

3. Richard G. Snyder, Martha L. spencer, C. L. O.; Schneider, L. W. *Physical Characteristics of Children*; 1975.

4. Hershler, C.; Milner, M. An optimality criterion for processing electromyographic (EMG) signals relating to human locomotion. *IEEE Trans. Biomed. Eng.* **1978**, *25*, 413–420.

5. Knaflitz, M.; Bonato, P. Time-frequency methods applied to muscle fatigue assessment during dynamic contractions. *J. Electromyogr. Kinesiol.* **1999**, *9*, 337–350.

6. Kadaba, M. P.; Ramakrishnan, H. K.; Wootten, M. E.; Gainey, J.; Gorton, G.; Cochran, G. V. B. Repeatability of Kinematic , Kinetic , and Electromyographic Data in Normal Adult Gait. *J. Orthop. Res.* **1989**, *7*, 849–860.

7. Van der Krogt M.M., Sloot L.H., Harlaar J. Overground versus self-paced treadmill walking in a virtual environment in children with cerebral palsy. Gait Posture. 2014 Sep;40(4):587-93.

Appendices

Appendix 1: Results of Task 6.1.1.2. Technical Quality assurance of measurements

Kinematic variables

In the following figures are presented the mean and the standard deviation of joint angle motion in the sagittal, frontal and transverse planes of the two subjects *between laboratories* and *within laboratory*.

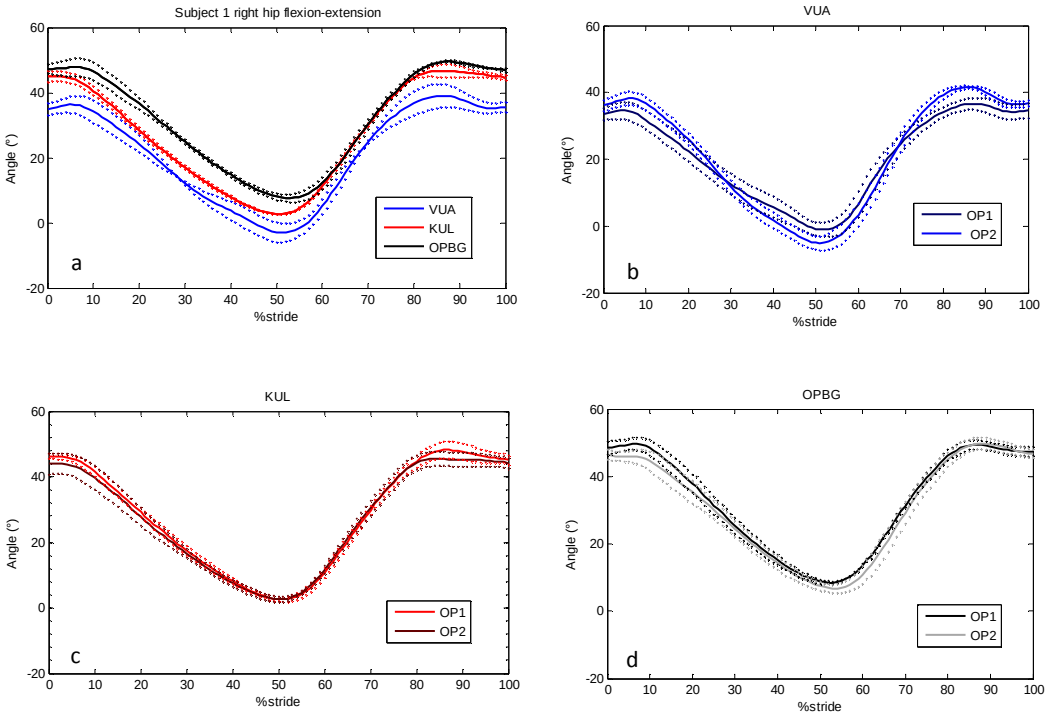


Figure 16 – Mean and standard deviation of normalized on stride hip flexion/extension of subject 1 *between laboratories* (a) and *within laboratory* (b, c, and d).

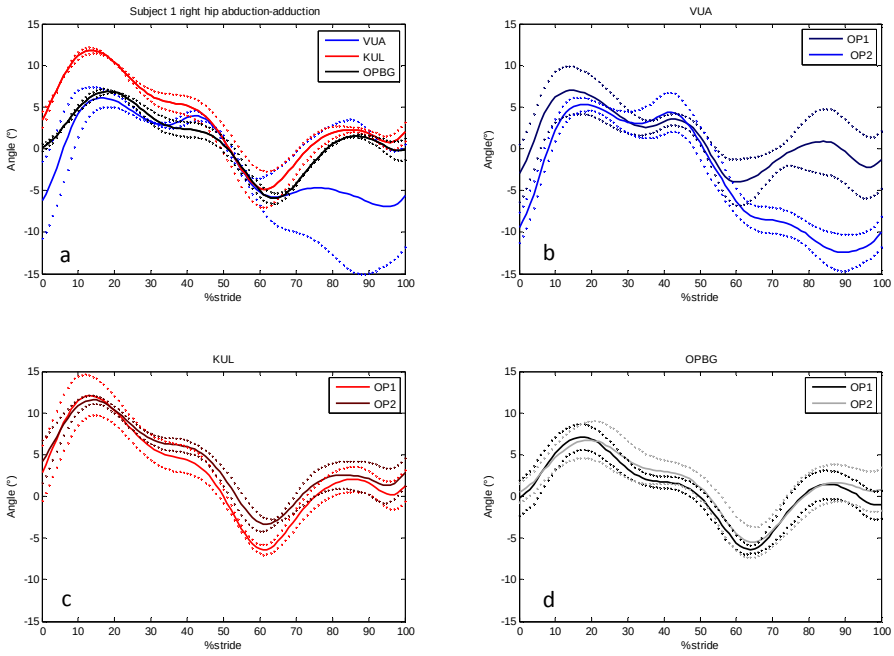


Figure 17 - Mean and standard deviation of normalized on stride hip abduction/adduction of subject 1 *between laboratories* (a) and *within laboratory* (b, c, and d).

