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A Novel Tool for the Detection of Osteochondral Defects in the Ankle Joint

TU Delft

A Novel Tool for the Detection of Osteochondral Defects in the Ankle Joint

By

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J.W. Zonneveld, Dr. Ir. G.J.M. Tuijthof, M. Stijntjes MSc, Prof. Dr. J. Dankelman

Abstract

Introduction. Ultrasound is known for cheap, fast and non-invasive diagnosis of numerous injuries. Sport-related injuries in the ankle joint and rehabilitation after surgical intervention are badly diagnosable using traditional ultrasound. Bones surrounding the surface of the articular cartilage blocks the ultrasound pulse and hides the talar surface where most injuries occur. Ultrasound wave propagation shows potential to be used in cheap, fast and non-invasive diagnosis of the cartilage regeneration after surgical intervention. The proposed technique uses a transmitter to send a pulse into the ankle joint whereas a transceiver records the propagated pulse on the other side. The recorded ultrasound wave contains information about the size and location of a lesion in the articular cartilage. Aim of this study is to collect the boundary conditions needed for ultrasound wave propagation through the ankle joint and quantify background noise, system noise and minor deviations of the transceiver on the recorded signal. Finally a novel coordinate system is proposed for the reliable recording of a propagated ultrasound pulse. *Methods*. Three sets of experiment were performed. Experiment 1 aimed to develop a procedure for consistent recording of an ultrasound wave propagated through the ankle joint. Using traditional ultrasonography the angle of the lower leg and the location of the transmitter and transducer was selected. Experiment 2 aimed to quantify the influence of background noise, system noise, and minor deviations of the transceiver on the recorded pulse. Influence was expressed in the normalized root of the mean square error (NRMSE) and the normalized mean cross correlation (NMCC). Using a robotic arm, displacements up to ±0.5 mm and rotations up to ±0.5° were made from the initial position. Experiment 3 aimed to test a novel coordinate system for the reliable recording of the propagated pulse in multiple recording sessions. *Results.* All three experiments were successful. The procedure resulting from experiment 1 is: angle of the tibia must be 73° relative to horizontal, ultrasound transmitter must be positioned on the posteromedial portal, and the ultrasound transceiver on the anterocentral portal, the forces of the probes on the skin must not exceed 15 Newton. This procedure has successfully been used in experiment 2 and 3. Experiment 2 quantified the background noise in the system to be white with a maximum value of -158 dB. System noise expressed in the NRMSE was between 0.2% and 4.9%. NMCC was between 0.9994 and 0.7147. Influence of displacements of the transceiver was up to a NRMSE of 5% and a NMCC of 0.6941. Rotation influence expressed in the NRMSE was up to 13%, NMCC was 0.7010. The novel coordinate system tested in experiment 3 repeated the recording with a NRMSE up to 34.1% and a NMCC as low as 0.2050. *Conclusion.* Background and system noise of ultrasound wave propagation through the ankle joint has been quantified. The influence of minor displacement and rotations of the transceiver on the recording of the propagated ultrasound pulse have been quantified. It provides us with knowledge of the position error needed to reproduce the results. Increased signal transfer between the transmitter and transceiver is needed for better signal analysis and assessment of the cartilage diagnosis. Ultrasound wave propagation through the ankle joint is possible and could be a new area of diagnosing and monitoring cartilage damage or regeneration.

Keywords: Osteochondral defect, ultrasound wave propagation, sensitivity analysis, cartilage regenerations.

Introduction

Every year over 15 million people in western countries suffer from a sprained ankle (1). Frequently these sprains result in torn ligaments (2). In some cases, a piece of cartilage in the ankle joint is damaged. This is characterized by a fissure or a (osteo)chondral lesion. Symptoms of these injuries are a painful and swollen ankle joint, increased stiffness and a limited range of motion (3). In case there is a small lesion in the cartilage, it is likely that this will not be diagnosed when the sprained ankle is presented at the emergency room. This because the surrounding tissue, such as the ligaments causes pain, which will draw the attention of the medical professionals to the swollen tissue. In cartilage, pain sensors are absent, and the damage could be so small that it is difficult to diagnose. A rough estimation is that every year one million of the 15 million ankle sprains sustain accompanying cartilage lesion in the ankle joint (4). These are a precursor of the development of larger osteochondral defects (OCD) and posttraumatic arthritis (Figure 1) (4). These trauma's may need surgical intervention and cause a longer rehabilitation and have a huge socio-economic burden on society (5).

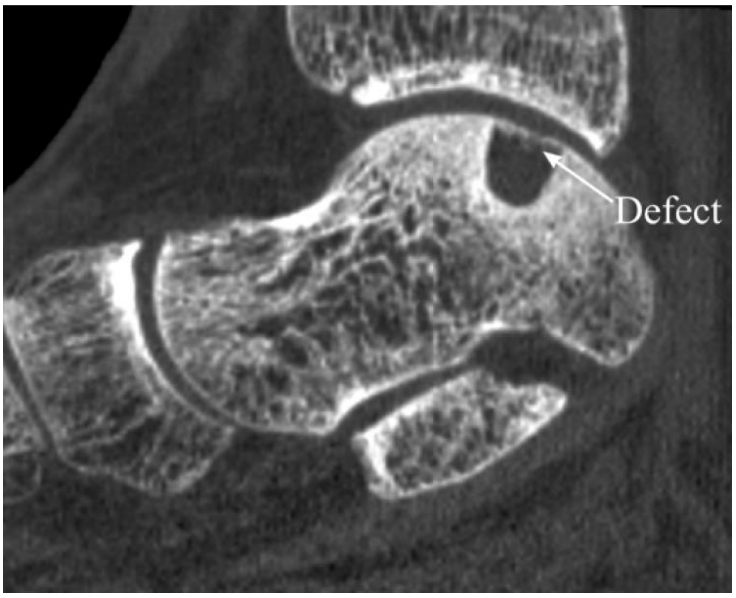

Figure 1. CT-scan of an osteochondral defect. A small lesion in the articular cartilage on the talar surface can erode to an osteochondral defect with bone loss as indicated by the arrow.

With surgical intervention the damaged cartilage is removed. Aim of the surgical intervention is to create micro-fractures by drilling holes in the surrounding area (6). These drillings create bleedings in the micro-fractured area. During rehabilitation these micro-fractured areas regenerate into new cartilage (3). Motion exercise and progressive weight bearing stimulates the regeneration of the cartilage (7, 8).

Cartilage does not contain a blood supply network, so all supplements needed for regeneration are transported through loading and unloading of the joint. This process is still not well understood (9). Conventional techniques for monitoring of the cartilage regeneration are Magnetic Resonance Imaging (MRI),Computer Tomography (CT) and diagnostic arthroscopy (10). However, all these techniques present some limitations if they are used in the longitudinal monitoring of the regeneration after a surgical intervention; they are expensive, time inefficient, invasive, and they lack resolution to detect cartilage lesions smaller than 0.5 mm (3).

In comparison, ultrasonography is able to detect small lesions in a non-invasive, cheap and time-efficient way (11). A restricting factor is that ultrasound is not able to penetrate the tibia and fibula surrounding the main cartilage surface of the talar bone, limiting the diagnosable area (Figure 2) (12, 13). Ultrasonography is, despite the limitations, an interesting medium to further explore for longitudinal monitoring of patients.

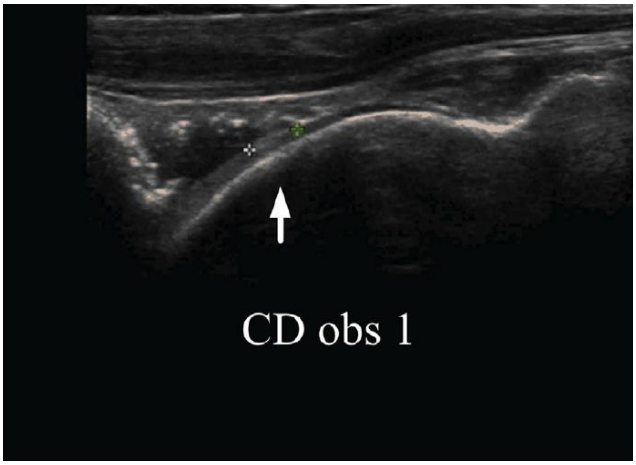

Figure 2. Ultrasound image of the ankle joint. The arrow indicates a defect in the cartilage. The visible cartilage surface is limited by the tibia which surround more than 60% of the talar surface. Source: Tuijthof et al. 2014 (11).

The reflection of an ultrasound (US) pulse is used in medical ultrasonography. This limits the visible area if the US pulse hits an impenetrable barrier (e.g. bone). A different application of US is wave propagation instead of wave reflection. A US pulse can propagate through the ankle joint and be used for medical purposes (14, 15). The broader end goal of this research is to be able to use wave propagation for the longitudinal monitoring of cartilage regeneration. We hypothesize that a US pulse propagated though the ankle joint space changes over time because the regenerated cartilage changes the shape of the ankle joint space. Comparing these two results provides information about the regeneration of the cartilage; thus marking cheap, non-invasive, fast and accurate assessment of the cartilage regeneration process possible.

Using this method, wave propagation can be used to monitor longitudinal regeneration after surgical intervention. The concept of wave propagation through the ankle joint space to assess the cartilage regeneration and monitor its repair is entirely new and only proven in theory (15). The practical feasibility is only based on small scale experiments performed by researchers. A US transmitter is positioned on the posterior side of the ankle joint and a US transceiver (US probes) on the anterior side (Figure 3). In some cases a wave propagated through the ankle joint space (US response) can be detected. However, these small scale experiments lacks consistency in detecting the US response.

Research question.

The exact boundary conditions for a consistent recording of a US response are unknown. First, what is the angle of the lower leg? Where do the US probes need to be positioned and under what angle? How much force must be applied between the US probe and the skin? Secondly, for reliable repeated recording, the difference between a primary and secondary US response must be as small as possible for optimal signal analysis. Since acoustic wave propagation

through the human ankle joint is an entirely new topic, knowledge about the presence and influence of noise on the recordings is missing. Thirdly, during a secondary recording, the position and orientation of the US probes around the ankle joint must be in the same configuration as the primary recording. Reproducing the position of objects inevitably introduces position errors. The influence of this position error is unknown.

The aim of this research is to set up the requirements for a device that is able to repeat the recording of a US response through the ankle joint space with a high reliability.

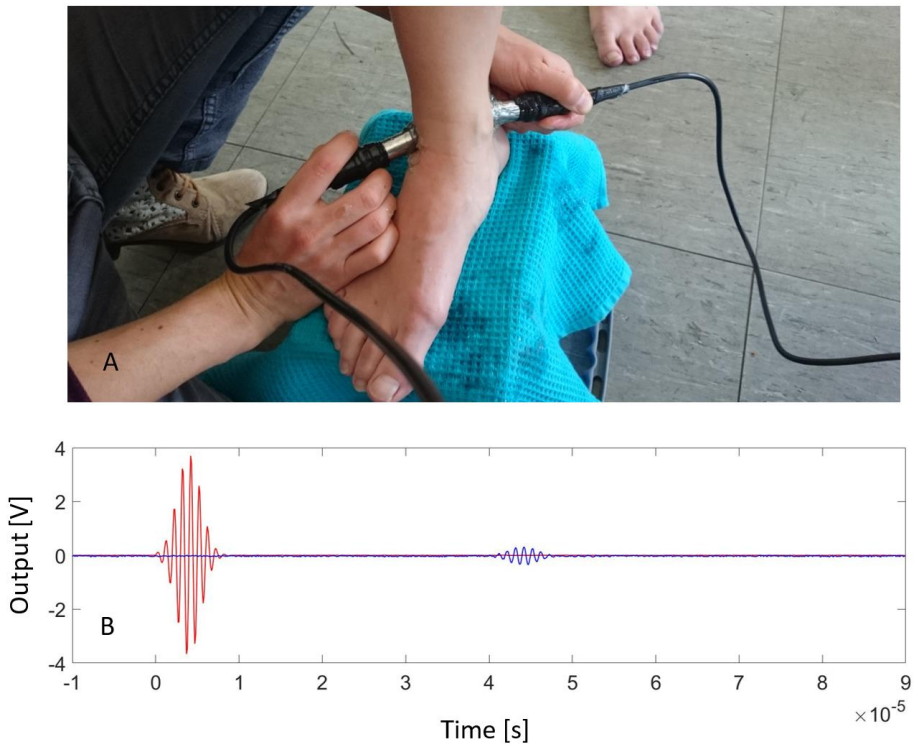

Figure 3. A) Setup of the US probes positioned around the ankle joint. The US transmitter is positioned on the posterior side of the ankle joint, the US transceiver is positioned on the anterior side. B) The red line indicates the input signals, a 1 MHz pulse. The blue line indicates the US response as measured by the US transceiver.

Methods

Throughout this study, three sets of experiments were performed. The first experiment aimed to develop a procedure for consistently recording the US response in each session. The second experiment includes a sensitivity analysis of US wave propagation through the ankle joint. Two smaller sub-experiments were performed as preparation for experiment 2. The third experiment tested a new technique for recording and reproducing the position of the US probes around the ankle joint. Data analysis of the experiments is explained in the end section of the methods.

Experiment 1. Procedure for consistent recording of US response.

The concept of US wave propagation through the ankle joint is proven in theory and on a Perspex reference model (15). However, the conditions in which a US pulse can be sent into the ankle joint space and be recorded on the other side are unknown. Aim of experiment 1 was to develop a procedure for consistently recording the US response in each session. A set of

parameters was recorded that provides the boundary conditions needed for consistently recording of a US response.

The ankle joint is surrounded by several layers of tissue, among them are arteries, veins and tendons. To minimize the influence of attenuation of the US pulse in the tissue, the US probes must be placed on a location with minimal tissue between the US probes and the joint space. Arthroscopic surgery is known for allowing access to the articular cartilage with instruments and with minimal damage to the surrounding tissue via surgical portals (Figure 4) (16). The surgical portals were used as locations to position the US probes around the ankle joint to reduce the amount of tissue between US probe and joint space.

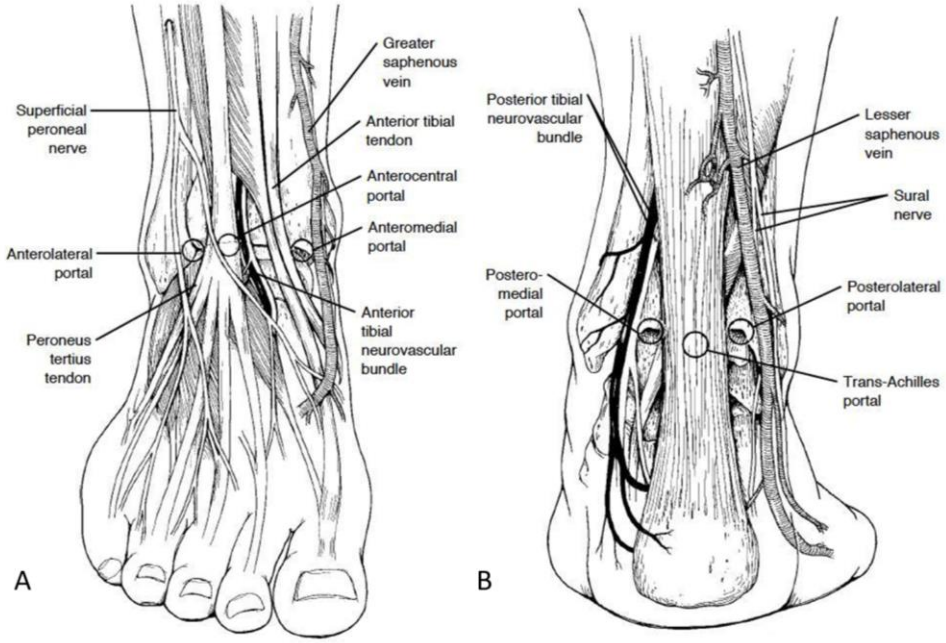

Figure 4. Tissue surrounding the ankle joint. A) shows the location of the anterior surgical portals indicated with the circles. B) shows the posterior surgical portals. The Trans-Achilles portal in B is not used for US wave propagation. Picture from: Oliva et al, 2015 (15).

Plantar- and dorsiflexion influences the opening of the ankle joint space on the anterior and posterior side. For optimal acoustic wave propagation, the opening of the joint space needs to be as large as possible. Plantar flexion opens the joint gap on the anterior side, whereas dorsiflexion opens the joint gap on the posterior side. For recording of the US response, the angle of the lower leg must be such that both the posterior and anterior joint space are opened. Getting the US probe as close to the joint space as possible for minimal attenuation of the US pulse is done by compressing the surrounding tissue. The forces needed for optimal signal transfer between US probe and joint space are unknown.

Setup experiment 1.

The experimental setup (Figure 5) consist of two unfocused 1 MHz transducers with one being used a transmitter and one as receiver (Olympus V303, transducer diameter: 12.7 mm, Panametric Inc.,Waltham, MA, USA) an arbitrary wave generator (33250A,Keysight Technologies, Santa Rosa, CA,USA), and a digital scope (DSO7054A, Keysight technologies, Santa Rosa, CA, USA) with a sampling frequency of 5 MHz. Both US probes are mounted on a friction arm (244N, Manfrotto, Cassola, Italy) allowing for zero-stiffness movement when

positioning the probes, but high-stiffness when locked. The US transmitter is mounted in series with a load cell (LCM300, Futek Advanced Sensor Technology Ins., Irvana, CA, USA). Data acquisition of the load cell is done using an analog amplifier (Feteris CPJ2S, Scaime, Juvigny, Franc) and a DAQ-card (USB6008, National Instruments, Austin, TX, USA) connected to a Labview program (National Instruments, Austin, TX, USA). The participants were placed on a chair with their foot placed in a custom build frame (Figure 6). An ultrasonography transducer (12 MHz musculoskeletal) was used to find the location of the surgical portals. The angle of the lower leg was measured using a protractor placed on the tibia.

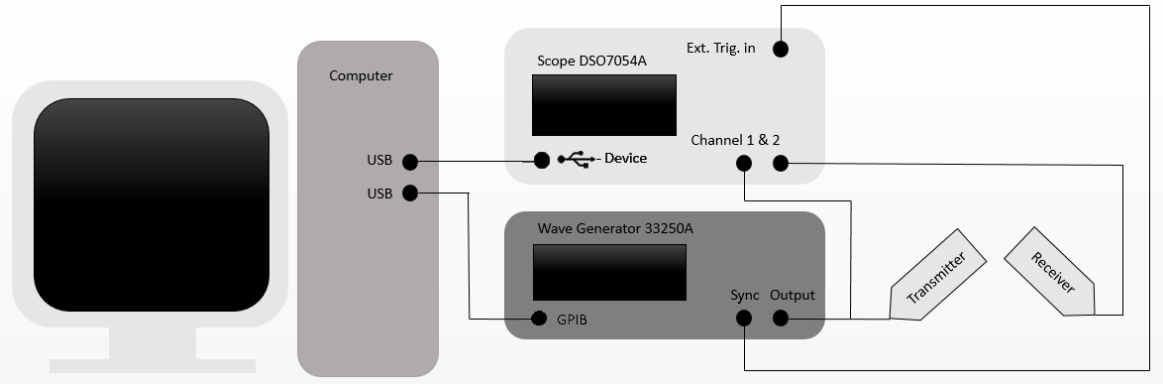

Figure 5. Setup scheme of the wave generator, US transmitter and transceiver and the digital scope. The digital scope and wave generator are clocked for a synchronized recording of the US pulse and response.

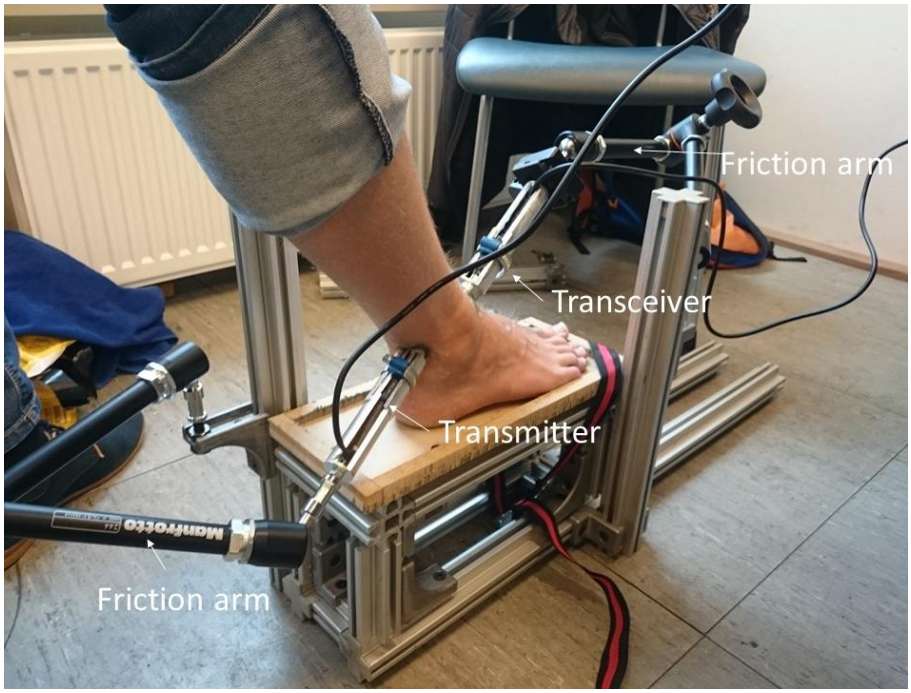

Figure 6. Setup of experiment 1. The US Probes are mounted on a friction arm, allowing for zero-stiffness movement when positioning the probes, but high stiffness when locked. In this picture the posterior probe is positioned on the posterolateral portal and the anterior probe on the anterocentral portal.

Protocol experiment 1.

7 participants joined experiment 1. Using ultrasonography, the lower leg was positioned in an angle such that both anterior and posterior joint space were opened. Subsequently, the US probes mounted on the friction arms were positioned on the surgical portal. The friction arms were locked when a US response was seen on the digital scope. From this point, the transmitter was excited by a short normally distributed pulse with a peak-to-peak voltage of 9V, a center frequency of 1 MHz, and a width of 4 µs (Figure 3). The following parameters were recorded: the angle of lower leg, the force applied by US transmitter on the skin and 5 US responses.

Experiment 2. Sensitivity analysis of US probe deviations on recorded US response.

Aim of experiment 2 was to quantify the influence of background and system noise, and minor displacements and rotations of the US probe on the recordings. As preparation of experiment 2, two smaller experiments were performed. A sensitivity analysis using computational software of wave propagation through the ankle joint and a pain versus force experiment containing the pain levels corresponding with the force applied by the US probe on the ankle joint. Aim of the computational sensitivity analysis was to provide an order of magnitude for the physical experiment. The results are provided in appendix A and indicated that a displacement of 0.1 mm and 0.5° in the relative positioning of the US probe was sufficiently large to prevent proper signal analysis of the US response. Aim of the force vs pain level experiment was to provide a safety requirement for experiment 2. The results are provided in appendix B and indicate that forces up to 150 N applied by the US probe on the skin do not result in damage.

Setup experiment 2

The experimental setup of experiment 2 (Figure 7) was largely similar as used in experiment 1. The US transceiver placed on the anterior side was mounted on a robotic arm (UR5, Universal Robots A/S, Odense, Denmark). The robotic arm is capable of performing deviations with an accuracy of ±0.1 mm and ±0.1°. Both US probes are mounted in series with a load cell similar as in experiment 1. Angle of the lower leg was measured using a protractor on the tibia, the angle of the US probe was measured post-experimentally using photo-analysis, and the distance between the US probes using a caliper.

Participant safety and Informed Consent.

The following safety limits were observed: Robot motion was limited to 2mm/min and 2°/min. Robot operation was interrupted if the normal forces applied on the tip of the robot would exceed 150 Newton. A protocol containing the safety features and the informed consent was approved by the Human Research and Ethics Committee (HREC) of the TU Delft. Protocol of the experiment is provided in appendix C, the Informed Consent is provided in appendix D.

Protocol experiment 2

Prior to the experiment, safety features were explained to the participants. 28 participants were placed on a chair with their foot and lower leg strapped to the frame. An ultrasonography transducer (12 MHz musculoskeletal) was used to locate and mark the posteromedial and anterocentral portal. Subsequently the US probes were positioned on the marked skin. Minor position adjustments were made manually if the US response was not obtained immediately. Following placement of the US probes, 5 recordings were obtained from a static situation.

Subsequently, displacements in steps of 0.1 mm were made laterally and medially up to +0.5 and -0.5 mm from the initial position. Rotation in steps of 0.1° were made laterally and medially up to +0.5° and -0.5° from the initial position (Figure 7). The following parameters were recorded: the angle of the lower leg, the force of the US probes on the skin, the distance between the probes, and the of angle probes.

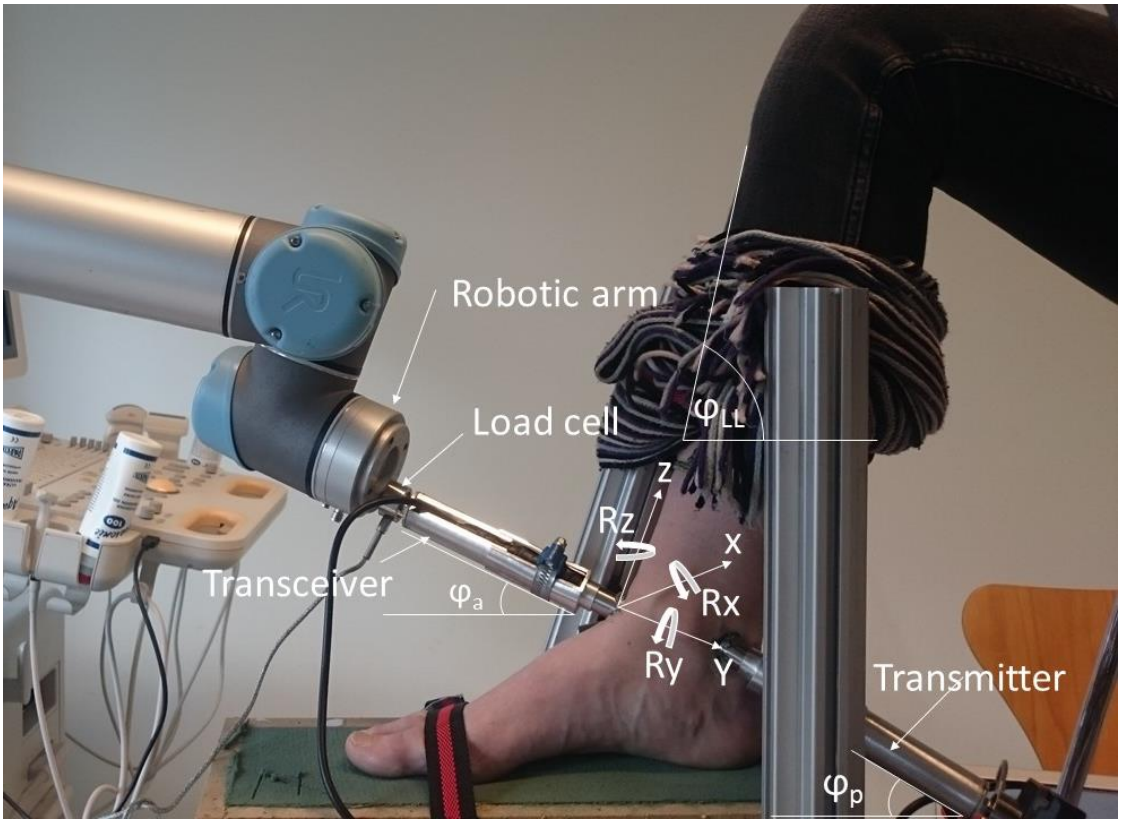

Figure 7. The US probe is mounted in series with a load cell to the robotic arm. Angle of the lower leg (φ_{LL}) is measured by a protractor on the tibia, and the angle of the probes (φ_a, φ_p) using post-experimental photo analysis. The coordinate system of the robotic arm originates at the tip of the probe. Displacements were in the X-axis, rotation around the Z-axis.

Experiment 3. Novel coordinate system

In order to repeat the US response measurement, both foot, lower leg and the US probes must be in the same configuration between different recording sessions. For reproducing the position of the ankle joint, the foot is positioned on a memory foam plate and the lower leg is strapped to a beam in a pre-specified angle of 73° (found in experiment 2). For reproducing the position of the US probes, a novel coordinate system is proposed. Figure 8 illustrates the working principle of the coordinate system.

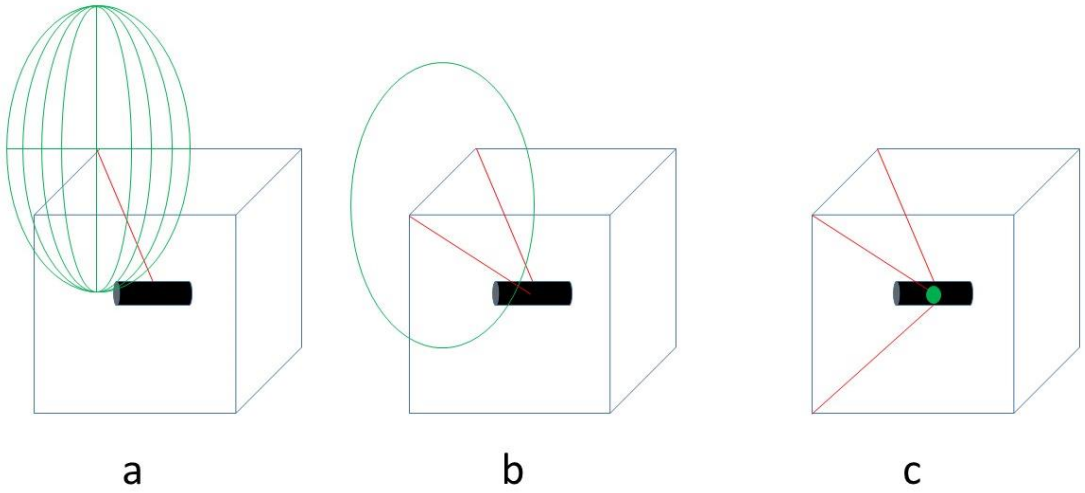

Figure 8. The working principle of the novel coordinate system. The US probe is attached to a friction arm and positioned manually in the frame (blue cube). a) A steel cord (red line) is attached to the frame and the US probe (black). With a tightened cord there is a sphere of all possible coordinates (green). b) Two steel cords are attached to the frame and the US probe. Now there is a circle of all possible coordinates when the cords are tightened. c) Three steel cords are attached to the frame and the US probe. Now there is only one possible position in the frame with the cords tightened.