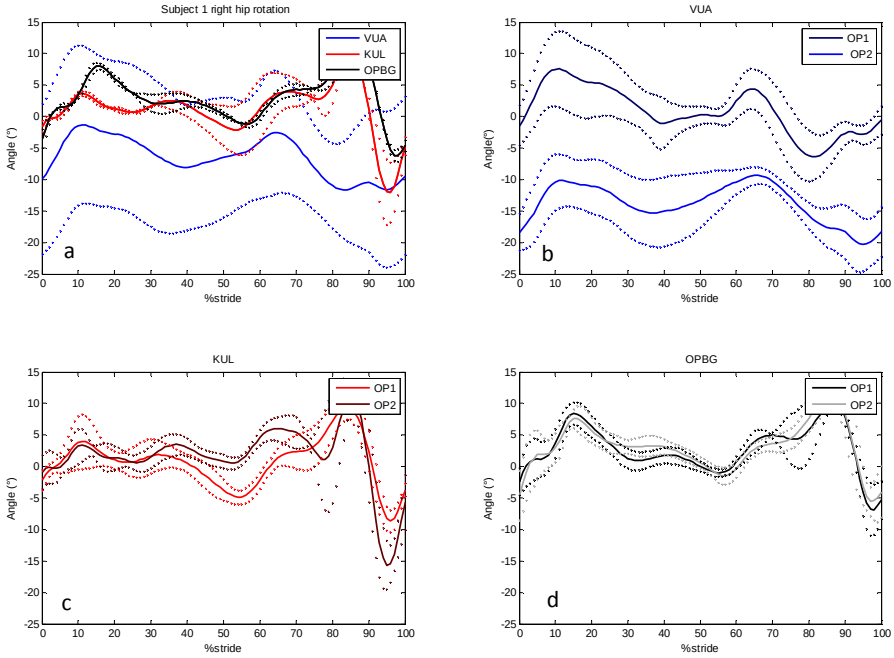


Figure 18 - Mean and standard deviation of normalized on stride hip rotation of subject 1 *between laboratories* (a) and *within laboratory* (b, c, and d).

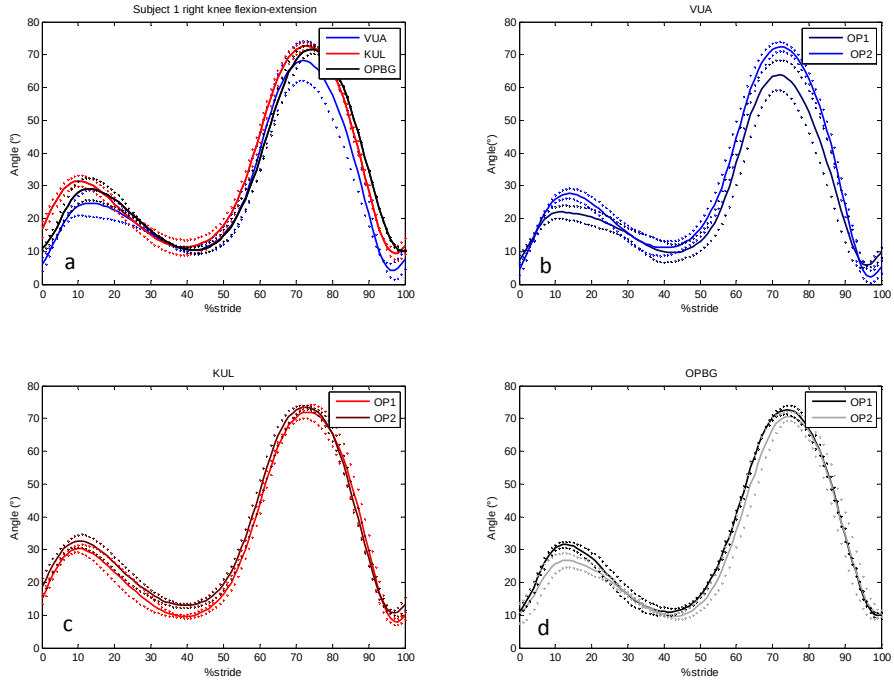


Figure 19 - Mean and standard deviation of normalized on stride knee flexion/extension of subject 1 *between laboratories* (a) and *within laboratory* (b, c, and d).

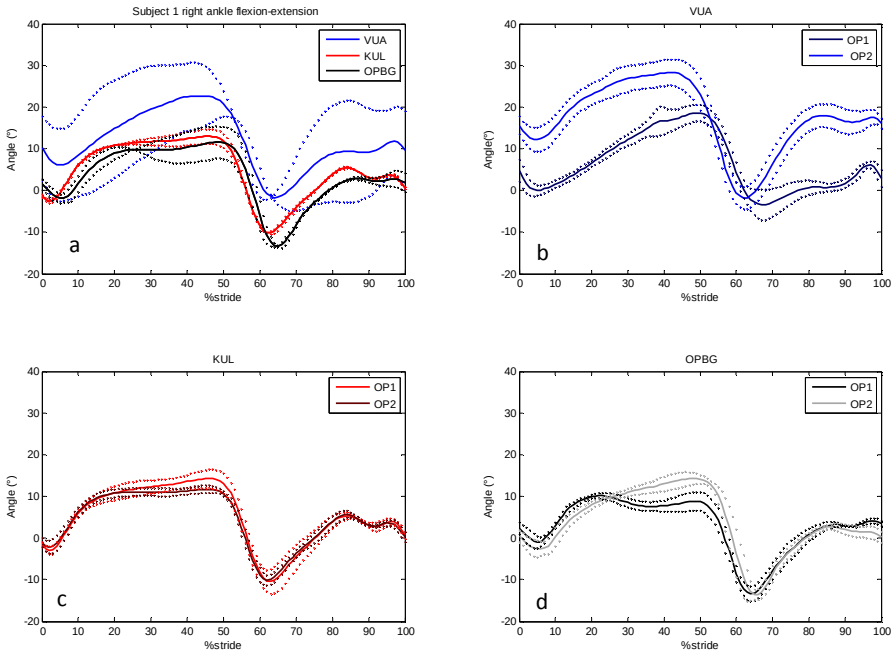


Figure 20 – Mean and standard deviation of normalized on stride ankle flexion/extension of subject 1 *between laboratories* (a)and *within laboratory* (b, c, and d).