The proposed method separated the coordinate system from the support system. Any deflections in the support system (e.g. friction arm) do not influence the recording of the position. However, forces applied by the user on the US probe do introduce deflections in the steel cords. To indicate the order of magnitude of the deflections, a worst case scenario loading of the cords was calculated. Worst case scenario was considered when all forces were held by one cord. Deflections in the steel cable are:

$$\Delta l = \frac{FL_0}{EA} \qquad \text{(Equation 1)}$$

Equation 1. Where Δl is the deflection introduced by force F, L_0 is the unloaded length of the steel cord (20 cm), E is the elastic modulus of steel (200 GPa) and A is the surface area of the steel cord ($\pi/4$ mm^2). For forces up to 80 N, the deflections are lower than 0.1 mm.

Following theoretical calculations of the deflections, a position reproducibility test was performed. A setup consisting of the custom built frame with a friction arm mounted on it was attached to the three metal cords (Figure 9). Passive reflectors were attached to the friction arm and the frame. The location of the reflectors on the friction arm were recorded using an optical tracking system (Polaris Spectra, NDI Medial, Waterloo, Ontario, Canada). The friction arm was positioned manually in the frame, locked and the cords were tightened. Position was recorded by three translation and three rotation coordinates of the optical tracking system. Subsequently, the friction arm was released and moved away from its position, the tension in the cords hereby released. All cords now have a fixed length. Reproducing of the primary position is now guided by the tightened cords. Once the cords were manually tightened by positioning the friction arm, it was locked and the position of the passive reflectors was obtained. This procedure was repeated 10 times.

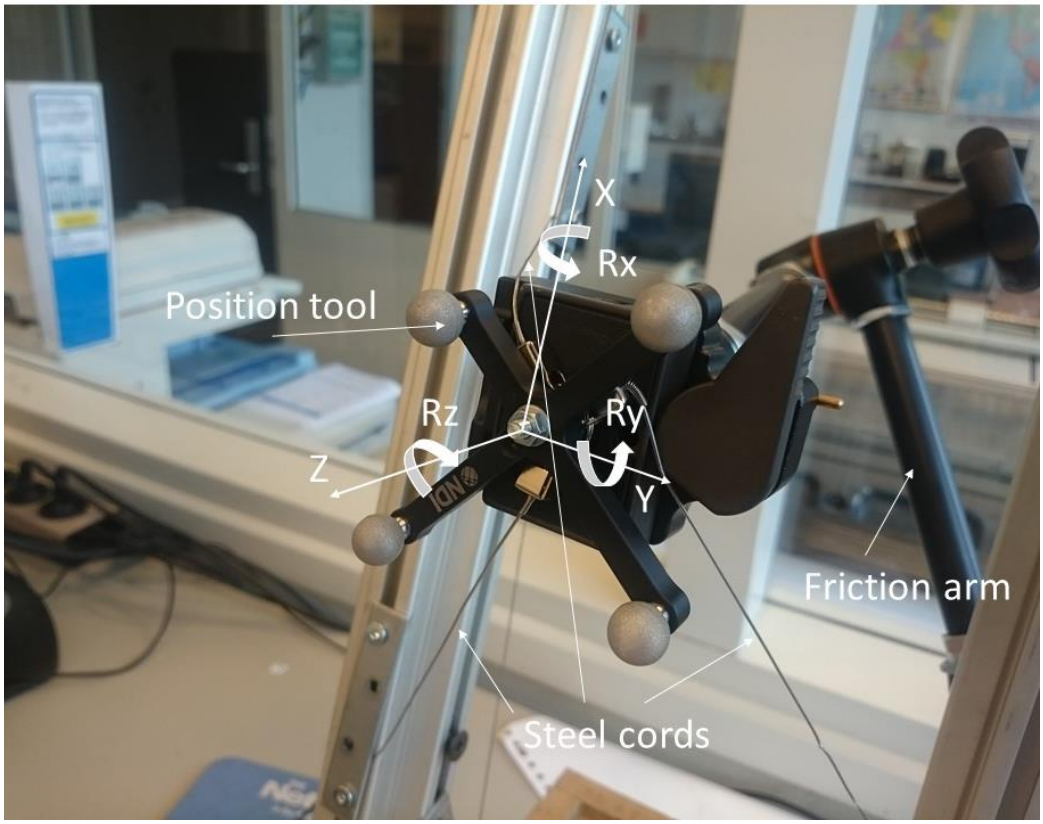

Figure 9. The friction arm with the passive reflectors mounted on the tip and attached to three metal cords. The position of the tool is recorded using 6 position parameters; the translations xyz and rotation around the axis Rx, Ry, Rz.

Position error between the 10 different positions was expressed in the absolute translation error (Equation 2) and relative rotation errors, Rx, Ry and Rz. Absolute error is defined as:

$$e_t = \sqrt{e_x^2 + e_y^2 + e_z^2} \qquad \text{(Equation 2)}$$

Equation 2. Translation error between the 10 different position. e_t = absolute translation error, e_x is the relative error in the x-direction, e_y is the relative error in the y-direction, e_z is the relative error in the z-direction.

Setup experiment 3.

The setup consist of a custom build frame containing a memory foam plate and a beam positioned in a pre-specified angle of 73° (Figure 10). The US probes are mounted on the same friction arms as used in experiment 1. The US transceiver positioned on the anterior side is connected to three steel cords (EG43, Card Vision, Rockanje, The Netherland). Inhibiting and recording of the US pulse and response is similar as in experiment 1 and 2.

Protocol experiment 3.

5 Participants were placed on a chair with their foot strapped to the frame and their foot sole firmly pressed in the memory foam. The lower leg is placed such that the tibia is parallel to the angled beam. The location of the anterocentral and posteromedial portal is found using the 12 MHz ultrasonography transducer and marked. Subsequently, the US probes are positioned on the marked skin. Following correct placement, the friction arms were locked and the three cords on the US transceiver were tightened. One US response was recorded. Following recording of the first US response, the US transceiver was removed from the foot by releasing the locking mechanism of the friction arm. The tension in the cords is released. Upon reproducing the position of the probe, the position is indicated by the length of the cords. A second US response was recorded. This was repeated 10 times.

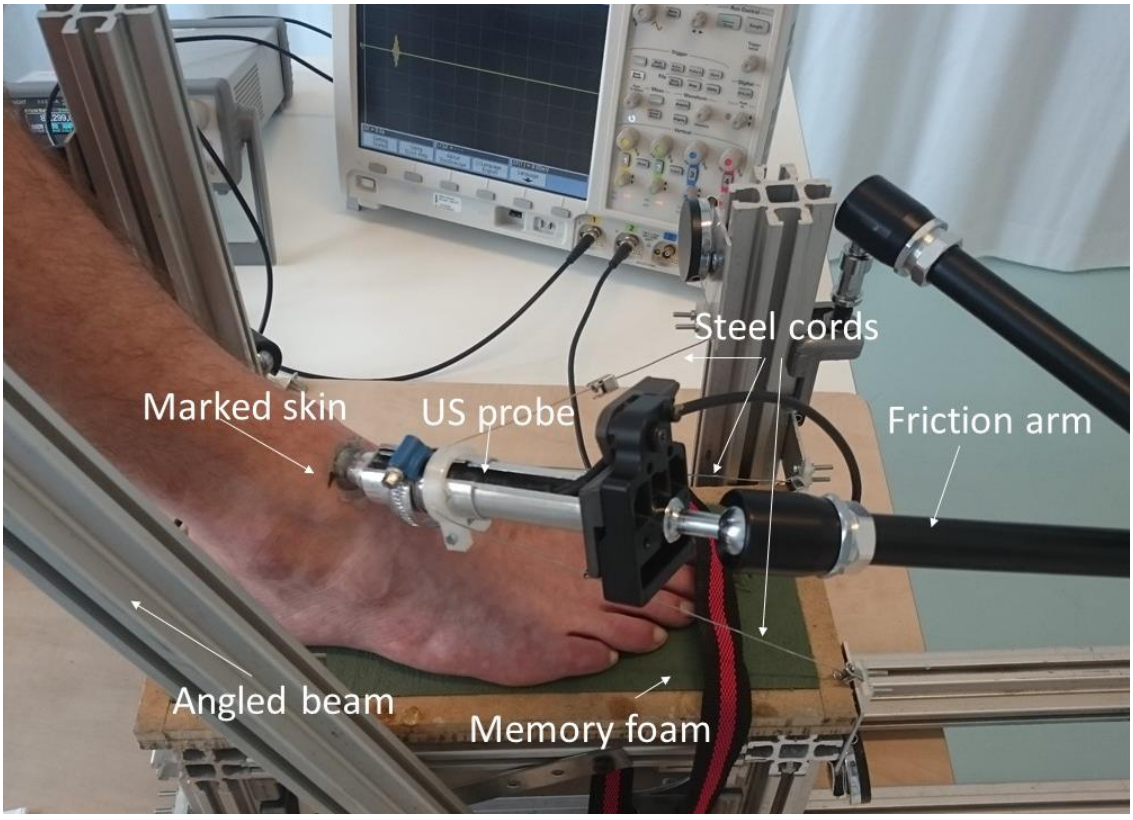

Figure 10. Picture of the prototype. The angled beam on the frame is set in an angle of 73°. The US transmitter is connected to three steel cords and tightened when positioned correctly. The tightened cords allow for reproducing of the initial position without considering deformations in the friction arm as introduced by the force between probe and skin.

Data analysis

The input US pulse of the system has a center frequency of 1 MHz and a normal distribution. The power of the input is -62 dB at the center frequency. The characteristics are shown in Figure 11. Frequencies with magnitudes differences of -40 dB relative to the magnitude of the center frequency were filtered using a 2nd order Butterworth filter and zero-phase filtering. The bandwidth of the filter was 0.69-1.32 MHz.

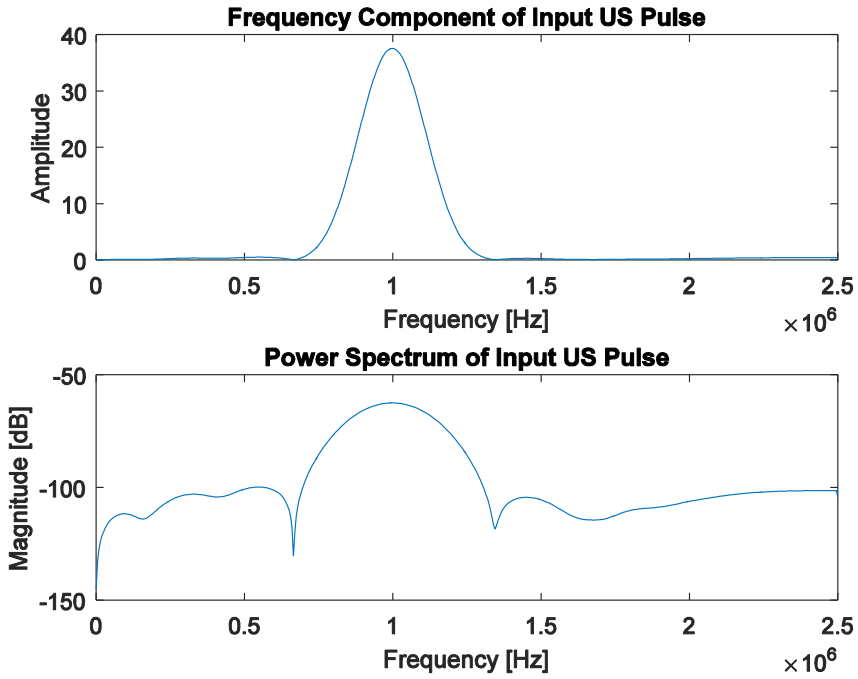

Figure 11. Characteristics of the input pulse. The frequency component indicates the center frequency of 1 MHz. The power spectrum indicates the center frequency at 1 MHz has a power of -62 dB. Frequencies outside the bandwidth 0.69-1.32 MHz have -40 dB power (1%) than the center frequency.

Prior to filtering of the signal, a drift correction was made (Figure 12) and it was cut at the time of receiving the propagated pulse. This moment of arrival of the pulse was based on the distance between the probes and the speed of sound through water (1540 m/s (17)). Figure 13 contains an original, and a filtered and cut US response.

Differences in the recorded US response was calculated using the Normalized Root of the Mean Square Error (NRMSE, Equation 3) and Normalized Mean of the Cross Correlation (NMCC, Equation 4). The first set of 5 US responses was taken to quantify the system noise in the signal, expressed in the NRMSE and NMCC. 5 US responses per participant gave us 10 values of NRMSE and NMCC. Variation in the US response as introduced by the displacement and rotation of the US transmitter is also expressed in the NRMSE and NMCC and plotted over the deviations. Recording of the US response was initiated 20 µs prior to inhibiting of the US transmitter. This part of the US response was used to quantify the background noise of the system.