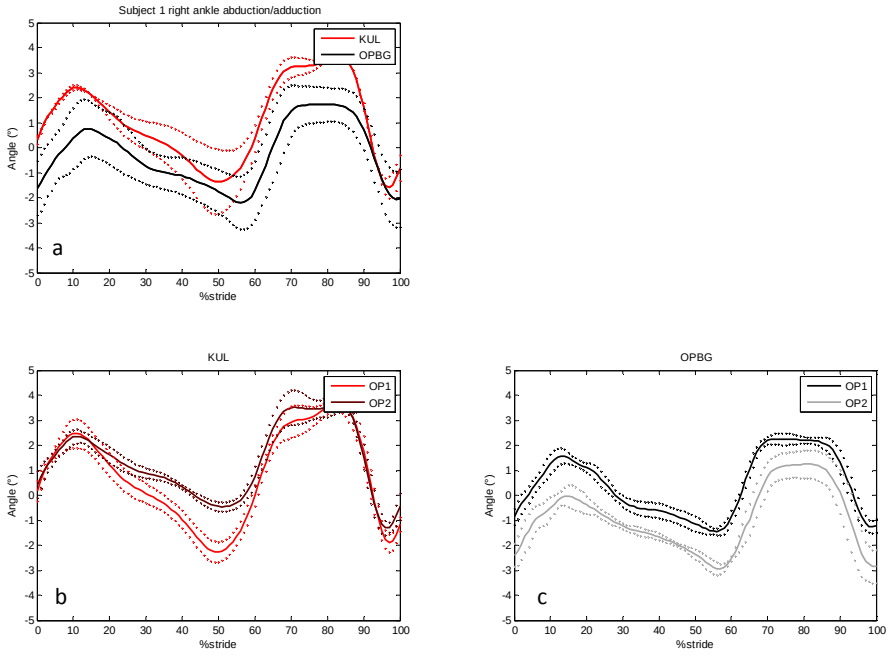


Figure 21 - Mean and standard deviation of normalized on stride ankle abduction/adduction of subject 1 *between laboratories* (a) and *within laboratory* (b and c).

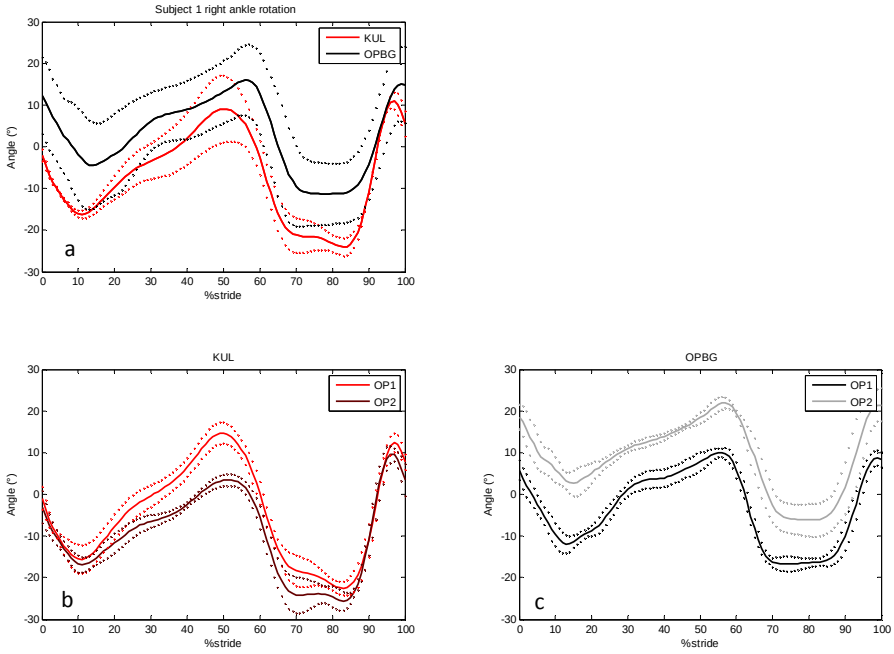


Figure 22 - Mean and standard deviation of normalized on stride ankle rotation of subject 1 *between laboratories* (a) and *within laboratory* (b and c).

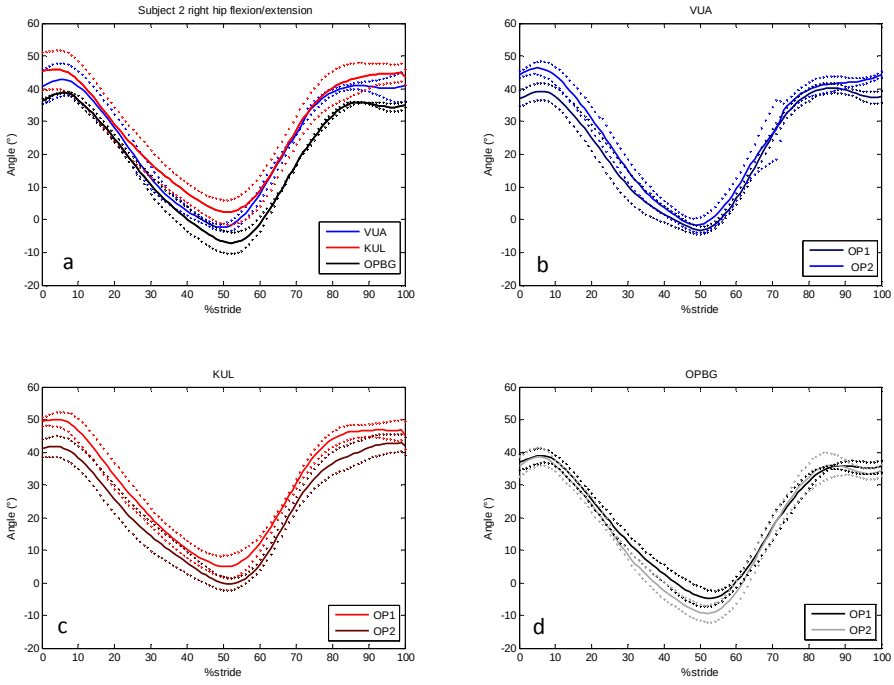


Figure 23 - Mean and standard deviation of normalized on stride hip flexion/extension of subject 2 *between laboratories* (a) and *within laboratory* (b, c, and d).