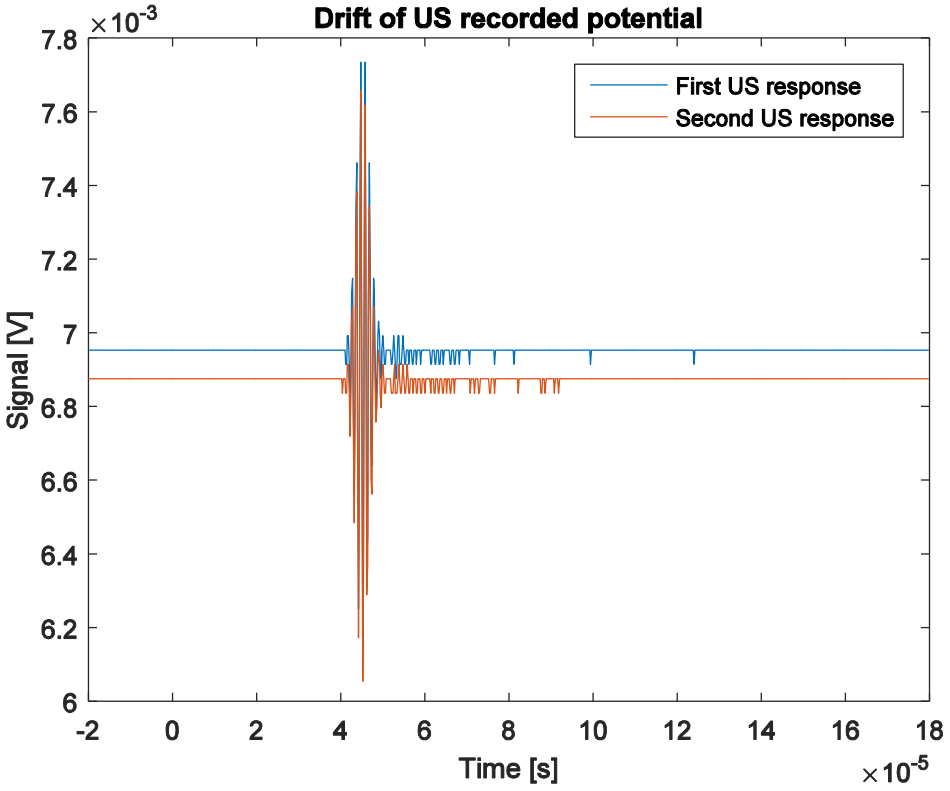

Figure 12. The recorded potential on the digital scope has a continuous drift. Prior to data analysis, the base line of all US responses is set equal to zero

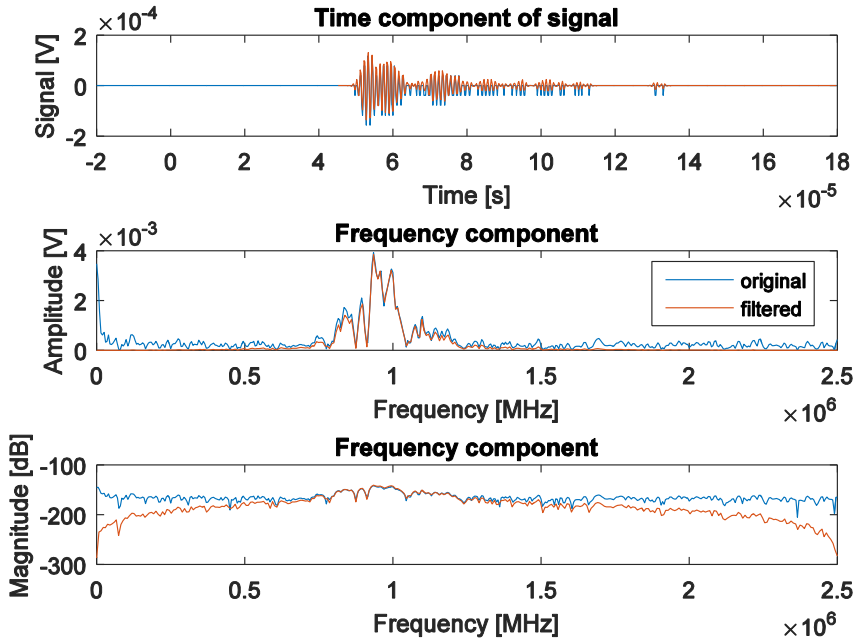

Figure 13. Time, frequency and power spectrum components of the original and filtered signal. The filter has a bandwidth of 0.69-1.32 [MHz]. Frequencies outside the bandwidth have significantly less power.

$$NRMSE = \frac{\sqrt{\frac{\sum_{i=1}^{n}\left(x_{1,i} - x_{2,i}\right)^2}{n}}}{x_{1,max} - x_{1,\min}} * 100\% \qquad \text{(Equation 3)}$$

Normalized Root of the Mean Square Error. Where x_1 and x_2 are the amplitude of the two US responses at time instance i, $x_{1,max}$ is the maximum amplitude of the reference US response, $x_{1,min}$ is the minimum amplitude of the reference US response, n is the number of elements in the US response vector. The lower the NRMSE the more the signals are alike.

$$NMCC = \frac{\max|x_1 \star x_2|\,[i]}{\sqrt{\sum_{i=1}^{n} x_1[i]^2} * \sqrt{\sum_{i=1}^{n} x_2[i]^2}} \qquad \text{(Equation 4)}$$

Normalized Mean of the Cross-Correlation. (X_1 * X_2) is the cross correlation between the two US responses. n the number of elements in the US response vector. The higher the NMCC, the more the shape of the signals is alike.

Displacement of the US probe introduces a change in path length between the probes. The time-shift introduces by this displacement cannot be visible with a sampling frequency of 5 MHz. However, the time shift of the US response relative to the input US pulse was calculated using the cross-correlation between the US input and US response. Difference in time shift as introduced by the displacement of the US transmitter was plotted over the displacement and normalized over the distance between the probes.

Magnitude of the recorded US responses was expressed in decibel.

Results

Experiment 1. Consistent recording of US response.

Recording of a set of 5 US responses was successful in all participants using the anterocentral and posteromedial portal for the positions of the US probes. Angle of the lower leg ranges from 68-80° relative to the horizontal. The force applied by the posterior probe ranges from 3-11 Newton. The recorded parameters from experiment 1 are shown in Table 1. For consistent recording of the US response, the following conditions are required:

- Foot sole horizontal and lower leg between angle 68 and 80° relative to horizontal.
- Use ultrasonography to localize the anterocentral and posteromedial portal and mark the skin.
- Position the US transmitter on the posteromedial and the US transceiver on the anterocentral portal.
- The normal forces between the US probes and the skin do not have to exceed 15 Newton.

Table 1.Recorded parameters from experiment 1. The angle of the lower leg is relative to the horizontal. In all cases the US probes were positioned on the anterocentral and posteromedial portal. Forces are the normal force between posterior probe and skin.

Participant	Angle lower leg [°]	Location anterior probe	Location posterior probe	Force posterior probe [N]	5 recorded US responses
1	72	Anterocentral	Posteromedial	3	Yes
2	73	Anterocentral	Posteromedial	4.5	Yes
3	68	Anterocentral	Posteromedial	7	Yes
4	73	Anterocentral	Posteromedial	6	Yes
5	77	Anterocentral	Posteromedial	11	Yes
6	78	Anterocentral	Posteromedial	6	Yes
7	80	Anterocentral	Posteromedial	9	Yes

Experiment 2. Sensitivity analysis of US probe deviations on recorded US response.

28 participant gave consent and joined experiment 2. (BMI 22,5 ± 1.9 kg/cm^2). Two participants indicated dizziness and interrupted the experiment, one participant interrupted the movement of the robot, data set of participant 1 was lost. The first set of 5 US responses from the static situation was successfully recorded in 27 participants. The second set of 12 US responses during displacement of the anterior probe was also successfully recorded in 27 participants. The third set of 12 US responses during rotation was successfully recorded in 24 participants. In total 770 US responses were recorded. Parameters of all participant is listed in Table 2.

The frequency component and power spectrum of the noise indicate low power over the entire bandwidth, indicating presence of white noise. Figure 14 shows the characteristics of the background noise. Maximum magnitude of the background noise is -158 dB within the bandwidth of the filter. Lower frequencies are higher indicating a DC-component, e.g. drift of the recorded potential.

The NRMSE between the 5 US responses from the static situation are shown in Figure 15. Lowest NRMSE was 0.2%, highest was 4.9%. Smallest range of the NRMSE was 0.3-0.5%, largest range was 1.00-4.8%. The NMCC from the static recording is shown in Figure 16. Highest NMCC was 0.9994, lowest was 0.7147. Smallest range was 0.9989-0.9971, largest was 0.9807-0.7147

Table 2. Parameters of all participant of experiment 2. The angle of the probes and lower leg is relative to horizontal. The distance between the probes is the minimal distance. The average force of the probes is over all 29 recordings per participant. Participant 8, 12 and 16 interrupted the experiment.

Participant	Angle anterior probe [°]	Angle posterior probe [°]	Distance US probes [mm]	Angle lower leg [°]	Average Force anterior probe [N]	Average force posterior probe [N]
2	-	-	69.8	81	5.3	6.1
3	15	22	68	83	4.7	3.8
4	25	25	57.5	73	6	1.5
5	-	-	72.8	80	3.9	4.3
6	24	29	63.9	69	9.8	3.6
7	28	31	60.1	67	9.6	3.4
8	34	34	83.6	74	10.6	4
9	22	19	78	72	12.2	2.7
10	20	22	69.5	71	7.7	2.3
11	18	26	66	71	2.1	1.4
12	-	-	65	-	5.2	1.4
13	-	-	62	-	5.2	2.9
14	-	-	64	-	6.4	1.7
15	26	33	56	70	8.7	1.9
16	30	31	55	67	9.4	2
17	32	34	61	71	8.9	1.1
18	25	31	69.5	74	8.5	1.7
19	25	27	59.5	75	8	2
20	23	30	65	74	8.9	0.9
21	21	31	64.5	66	9.3	0.7
22	23	30	66	72	6.2	6.8
23	29	32	66	73	6.5	7.4
24	28	29	64	73	5.5	6
25	32	29	60	68	5.8	6.5
26	37	33	68	71	5.5	6.7
27	37	-	64	71	5.6	6.2
28	38	30	66	69	5.3	5.7
Mean (SD) or median (min,max)	27 (6)	30 (19,34)	65.4 (6.1)	73 (4)	7.1 (2.3)	3.1 (0.7,7.4)

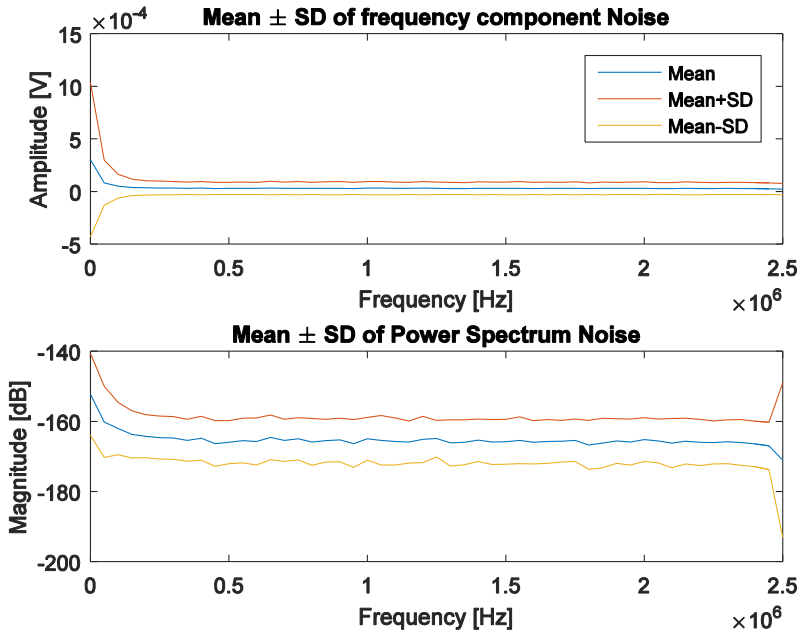

Figure 14. Frequency and power spectrum components of the noise. Taken from the 20 microseconds prior to inhibition of the US transmitter of all 770 recorded US responses. All the frequencies are present in the noise at low power, indicating presence of white noise. The higher magnitude for the low frequencies indicate a DC-component. Magnitude of the noise within the bandwidth of the Butterworth filter does not exceed -158 [dB].

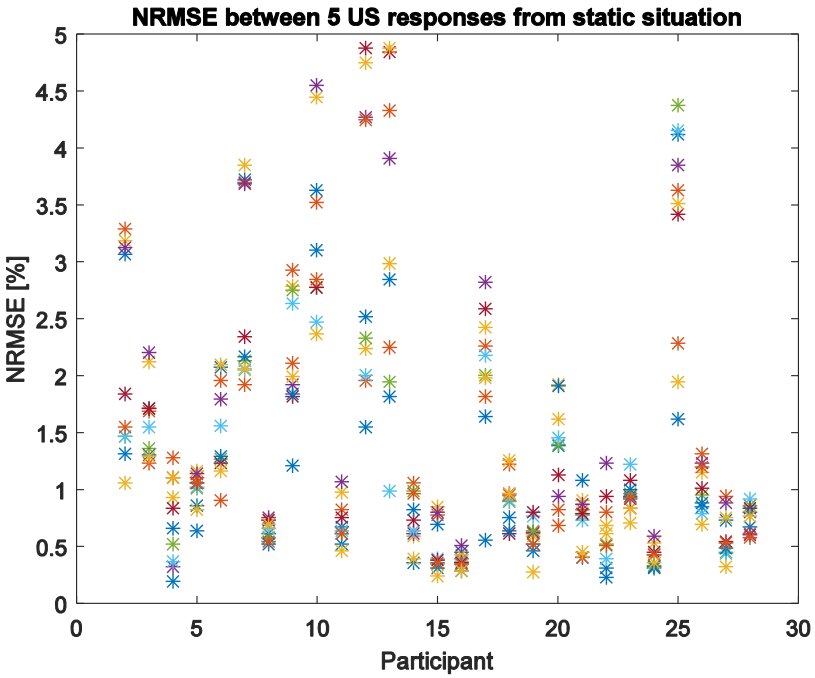

Figure 15. Differences between the 5 US responses recorded from the static situation expressed in the NRMSE. 5 US responses results in 10 values per participant. The lower the NRMSE the more similar the two US responses are.

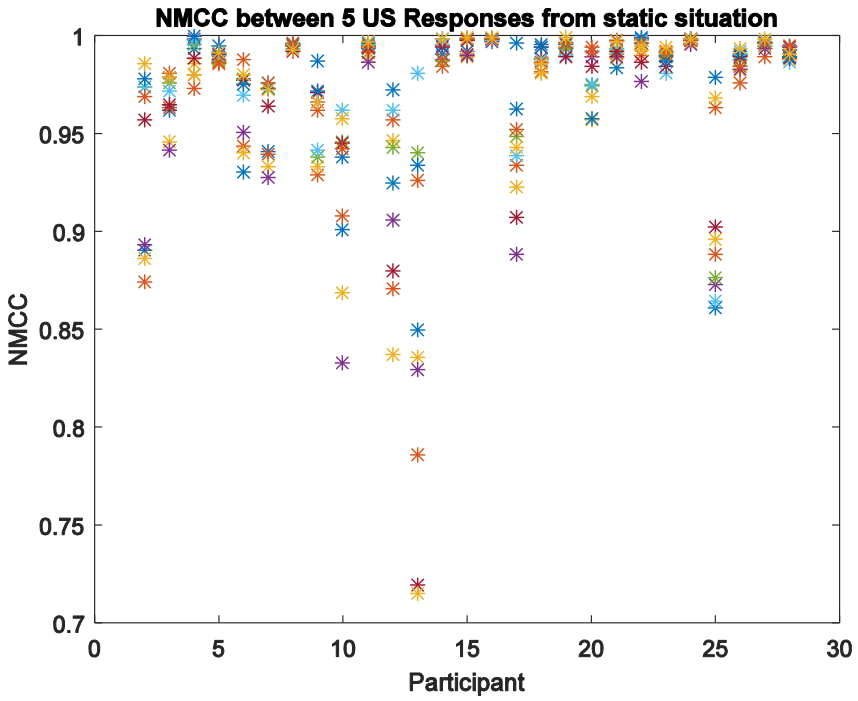

Figure 16. Differences between the 5 US responses recorded from the static situation expressed in the NMCC. 5 US responses results in 10 values per participant. The higher the NMCC the more similar the shape of the two US responses are alike.