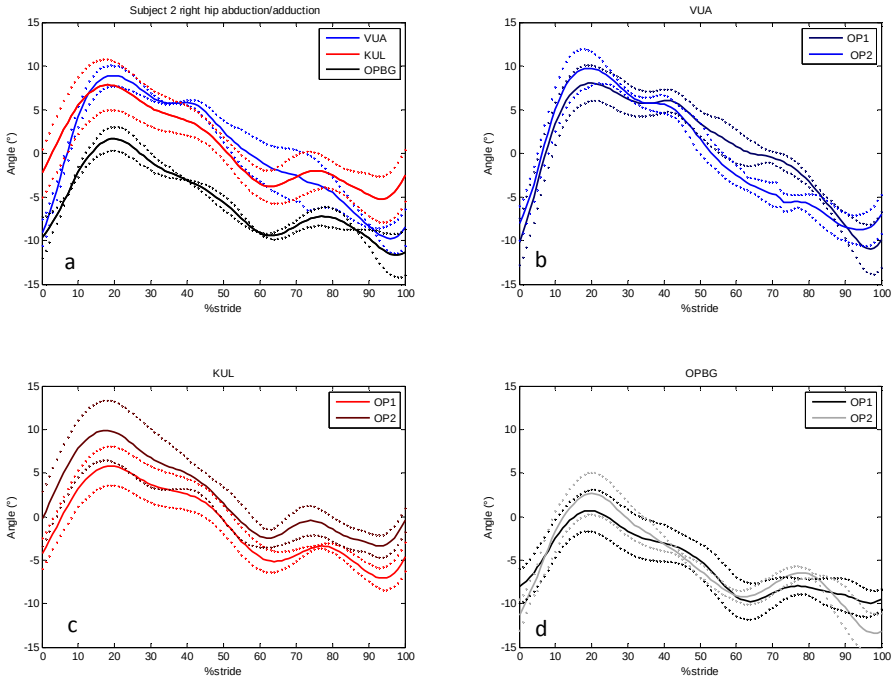


Figure 24 - Mean and standard deviation of normalized on stride hip abduction/adduction of subject 2 *between laboratories* (a)and *within laboratory* (b, c, and d).

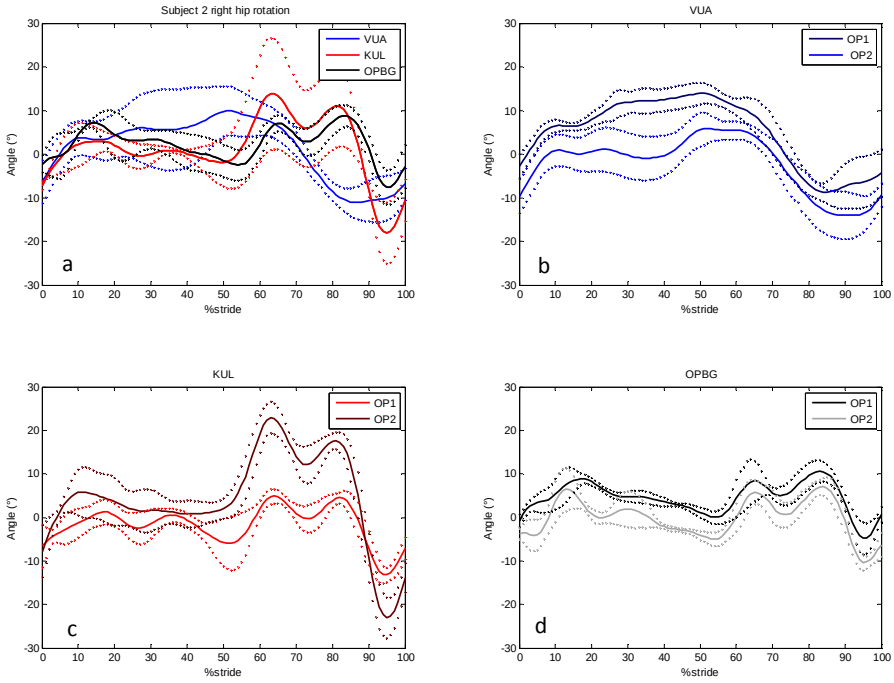


Figure 25 – Mean and standard deviation of normalized on stride hip rotation of subject 2 *between laboratories* (a)and *within laboratory* (b, c, and d).

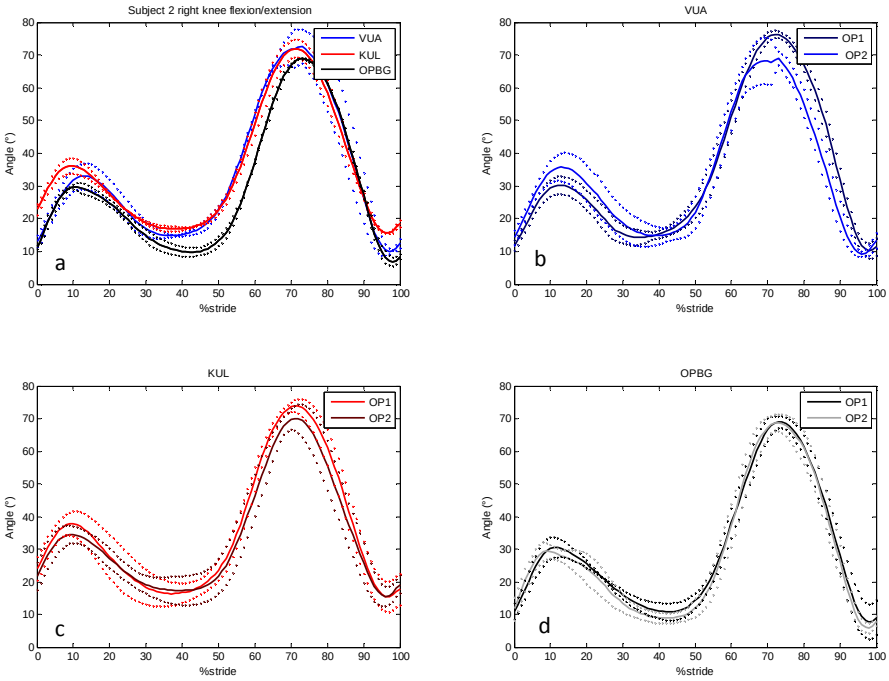


Figure 26 – Mean and standard deviation of normalized on stride knee flexion/extension of subject 2 *between laboratories* (a)and *within laboratory* (b, c, and d).

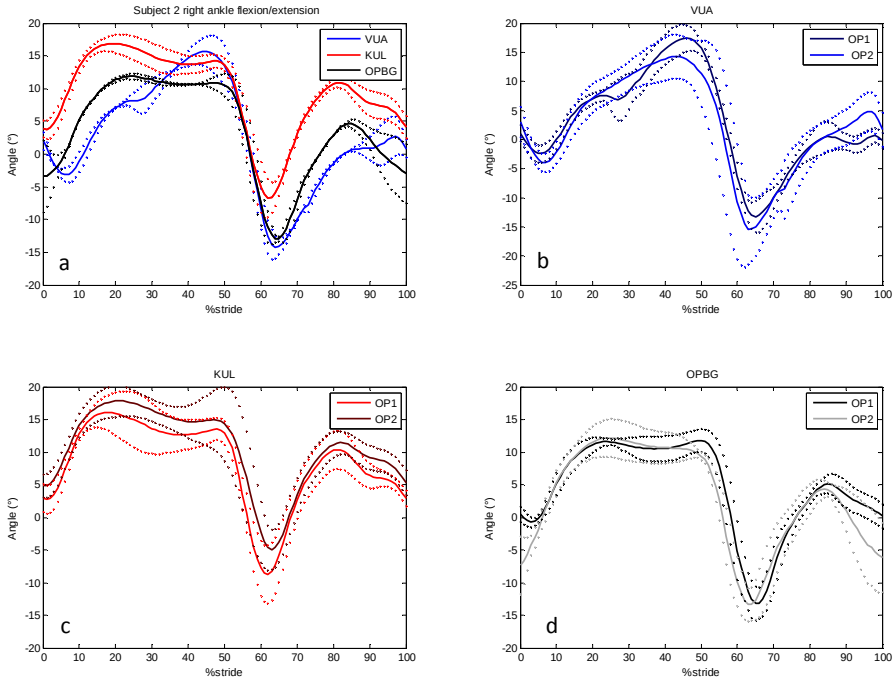


Figure 27 – Mean and standard deviation of normalized on stride ankle flexion/extension of subject 2 *between laboratories* (a)and *within laboratory* (b, c, and d).

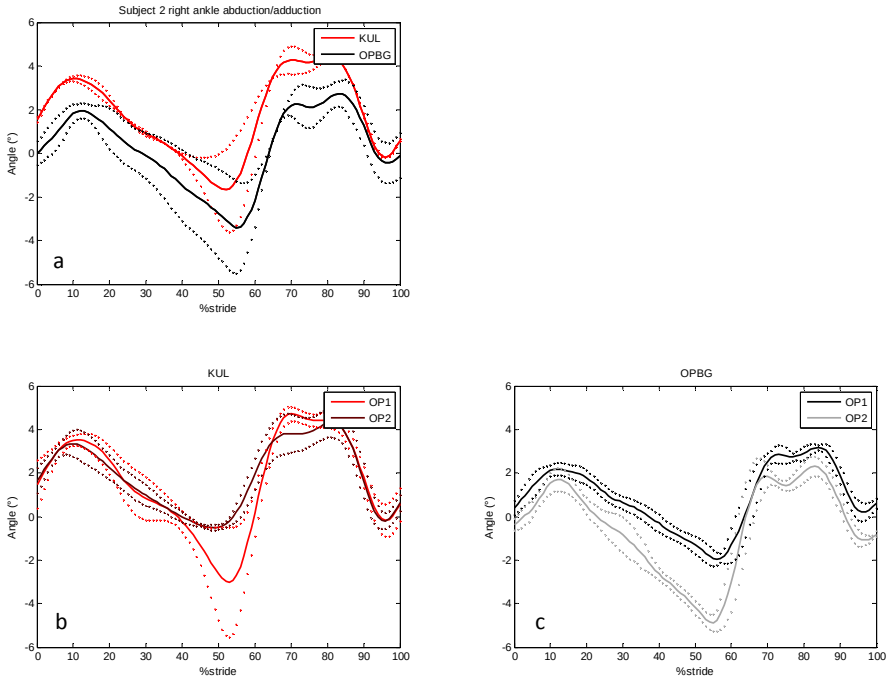


Figure 28 – Mean and standard deviation of normalized on stride ankle abduction/adduction of subject 2 *between laboratories* (a) and *within laboratory* (b and c).