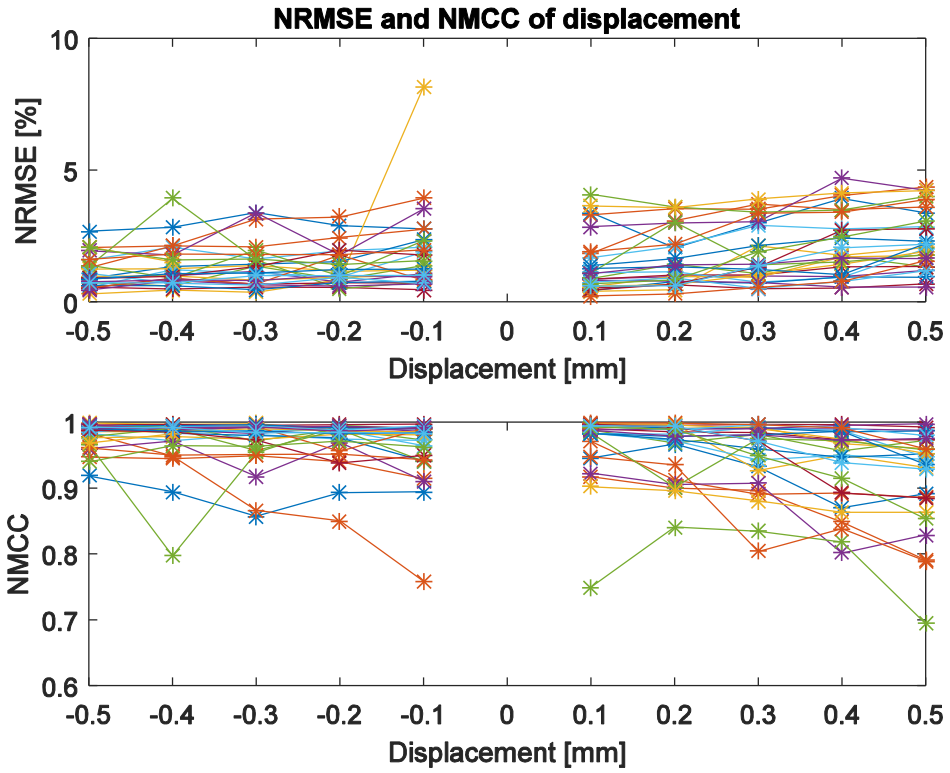

Figure 17. NRMSE and NMCC of the displacement of all 27 participants. The smaller the NMRSE the more similarity there is between the signal recorded at the initial position and the displaced position. The dots are connected via lines to indicate which correspond.

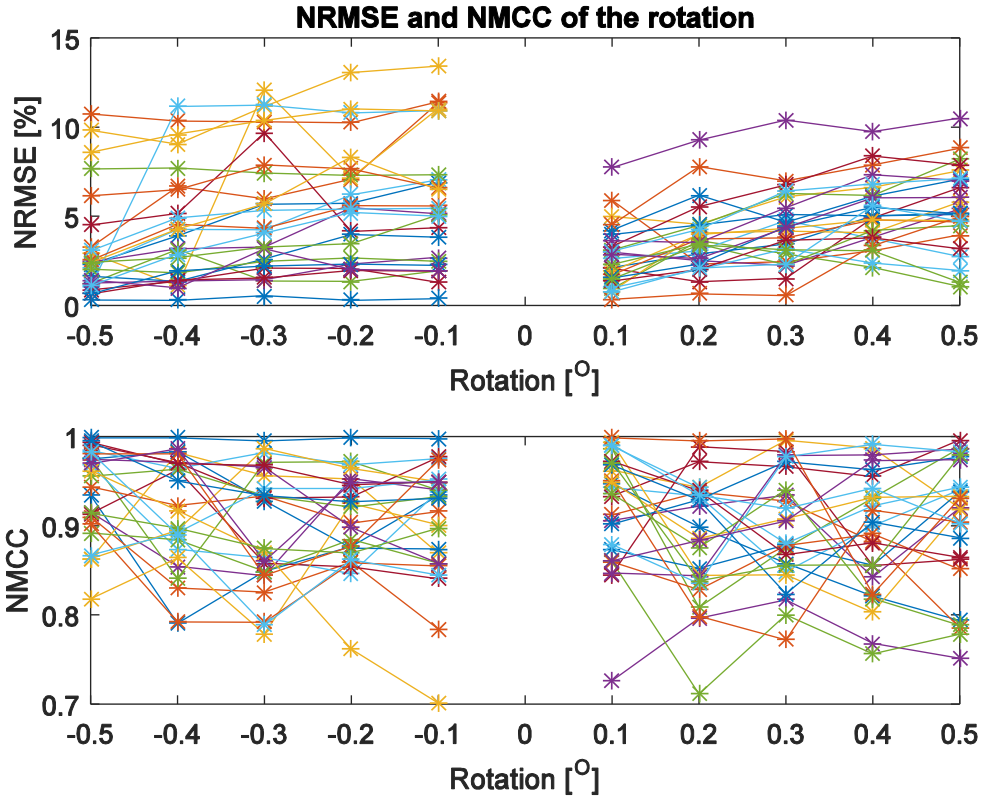

Figure 18. NRMSE and NMCC of the rotation of 24 participants. The higher the NMCC, the more similar is the shape between the US responses. The dots are connected via lines to indicate which correspond.

NRMSE and NMCC calculated between the US response from the initial position and the displaced position are shown in Figure 17. The bandwidth of the NRMSE introduced by the displacement ranges between 0.2% and 5%. With one outlier at 8.1% from a -0.1 mm displacement. Bandwidth of the NMCC introduced by the displacement ranges from 0.9993 and 0.6941.

NRMSE and NMCC from the rotation set are shown in Figure 18. Bandwidth of the NRMSE introduced by the rotation is 0.2% - 13%, bandwidth of the NMCC is between 0.9986 and 0.7010.

The delay as introduced by the displacement of the US probe was consistent not visible in 20 participants. The delay was visible in 7 participants, these outliers are shown in Figure 19. Participant 7 had a major time-shift on displacement of -0.4 and -0.5 from the initial position.

Maximum magnitude of the recorded responses per participant are shown in Figure 20. Maximum power was -121 dB, minimum was -142 dB.

Ultrasound images from the ankle joint are collected from 7 participants. The US images of participant 4 and 7 are shown in Figure 21. The maximum magnitude is included.

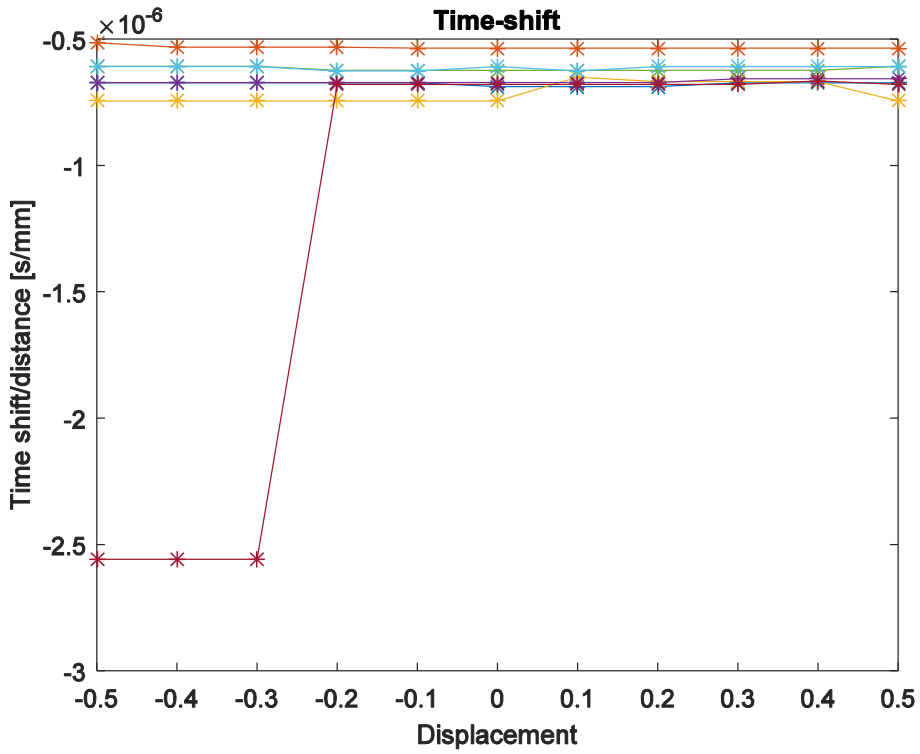

Figure 19. Time-shift of the US response normalized by the distance between the probes. The dots are connected via lines to indicate correspondence between dots. The largest outlier is participant 7.

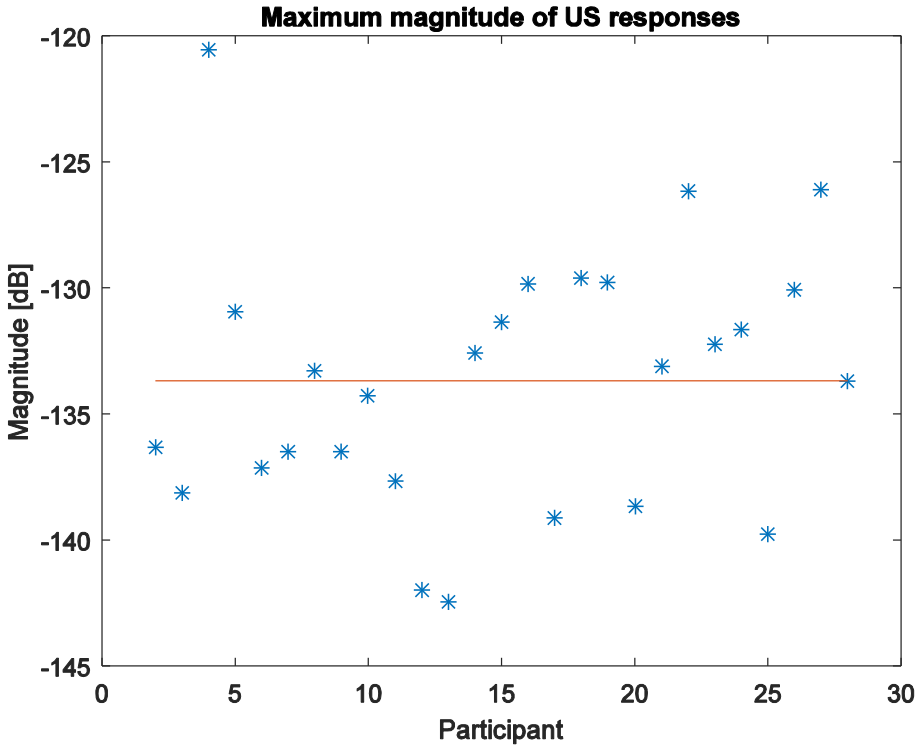

Figure 20. Maximum magnitude of the participants US responses within the bandwidth. Participant 4 had the highest magnitude of -121 dB, participant 13 the lowest, -142 dB. The line indicates the mean value of all the magnitude and is -133.7 dB (SD = 5.1).

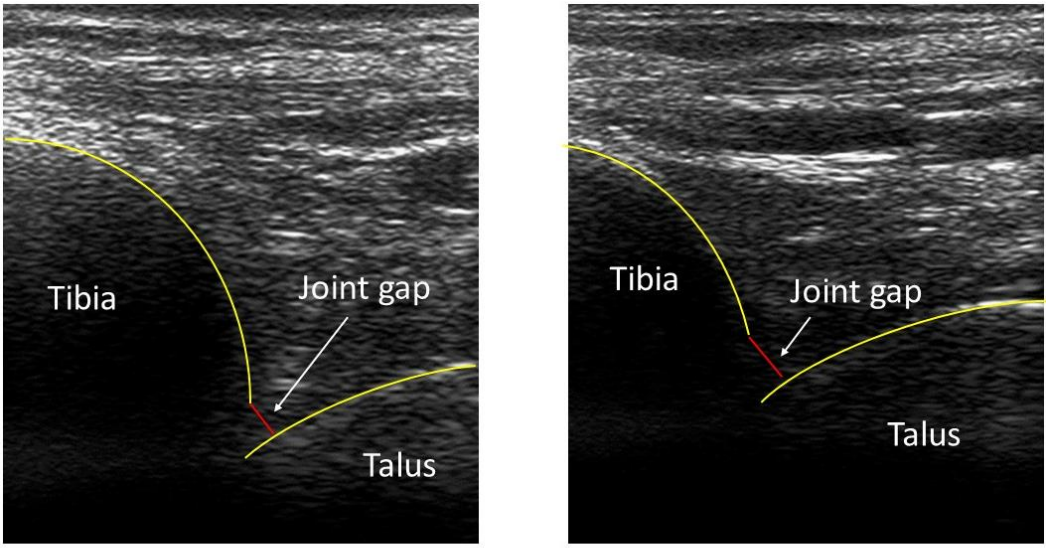

Figure 21.US images of anterocentral portal of participant 4 (a) and 7 (b). The yellow line indicates the surface of the Tibia and Talus. The red line indicates the joint gap.

Experiment 3. Novel coordinate system.

Optical tracking of the position tool attached to the novel coordinate system was successful in 10 recordings. The mean absolute translation error was 5.1 mm ± 3.7. The mean relative errors of the rotation were Rx = -0.28° ± 0.91, Ry = -0.90° ± 0.79, Rz = -0.37° ± 0.76.

Using the novel coordinate system was successful in all 5 participants. Reproducing the position of the anterior US transceiver was successful in all cases. 50 US responses were recorded. NRMSE and NMCC between all signals per participant are shown in Figure 22. Lowest NRMSE was 1.1%, highest was 34.1% (not considering the outlier of 53%). Smallest range of the NRMSE was between 2.44% and 11.65%, largest range was 2.0% and 31.9%. Highest NMCC was 1, lowest was 0.2050. Smallest range was 0.9849 and 0.7895, largest was 1-0.2573.

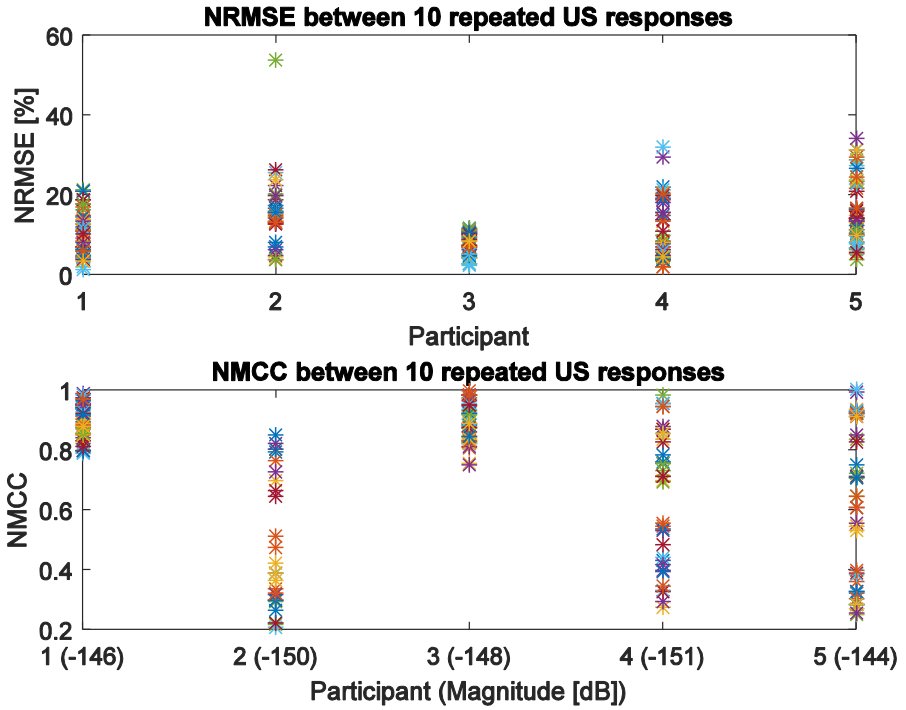

Figure 22. NRMSE and NMCC between 10 US responses taken from 5 participant during prototype testing. 10 US responses results in 45 values for the NRMSE and NMCC per participant.