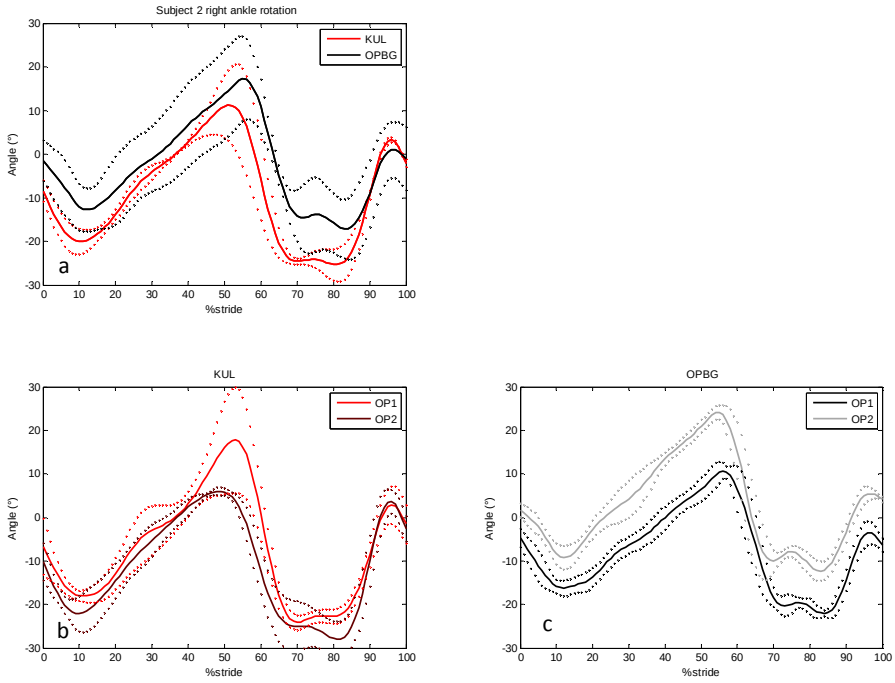


Figure 29 – Mean and standard deviation of normalized on stride ankle rotation of subject 2 *between laboratories* (a) and *within laboratory* (b and c).

In the sagittal plane, the repeatability of joint angle motion of hip and knee were excellent both *within laboratory* as well as *between laboratories* for both subjects (Figure 16, Figure 19, Figure 23 and Figure 26) and good for ankle joint (Figure 20 and Figure 27). Instead the repeatability in the frontal and transverse plane was lower than that in the sagittal plane (Figure 17, Figure 18, Figure 21, Figure 22, Figure 24, Figure 25, Figure 28 and Figure 29).

Kinetic variables

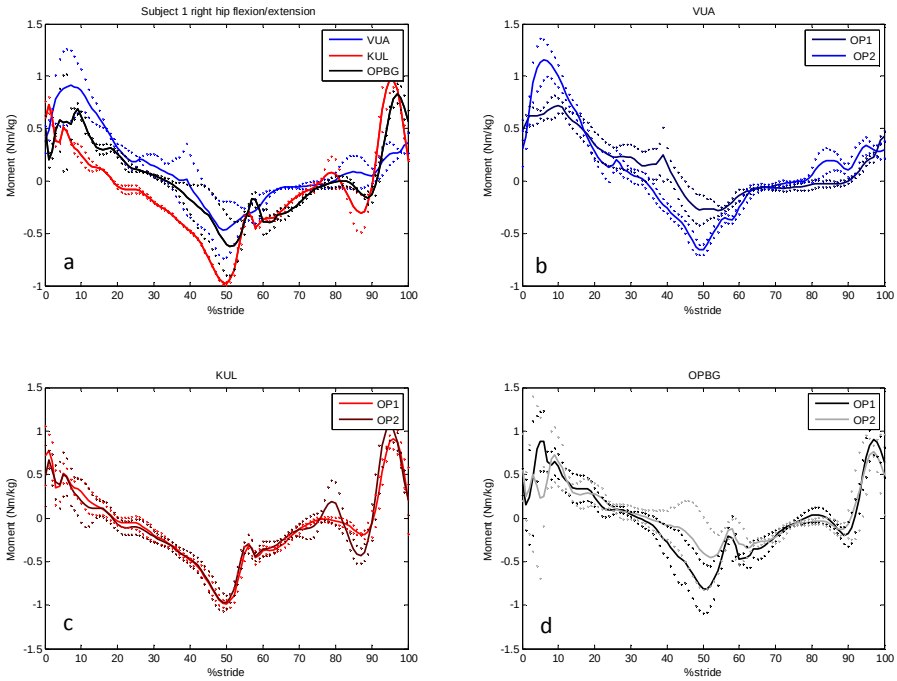


Figure 30 – Mean and standard deviation of normalized on stride hip moment flexion/extension of subject 1 *between laboratories* (a) and *within laboratory* (b, c, and d).

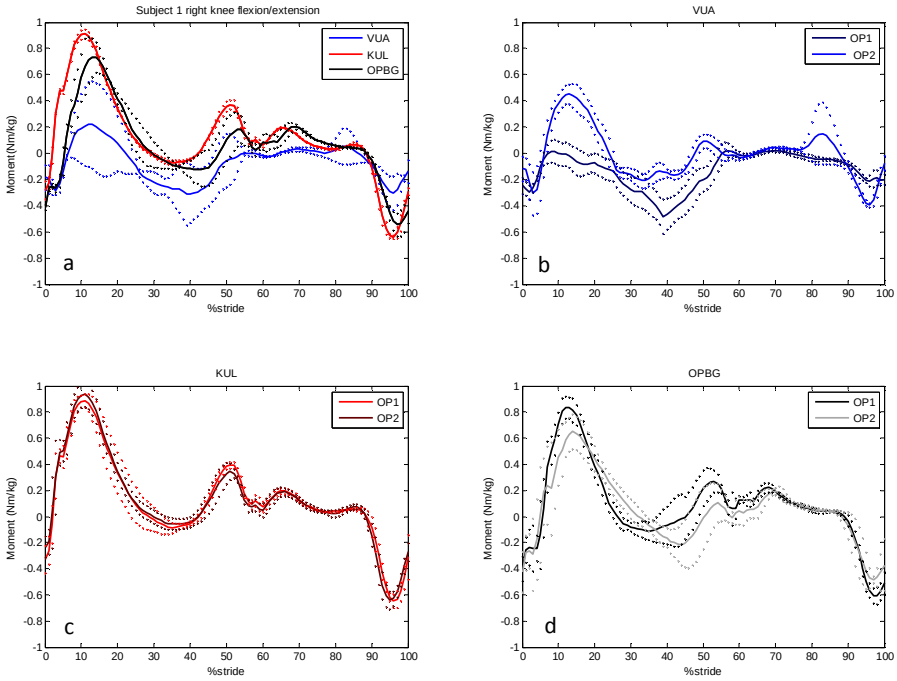


Figure 31 – Mean and standard deviation of normalized on stride knee moment flexion/extension of subject 1 *between laboratories* (a) and *within laboratory* (b, c, and d).