Discussion.

The primary goal of this research is studying the boundary conditions needed for consistent recording of US wave propagation through the ankle joint and quantifying the influence of minor deviations of the US probes on the recordings. Experiment 1 resulted in a procedure for consistent recording of a US response in each session. Experiment 2 produced the set of requirements to reliably repeat a US response recording. Experiment 3 aimed to test a novel coordinate system to reliably repeat a US response recording.

Experiment 1. Consistent recording of US response.

The following set of requirements is needed for consistent recording in each session: the angle of the tibia is 73° relative to the horizontal, the location of the anterocentral and posteromedial portal is found using ultrasonography and marked, the US transmitter is positioned on the posteromedial portal, and the US transceiver is positioned on the anterocentral portal. Forces of the US probes on the skin must not exceed 15 Newton.

Locating the portals without the ultrasonography was difficult and not successful in some cases prior to experiment 1. Prior attempts to record a US response required applying considerable force on the skin. Using the procedure, each recording session has been successful from experiment 1 onwards. However, it is only performed by one experimenter. Nonetheless, it contains a set of simple actions; another experimenter should not have difficulties successfully performing this procedure.

Experiment 2. Sensitivity analysis of US probe deviations on recorded US response.

As in most measurement systems the background noise is white. Magnitude of the background noise is higher in lower frequencies due to a drift on the potential of the scope and possibly a slight indicator of colored noise. The consistent magnitude of the noise off the higher frequencies allows us to predict the minimal magnitude of two recorded US responses with a NRMSE <1%. The NRMSE is taken between two US responses recorded from two different moments in time with the goal to monitor cartilage regeneration. If both of these US responses have a magnitude 40 dB higher than the magnitude of the background noise, the background noise influence on the NRMSE should be 1%. Other influences contain system noise and information about the cartilage regeneration.

Maximum magnitude of the background noise is -158 dB, the magnitude of the US responses must be -118 dB for a consistent NRMSE<1%. A NRMSE<1% has been recorded at some participants, however, only 7 participants had all the 10 NRMSE values below 1%. An increased signal transfer between the probes must be achieved to give all US responses of all participants a magnitude of -118 dB. A suggestion for future research is averaging over multiple recording to reduce the effects of background noise. The length of the recording is 200 microseconds, in 10 millisecond 50 recordings can be performed. During this 10 milliseconds, a major change in the US response seems highly unlikely.

The low magnitude of the US responses is shown by the NRMSE of the first set of recordings of experiment 2; the static situation. A NRMSE<1% was consistent in 7 of the 28 participants. For all those 7 participants, the magnitude of the US response was above the mean value of -133.7 dB. However, other participants' results also contained a US response with magnitude above the mean but did not show a consistent NRMSE<1%. As the shape of the recorded US response is affected by the medium between the two probes, a continuous movement in the medium could explain these inconsistencies.

Between the talar and tibial surface in the ankle joint there is little movement. However, tissue outside the ankle joint between the joint space and the probe could show continuous and inconsistent movement. Blood vessels, nerves and tendons have continuous movement and introduce continuous change of the medium between the probes. At some participants, the probes could have been positioned on a small blood vessel or tendon; resulting in a high variation between the US responses in the static situation, whereas in others it did not. Although the anterocentral and posteromedial portals are locations around the ankle joint with minimal tissue surrounding it, in some cases, a blood vessel, nerve, or tendon could have been located there.

The change in the recorded US response as introduced by the displacement of the US transceiver did not significantly increase the NRMSE and decrease the NMCC. The continuous and consistent background and system noise already provided us a minimum value of the NRMSE and maximum of the NMCC. The distance between the probes was between 55 and 82 mm in the participants. The largest part of the medium between the two probes was the joint space, the tissue between the probes and the joint space was relatively small. Displacement up to ±0.5 mm did not result in a significant change of the medium between the probes and the NRMSE and NMCC. The movement of the robot could remove a small nerve between the probe and joint space and explain an outlier in the NRMSE and NMCC. This is highly unlikely due to the size of the displacement. Another parameter influencing the NRMSE and NMCC over the displacement is the actual position of the robot. The specifications of the robot indicate that it has an accuracy of ±0.1 mm and ±0.1°. A displacement of 0.2 mm could be a 0.1 or 0.3 mm displacement in reality. An absolute measurement of the position is not recorded and is advisable for future studies. This indicates that translations of ±0.5 mm do not significantly change the recording of the US response.

Rotation of the US transceiver does show significant influence on the NRMSE and NMCC between the recorded US responses. The system noise has a small range in the static setup with a maximum not exceeding an NRMSE of 5%, whereas during the rotation the NRMSE had a maximum value of 13%. Almost all cases of the rotation set show a consistent increase of the NRMSE on the positive rotation and a decay of the NRMSE in the negative rotation. However, this effect is not directly seen in the NMCC. The NMCC shows a larger spread in the positive rotation compared to the negative rotation. This effect is not well understood and merits further research. The angle of orientation between the probes has a large effect on the recorded signals, and an optimum may be when the probes are aligned. This indicates that during the recording of the US response, the US probes must be aligned in at least one plane. Another effect that could have caused the large spread in the NRMSE and the NMCC is the time of recording. The participants have to sit still during the entire recording session. The rotation set is recorded last after the static and displacement set. Some participants may have moved slightly towards the end of the recording session.

The differences in magnitude of the US response between participants were considerable. Smaller distance between the probes could result in a higher magnitude, larger distance in a lower magnitude. However, we did not find a significant correlation between those two parameters. Moreover, the orientation of the probes relative to each other may have a direct influence on the recorded magnitude. As seen by the change in the NRMSE upon rotating, the orientation of the probes has a large influence on the recorded US response. Each probe has three rotation variables; translations X, Y and Z, rotations Rx, Ry and Rz. Rotation around its own axis (Ry) does not change the recording. However, signal transfer between the probes may be increased when the probes are aligned in the zy-plane. During the experiments, the alignment was sufficient if a US response was obtained, an optimal value of the alignment and position of the US probes was not studied.

The laterally and medially displacement of the US transceiver should not have resulted in a visible time-shift between the US responses. A displacement up to ±0.5 mm does not change the path length between the probes such that a time-shift is visible using a sampling frequency of 5 MHz. However, we did see a time-shift in some cases. A slight time-shift could be explained by the discretization of the signal where a minor shift of the US pulse results in sampling just before of just after a peak. This does not explain the large time-shift in some cases. The theoretical time-shift is based on a straight and direct path between the probes with an acoustic velocity of 1540 m/s throughout the entire medium. However, the curved surface

of the talus increases this path length. Furthermore, different tissues are present in the ankle joint; the acoustic velocity is different in each of them. The time-shift is calculated using the cross-correlation between the input and US response, a combination of continuous blood flow, minor muscle contractions, noise effects and slight movement of the participant could explain the inconsistent change in the time-shift.

Experiment 3. Novel coordinate system

The aim of experiment 3 was to test a novel coordinate system for consistent, repeatable and reliable recording of the US response in two different recordings. Consistent recording is defined as being able to obtain a US response in each participant, repeatable is defined as obtaining the US response in all recordings of participants following the first one. Reliable is defined as the NRMSE between two US responses being under 5% as provided by experiment 2. The proposed coordinate system was able to repeat the US response consistently, repeatably, and reliably. However, the NRMSE was not below 5% between all recorded US responses of one participant. Nonetheless, recording a US response consistently and repeatably was possible. After attempting to reproduce the initial position of the probe the recording was repeated. During the static situation, the NRMSE did not exceed 5%. Reproducing the position of the US transceiver such that the medium between the probes is exactly the same, requires more than simply reproducing the position. The tissue between the probes and the ankle joint space on the anterior side might be in another configuration because the skin is compressed differently. The compressing of the tissue during recording of the initial US response could have increased the blood flow and changed the shape between the probes. Also, the ultrasound gel could be spread differently between the probe and the skin.

Future recommendations.

Primary improvement in the prototype must be focused on increasing the signal transfer between the probes. This study used a center frequency of 1 MHz because it builds upon a computational analysis of Sarkalkan et al (15). The signal transfer may be higher with a different frequency and be dependent on the size of the ankle joint and the wave length of the pulse. The first step is to create the frequency response function of a human ankle joint. Putting multiple sinusoid functions in the system and calculate the signal transfer to create the frequency response function (18). However, this is highly time consuming on participants. Computational analysis with a more anatomically alike model could act as a first estimate to get the best suitable frequency and signal.

A second major influence is the contact area between the probes. The tip of the probe is round, flat with sharp edges, whereas the skin surrounding the ankle joint is shaped highly irregular. The skin surrounding the anterocentral portal is flexible and provides a high contact surface between the probe and the skin, the opposite goes for the posteromedial portal (Figure 23). Although ultrasound gel can increase the signal transfer between skin and probe, more contact area would result in a higher signal transfer.

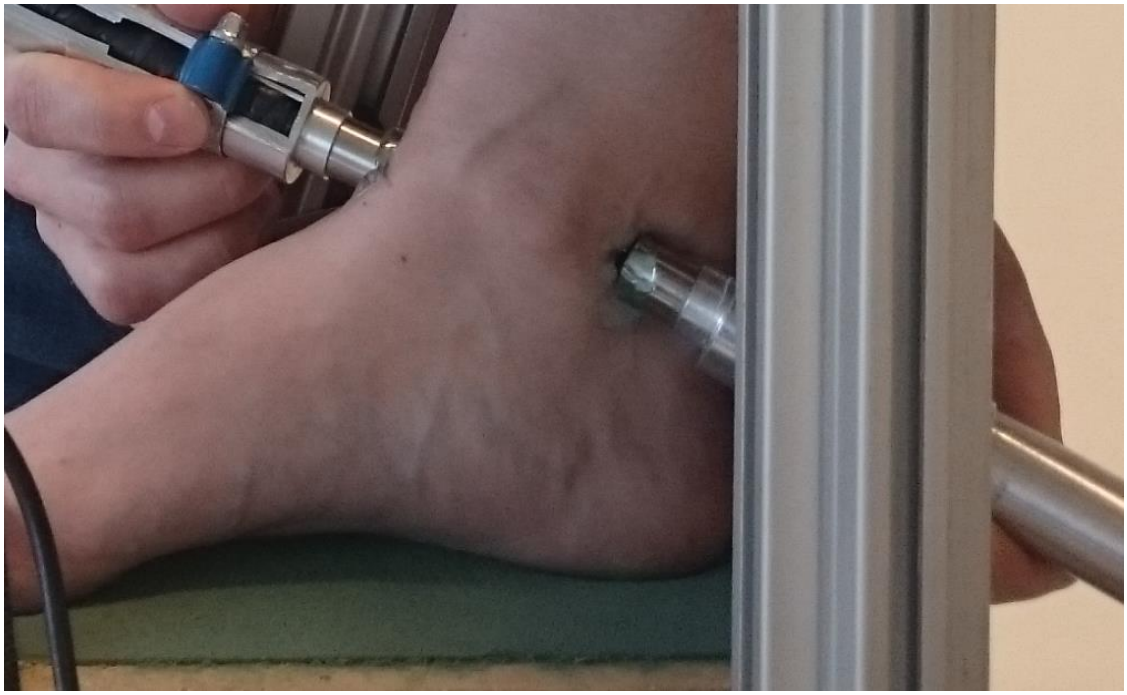

Figure 23.The contact area between the skin and the probe on the posteromedial portal is not optimal. The irregular shape of the ankle joint around the posteromedial portal makes it difficult to create a high contact area while still keeping the probes aligned.

The recorded parameters; the angle of the lower leg, the angle of the probes, the position of the probes, and the force applied by the probes were sufficient if a US response was obtained. Optimal values of the parameters have not been studied. However, optimal parameters could increase the signal transfer between the probes, increase the SNR and magnitude of the US response and result in a consistent NRMSE<1%. The angle of the lower leg influences the opening of the joint gap on both the anterocentral and posteromedial portal. An optimal angle may be when both portals are opened equally. However, the US pulse has more energy on the transmitter side than on the transceiver side. A larger opening of the portal at the transceiver may have more effect. Furthermore, the optimal angle of the US probes depends on the orientation of the joint gap. Previous computational simulations indicated that the orientation of the probes must be perpendicular to the joint gap (15). However, the simulation used a model with some simplifications of the ankle anatomy. Positioning a US probe perpendicular to the joint gap might not always be physically possible as the foot prevents positioning the probe in this manner. This parameter would also be different in each person due to anatomical variations. An optimal set of parameters would likely be different in each person and difficult to assess.

The robot used in this study is capable of repeating a position with an accuracy of ±0.1 mm and ±0.1°. Future experiments should focus on quantifying the influence of the recorded US response when the position of one US probe is reproduced with very high accuracy, leaving the foot, lower leg and other probe unmoved. Although the results from this study indicate that the position error between the initial and secondary recording can be ±0.5 mm and ±0.1°, the influence of skin compression and spread of ultrasound gel between skin and probe have not been studied.

Ultimate goal of this project is to monitor the regeneration of cartilage after a surgical intervention and monitor the longitudinal rehabilitation of the patient. Current monitoring of the cartilage regeneration is time-inefficient, costly and invasive (9). For efficient rehabilitation a better understanding of the effects the different healing components have on the cartilage regeneration is needed (4). Although clinical application of ultrasound wave propagation is not applicable in the near future, prototype design must be driven towards a handheld device.

Conclusion

The concept of US wave propagation though the ankle joint is an entirely new topic and awaits numerous thriving challenges. A procedure for the consistent and repeatable recording has been developed and the influence of background noise, system noise and minor deviations of the US probe have been quantified. A first step for the development of a tool that is able to consistently, repeatedly and reliably record a US response at each participant has been made. Further studies must focus on increasing the signal transfer between the probes by collecting the optimal set of parameters and designing the best suitable signal. Traditional ultrasonography already has established itself as a viable technique for diagnosing multiple injuries. Expanding the use of ultrasound diagnosis with wave propagation seems the logical choice.