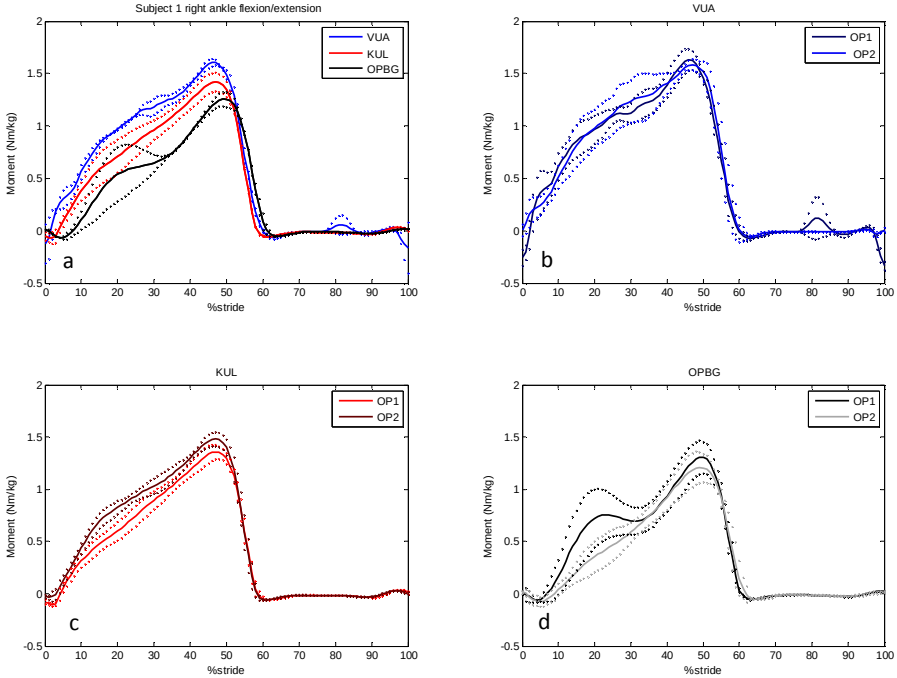


Figure 32 – Mean and standard deviation of normalized on stride ankle moment flexion/extension of subject 1 *between laboratories* (a) and *within laboratory* (b, c, and d).

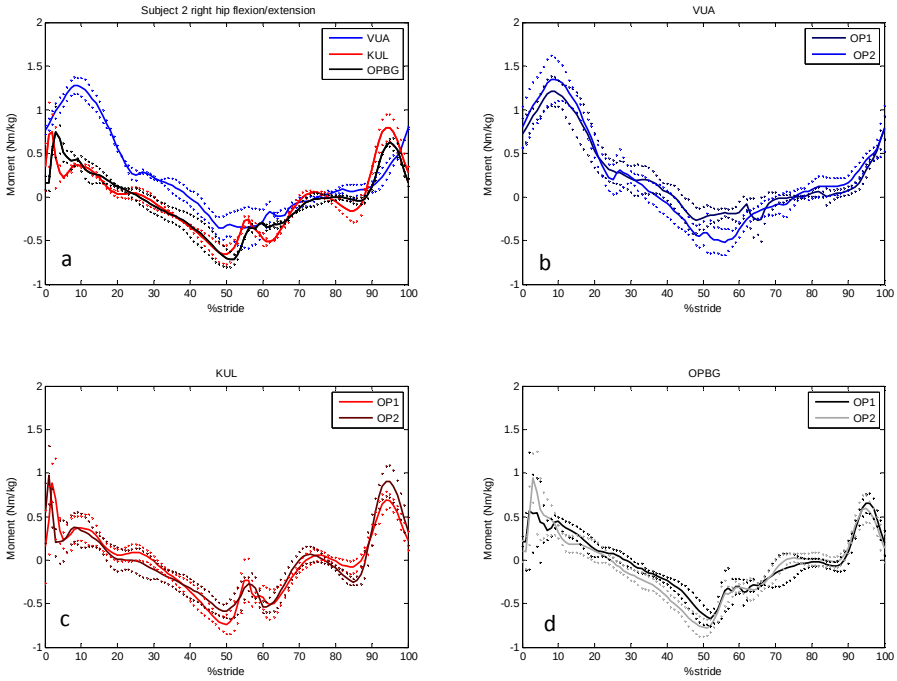


Figure 33 – Mean and standard deviation of normalized on stride hip moment flexion/extension of subject 2 *between laboratories* (a) and *within laboratory* (b, c, and d).

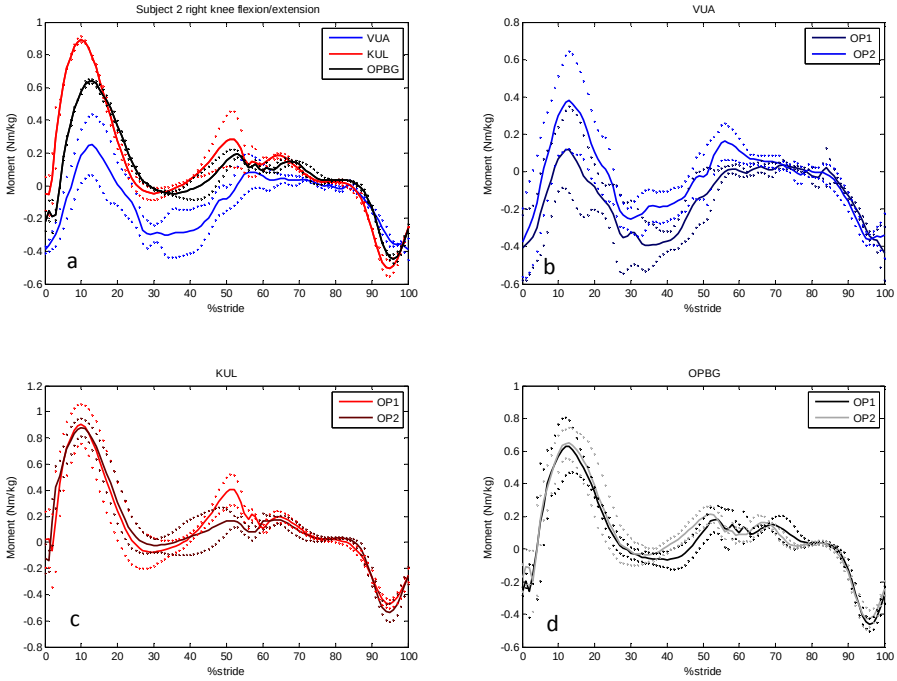


Figure 34 – Mean and standard deviation of normalized on stride knee moment flexion/extension of subject 2 *between laboratories* (a) and *within laboratory* (b, c, and d).

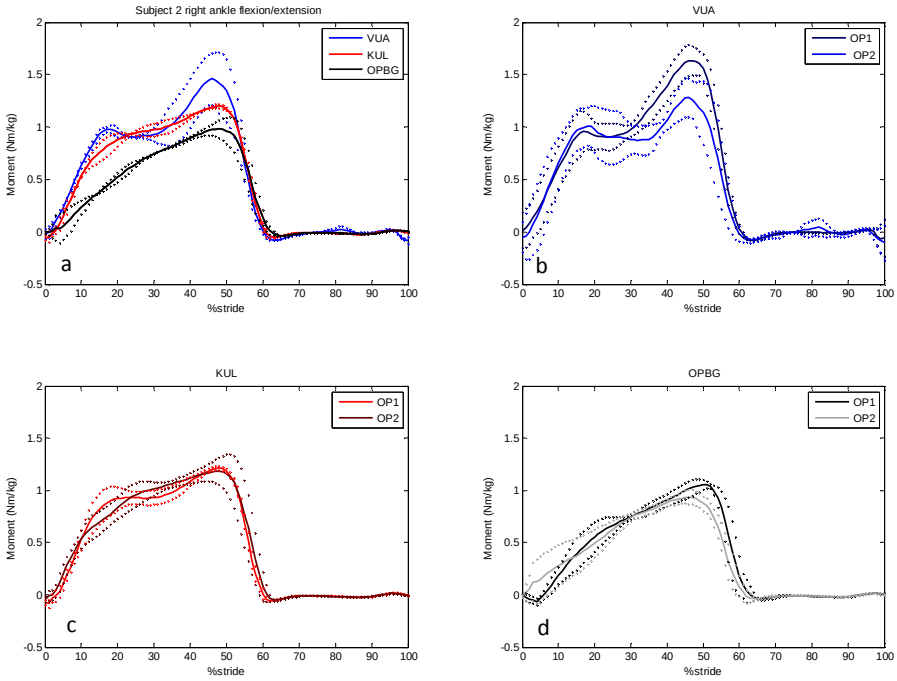


Figure 35 - Mean and standard deviation of normalized on stride ankle moment flexion/extension of subject 2 *between laboratories* (a) and *within laboratory* (b, c, and d).

The *within laboratory* repeatability in VUA of the moment at knee was lower than ankle and hip moment in both subjects (Figure 31 and Figure 34). The repeatability *between laboratories* was lower than the repeatability within laboratory, however always in the range of a good repeatability.

Appendix 2: Detailed status of data collection

NND OPBG																	
Patient Reference	Standardised anamnesis	Standard clinical exam	CGA: Kinematics	CGA: Kinetics	CGA: sEMG	HHD	MRI	O2	6 minutes walk test (6MWT)	electrocardiographic	echocardiographic	North Star Ambulatory Assessment (NSAA)	CMTpediatricScale	Xrays (if applicable)	Complete Acquired	Complete Integrated	GOAL
TOTAL OVERALL	69	30	69	68	63	28	22	25	28	8	8	8	8	0	69	0	
Total CP prospective extended	6	6	6	6	6	6	6	6	6	0	0	0	0	0	6	0	10
Total CP prospective clinical	8	8	8	8	8	8	0	6	6	0	0	0	0	0	8	0	40
Total CP retrospective	39	0	39	38	33	0	0	0	0	0	0	0	0	0	39	0	200
Total DMD T0	8	8	8	8	8	6	8	7	8	8	8	8	0	0	8	0	10
Total DMD T1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
Total CMT T0	8	8	8	8	8	8	8	6	8	0	0	0	8	0	8	0	10
Total CMT T1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10

NND KUL																	
Patient Reference	Standardised anamnesis	Standard clinical exam	CGA: Kinematics	CGA: Kinetics	CGA: sEMG	HHD	MRI	O2	6 minutes walk test (6MWT)	electrocardiographic	echocardiographic	North Star Ambulatory Assessment (NSAA)	CMTpediatricScale	Xrays (if applicable)	Complete Acquired	Complete Integrated	GOAL
TOTAL OVERALL	113	113	113	96	101	0	0	2	0	0	0	0	0	0	113	0	490
Total CP prospective extended	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
Total CP prospective clinical	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	0	40
Total CP retrospective	111	111	111	94	99	0	0	2	0	0	0	0	0	0	111	0	400
Total DMD T0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
Total DMD T1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
Total CMT T0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
Total CMT T1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10

NND VUMC																	
Patient Reference	Standardised anamnesis	Standard clinical exam	CGA: Kinematics	CGA: Kinetics	CGA: sEMG	HHD	MRI	O2	6 minutes walk test (6MWT)	electrocardiographic	echocardiographic	North Star Ambulatory Assessment (NSAA)	CMTpediatricScale	Xrays (if applicable)	Complete Acquired	Complete Integrated	GOAL
TOTAL OVERALL	6	6	8	8	8	1	1	1	0	0	0	0	0	0	9	0	50
Total CP prospective extended	0	0	1	1	1	0	1	0	0	0	0	0	0	0	1	0	10
Total CP prospective clinical	5	5	5	5	5	0	0	0	0	0	0	0	0	0	5	0	40
Total TD reference data	1	1	2	2	2	1	0	1	0	0	0	0	0	0	4	0	20