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Abbreviations

US = Ultrasound
NRMSE = Normalized Root of the Mean Square Error
NMCC = Normalized Mean of the Cross Correlation
MRI = Magnetic Resonance Imaging
CT = Computer Tomography
SNR = Signal to Noise Ratio

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Appendix A. Sensitivity analysis of ultrasound wave propagation through the ankle joint

Master Thesis project: Julius Zonneveld

Abstract

Intro **Ultrasound wave propagation is able to detect small cartilage cracks in the ankle joint in a cheap, fast and non-invasive way. Aim of this sensitivity analysis is to gain insight in the change of a ultrasound signal when the position of the ultrasound transceiver is changed.**

Method. **Using computational software we created the signal of a ultrasound wave propagated through the ankle joint and changed the position and orientation of the transceiver in increments of 0.1 mm and 0.1°. Difference in signals is expressed in the Normalized Root Mean Square error. The relation between the NRMSE and the displacement or rotation is made. There is 1% white Gaussian noise added to the signals.**

Results. **With a clear noise free signal, the NRMSE > 1% when the transceiver is 1 mm or 0.8° from its initial position. With the added noise, the NRMSE >1% when the transceiver is 0.1 mm or 0.5° from its initial position.**

Discussion and conclusion. **The added noise is an educated guess of the noise present in a real setup. The high influence of the displacement and rotation of the transceiver on the similarity of the signal indicates that a setup that propagates ultrasound wave through the human ankle joint in multiple instances in time has to have a repositioning accuracy of at least 0.1 mm and 0.1° to repeat the recording with a high accuracy.**

Introduction

The Vibrant Vision project is a collaboration between the TU Delft and the Amsterdam Medical Center (AMC) to develop a new diagnostic technique to assess damage to the articular cartilage in the ankle joint. The new technique that is being developed uses wave propagation through the ankle joint space. Cartilage damage changes the shape of an ankle joint, and thus a propagated ultrasound wave will have a different shape (1). For reliable measuring of cartilage over time, a setup is needed that can reliably reproduce the results with a high accuracy. A device that can repeat the relative position of the ultrasound probes around the ankle joint in the same configuration in each repetition.

As parts of the development of this prototype, a better understanding of the influence of displacement of the ultrasound probes is needed.

Methods

Two sets of computational simulation are performed in Wave2000 (Cyberlogic INC., New

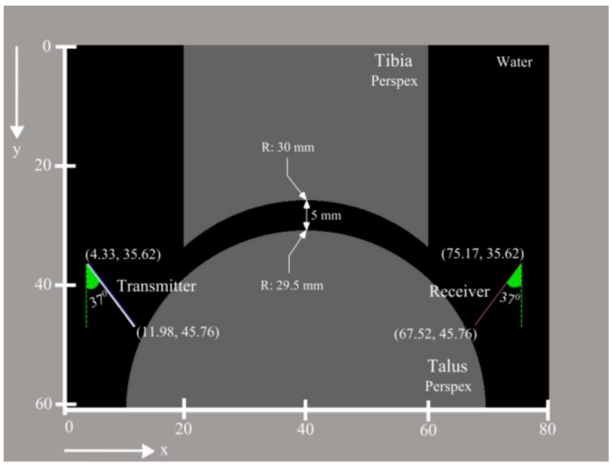

Figure 1. Model of the Ankle joint in the simulation program. The upper part represents the Tibia, the lower part the Talus bone. The transmitter and transceiver are placed on the outer side of the model. Picture from: (1)

York, NY, USA). A model of the ankle joint is created (Sarkalkan, Loeve (1) and a transmitter

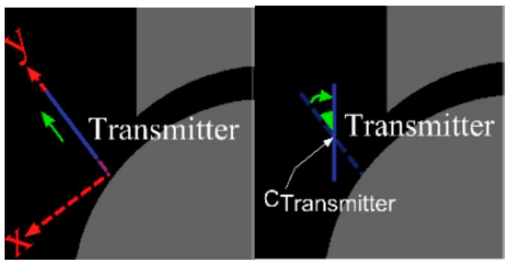

Figure 2. Changing the position of the transmitter in y-directions (left) and the orientation around its own axis (right). In our sensitivity analysis the location of the transceiver is changed. Picture from: (1)

and transceiver are positioned on either side. First simulation is performed of the initial position with the transmitter and transceiver perpendicular to the ankle joint space and 4 mm distance.

During the first sensitivity analysis is moving the transmitter further away from the ankle

$$NRMSE = \frac{\sqrt{\frac{\sum_{i=1}^{n}\left(x_{one,i} - x_{two,i}\right)^2}{n}}}{x_{one,max} - x_{one,\min}} * 100\%$$

Formula 1. Normalized Root Mean Square Error (NRMSE). Where $x_{one,i}$ = the value of the first measurement at time i, $x_{two,i}$ = the value of the second measurement at time i, $x_{one,max}$ = maximum of the first data, $x_{one,min}$= minimum of the first data, and n = number of datapoints

joint space (Figure 2). Displacement goes in steps of: 0.1 mm to 1 mm in steps of 0.1mm; from 1 mm to 2 mm in steps of 0.5mm; from 2mm to 4 mm in steps of 1 mm.

Second sensitivity analysis is changing the orientation of the transceiver around its own axis(Figure 2). Changing of orientation goes in steps of: 0.1° to 1° in steps of 0.1°; from 1° to 2° in steps of 0.5°; from 2° to 4° in steps of 1°.

Comparing of the signals.

To see the change of the signal with the change of position and orientation, the displaced and oriented signals will be compared to the signal of the initial positions. From each change of position or orientation, the Normalized Root Mean Square Error will be calculated.

The simulation will reveal a perfect signal. For better understanding of the NRMSE relation, 1% white Gaussion noise will be added to the signals and the NRMSE over these set of signals will be taken. Noise is added using computational program Matlab, Natick, United States. According to ultrasound specialist, 1% white Gaussion noise is common (Koen van Dongen).

Results

Figure 3 shows the results of the sensitivity analysis in the y-direction of the transceiver. The blue line indicates the 'clean' signal, the red line contains 1% added noise. The NRMSE between the initial signal and the clean signal with the displaced transceiver is above 1% when the displacement is 1 mm from its initial position.

The red line shows the results of the second

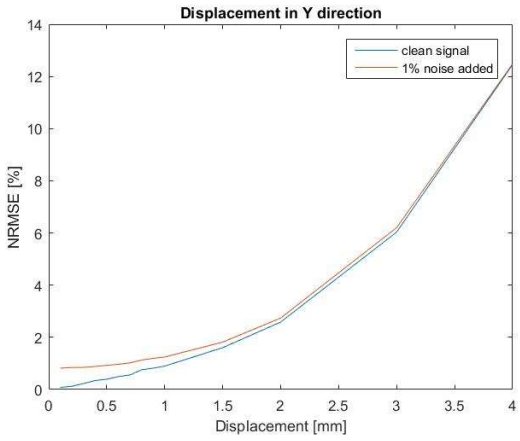

Figure 3. The change of signals expressed in the NRMSE plotted over the displacement in the y-direction.

sensitivity analysis without additional noise added. The difference in the signals, expressed

in the NRMSE, is above 1% when the rotation is 0.8°.

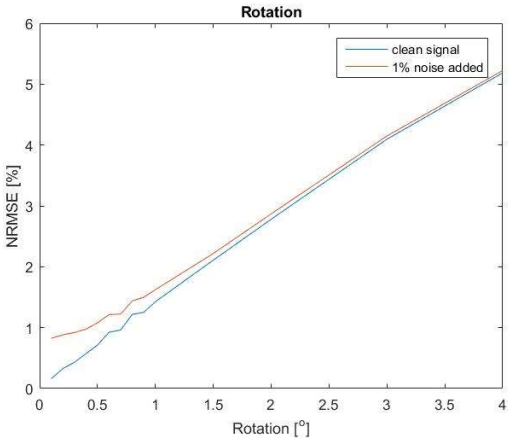

Figure 4. The change of signal expressed in the NRMSE plotted over the change of orientation of the transceiver

Figure 5 shows the relation between the change of signal, expressed in the NRMSE, with the 1% white Gaussian noise added. The 1% NRMSE is reached from a displacement of 0.1 mm.

Figure 6 shows the relation between the change of signal, expressed in the NRMSE, with the 1% white Gaussian noise added. The 1% NRMSE is reached from a rotation of 0.5°.

Discussion and conclusion.

It is expected that the signal of a displaced transceiver is slightly different from the signal with the transceiver in his initial position. The goal of this simulation sensitivity analysis was to predict the relation between the NRMSE and displacement. Future purpose of this application requires a setup where the position of the ankle joint, transmitter and transceiver are the same in each configuration. As any system that repositions an object, a reposition error is inevitably. This simulation gives us insight in the influence of that reposition error.

Although the ideal simulation would not give us the relation between NRMSE and the displacement, is does give us an indication. A displacement of 1 mm or a rotation of 0.8° is only a minor change of position in the ideal world, and it shows a NRMSE>1%.

A better indication is the simulation with the white Gaussian noise added. Although we do not know the actual influence of noise in this application. Adding this type of noise is only quantified by an experts opinion and not with a scientific publication. However, it does show that minor influences have a significant influence on the NRMSE. This indicates that the future device that measures the ultrasound wave propagation through the human ankle joint in multiple instances in time has to reposition the human ankle joint, transmitter and transceiver with a accuracy as high as 0.1

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Appendix B. Force vs Pain on the ankle joint experiment.

Explicitly made for the HREC application

Author: Julius Zonneveld

Introduction

This report is part of the HREC application of the experiment: 'Vibrant Repeater, Displacement of US probes and lower leg on accuracy in propagated ultrasound waves through the ankle joint.' In here we show the results of the experiment: 'Pain vs Force'.

The designing of the Vibrant Repeater, the device that can repeat a US response with high accuracy, has to position the Ultrasound probes around the ankle joint. These probes need to apply a force upon the skin for maximum signal transfer between probe and skin. The Vibrant Repeater must withstand these forces and must therefore have a certain stiffness. However, there is no information about the normal force acting the probe acts on the skin and the pain.

A small experiment has been performed to collect these data, so the stiffness of the Vibrant Repeater can be quantified.

Method

An aluminum replica with the same dimensions of the US probes was attached a load cell (LCM300, Futek, Irvine, CA, USA) and connected to a Labview program (National Instruments, Austin, Texas, USA) with an amplifier (CPJ Rail, Scaime, Juvigny, France) and DA-converter(NI USB-6008, National Instruments, Texas, USA). The maximum applied force was recorded.

The experimenter pushed the replica on six different positions around the ankle joint (figure 1) with increasing force. The participants were asked to indicate when it hurts. The maximum measured value was recorded and set as the pain level.

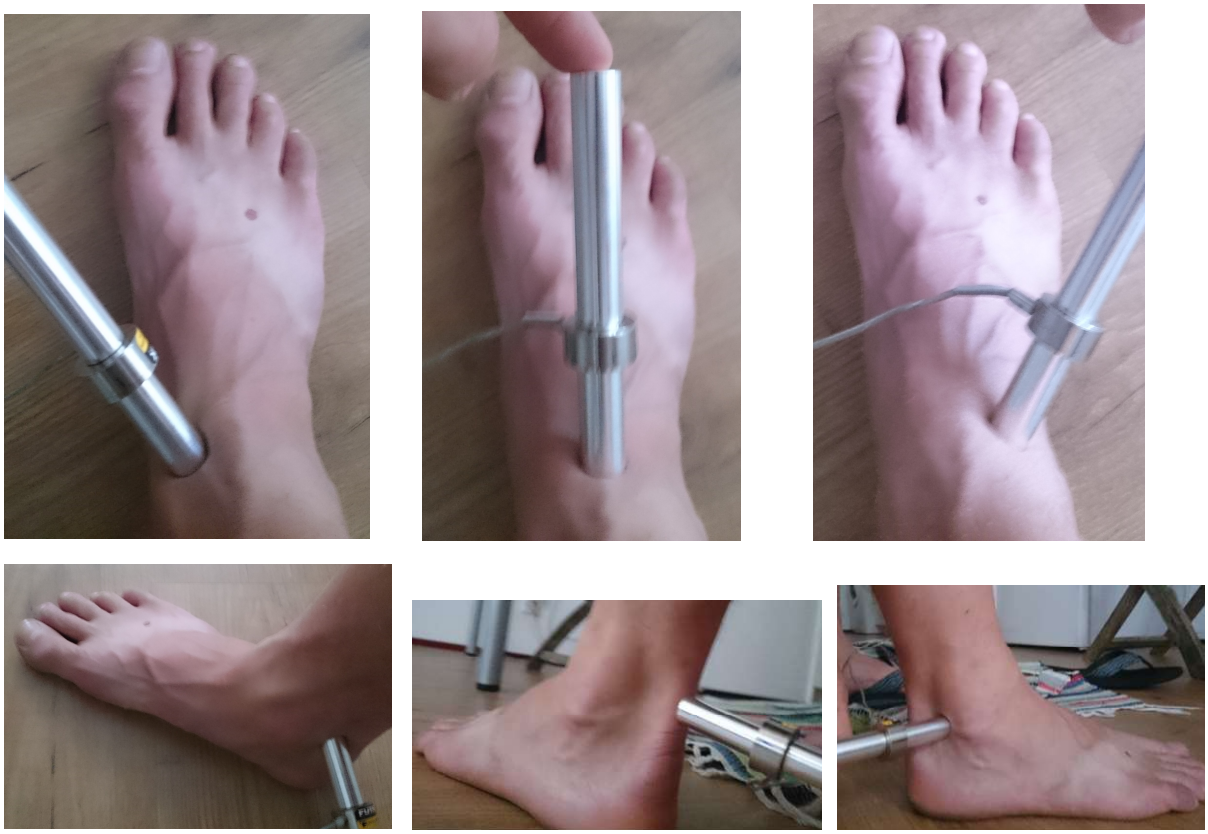

Figure 1 The six different locations where the pain level was measured. Top left, medial front. Top center, middle front. Top right, lateral front. Bottom left, medial of Achilles. Bottom center, on Achilles. Bottom right, lateral of Achilles.

Results

Data has been collected of 13 right and 11 left feet. The collected data is shown in a boxplot in figure 2 and 3.

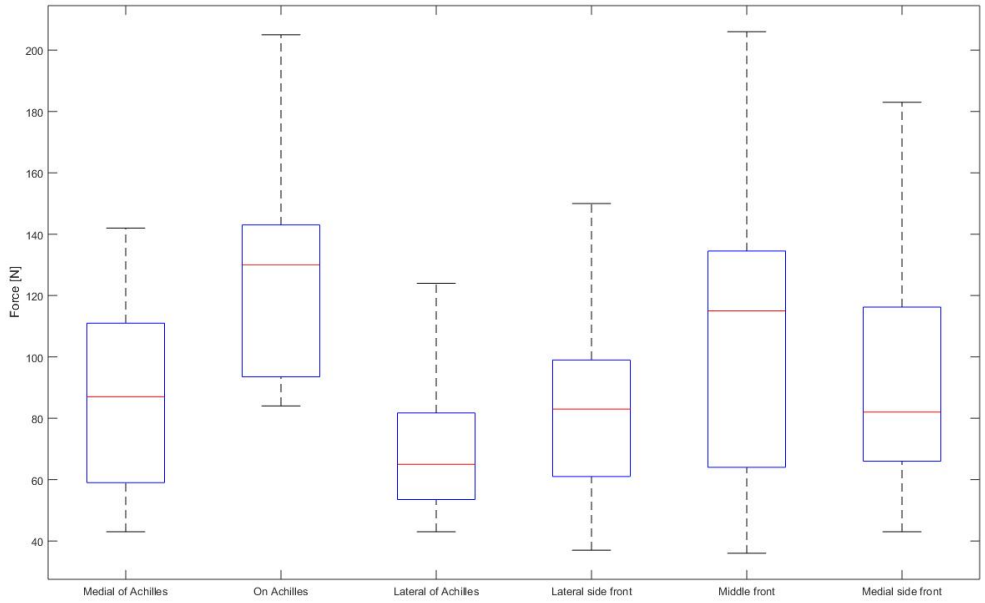

Figure 2 Pain vs Force data collected from 11 left feet represented in a boxplot.

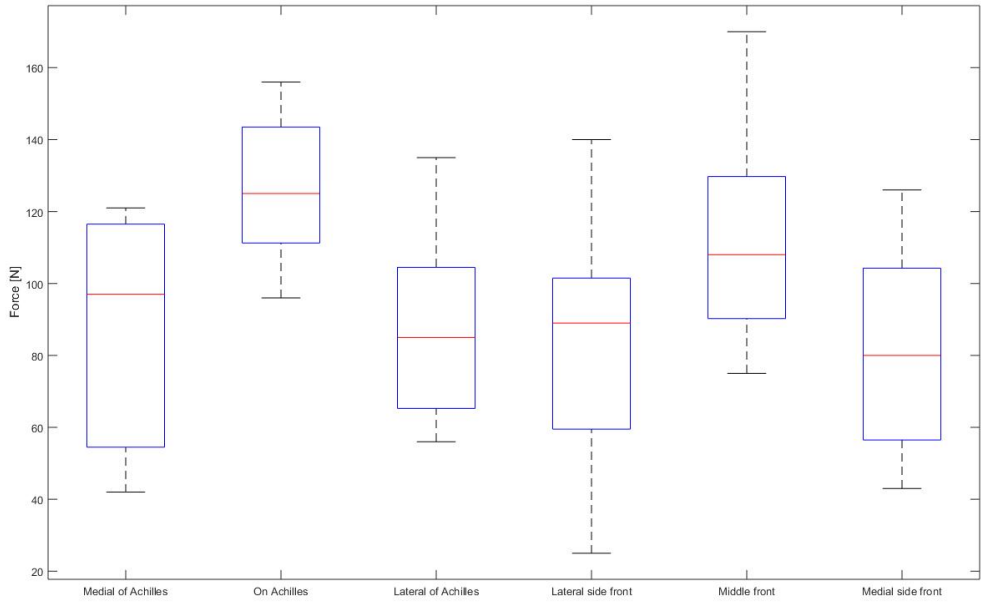

Figure 3 Pain vs Force data collected from 13 right feet.

Conclusion

With this report we want to show the HREC the risks of applying a force of 100 [N] on the skin with the Ultrasound probes. We expect to press with a force of 100 [N] to have an optimal signal transfer between probe and skin. However, previous manually experiment with retrieving an Ultrasound response traveled through the entire ankle joint space indicated that a higher applied force is needed in some occasions, this if different for each participant. The results above show that a force up to 150 [N] probably will hurt and result in a bruise, but will not cause severe damage.

Appendix C. Protocol experiment 2: Vibrant Repeater, Displacement of US Probes and lower leg on accuracy in propagated ultrasound waves through the ankle joint.

Project: Vibrant Vision, subproject: Vibrant Repeater.

Author: Julius Zonneveld, Studentnumber: 4177851

Supervisors: Dr.Ir. G.J.M. Tuijthof, M Stijntjes MSc, N Sarkalkan Msc.

Content

Introduction

Yearly many people suffer a sport injury which can lead to damage in the articular cartilage of the ankle joint [1]. If these lesions are not recognized and adequately treated, they can result in severe loss of joint mobility and disabling pain reducing the patients quality of life and leading to huge socioeconomic burden on society [3].

Current techniques to analyse and image the damage to the articular cartilage in the ankle joint are Magnetic Resonance Imaging (MRI), Computer Tomography (CT) and Arthroscopy [2]. Arthroscopy is highly invasive, CT is radiant and all three techniques are expensive. Therefore they are only performed when the symptoms and damage are severe, causing the patient to have a longer rehabilitation.

Ultrasonography (US) is an imaging technique that is low cost, fast and non-invasive. US is able to detect defects in the articular cartilage on the talus [5]. However this technique can only reach a small part of the talus because the surrounding bone constraints the visible area.

For the detection of damage to the articular cartilage in the ankle joint a non-invasive, non-radiant, fast and new technique has to be developed. TU Delft proposes a new diagnostic technique for the monitoring of articular cartilage in the ankle joint over time [6]. This technique, Vibrant Vision, uses the propagation of US waves through the ankle joint, using a separated transmitter and transceiver (Figure 1).

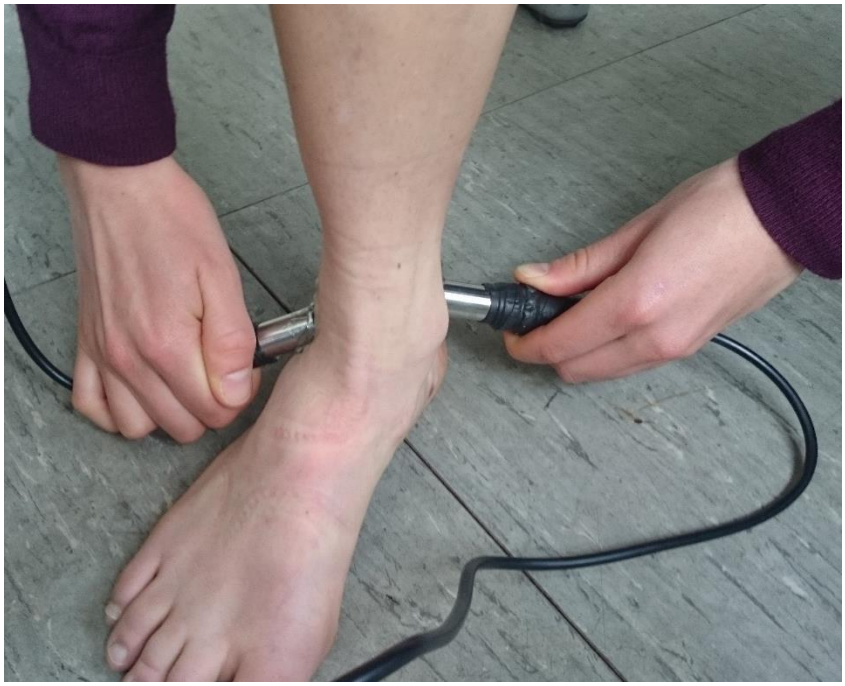

Figure 1 The US Transmitter and Transceiver placed around the ankle joint

The Vibrant Vision uses the principle of an US pulse propagating through the entire joint space. By comparing an US signal of an unhealthy joint to a reference signal of a healthy joint, we aim to detect damage to the articular cartilage and ultimately we want to monitor cartilage repair over time.

Part of the development of this new technique is the need for a device (Vibrant Repeater) that can accurately and reliable reproduce the results. This means a device that can position and reposition the US Transmitter and Transceiver around the ankle joint with high accuracy.

Goal of the experiment

The goal of the Vibrant Repeater is to reproduce the same results in two different moments in time. However, we don't know the influence of small deviations of the US probes on the recorded signal. This is essential information because it tells us with what accuracy the US probes needs to be placed and repositioned around the ankle joint to obtain the same output signal. The goal of the experiment: 'Vibrant Repeater, Displacement of US Probes and lower leg on accuracy in propagated ultrasound waves through the ankle joint' is to quantify the influence of these minor deviations of the US probes and the lower leg.

Experimental setup

To perform the experiment, the following devices are used:

- Frame. Build up from aluminium frame parts.
  - Memory foam.
  - Plywood.
  - Straps.
- Chair.
- Table.
- Wave Generator 33250A, Keysight Technolgies Inc., Santa Rosa, CA, USA.
- Digital Scope DSO7054A, Keysight Technolgies Inc., Santa Rosa, CA, USA.
- 2 ultrasound probes, Olympus V303, Panametric Inc., Waltham, MA, USA.
- 2 UR5 robotic arms, Universal Robots, Odense, Denmark.
- Photo camera.
- Ultrasound gel.
- Laptop.

Build up:

The frame is set upon the table. On the frame are two extensions where the robotic arms are connected. One UR5 is connected with a clamp on the side of the frame. The other UR5 is already mounted on a table, this table will be screwed to the frame on the front side of the frame. (figure 2).

Right behind the frame the chair for the participant is placed.

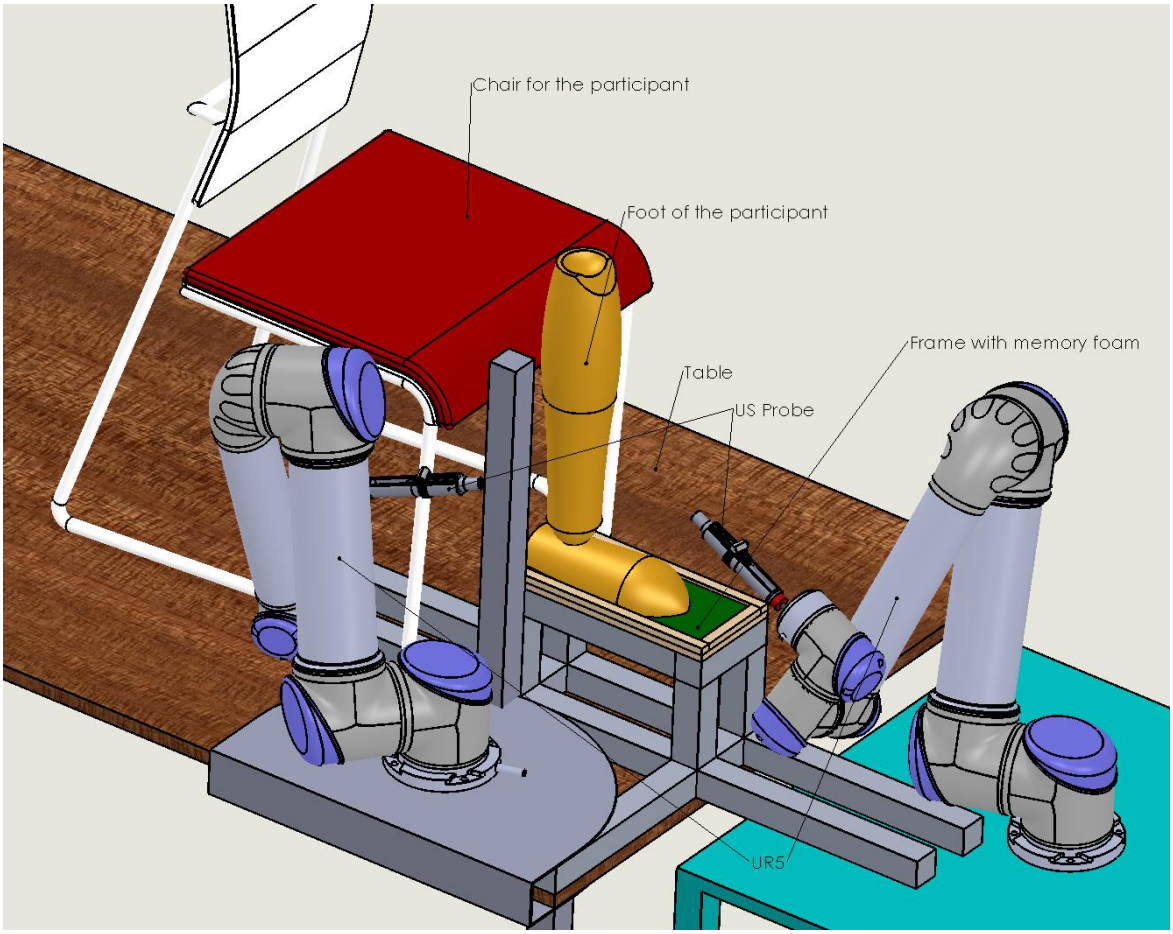

Figure 2 Computer sketch of the experimental setup

Connecting the US probes.

The US probes are connected to the Digital Oscilloscope and Wave Generator accordingly:

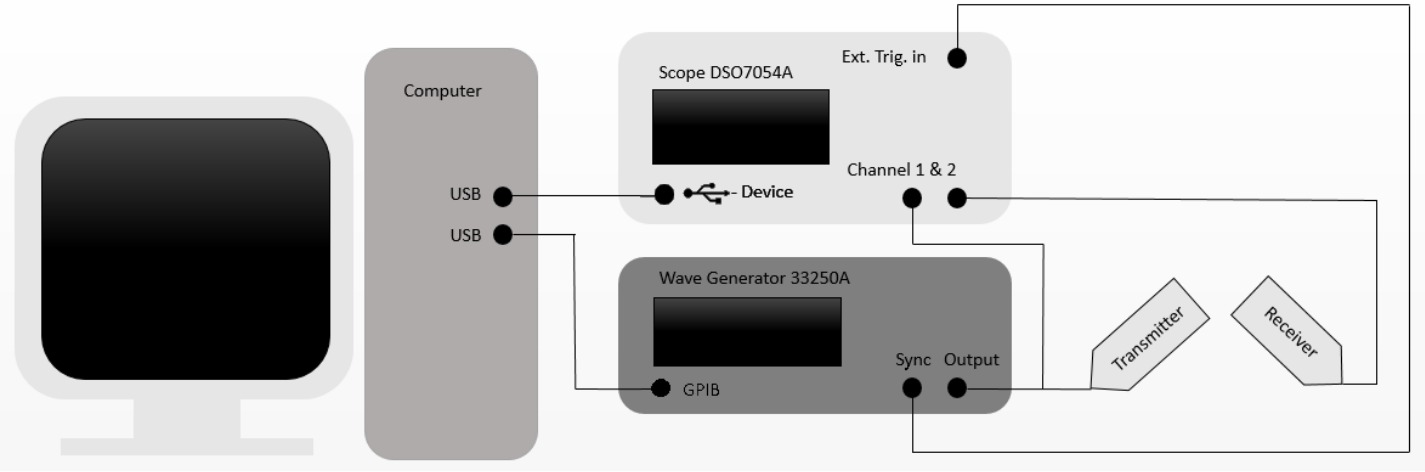

Figure 3 The wiring of the setup

1. Connect the transmitter to the output port from the Arbitrary Wave Generator. Use a splitter, so that the output of the AWG can also be connected to channel 1 of the scope.
2. Connect the receiver to channel 2 of the scope.
3. Connect the sync port of the AWG to the Ext. Trig. In port of the scope.
4. Connect the PC to the scope via the USB connection.
5. Connect the pc to the AWG via the USB-GPIB connection.
6. Connect all devices to the power net.
7. Turn on the PC, scope and AWG.

Figure 4 Probes positioned around ankle

Protocol

The protocol describes all steps that are to be taken from the moment the participant enters the experimental location until the moment he/she leaves.

One week prior to the experiment, the participant has received the 'Informed Consent' via email.

- Participant entering the room.
- Read 'Voluntary participation, Procedures, protocol and description of the process, Risks and Right of refuge' of Informed consent.
- Take the US probes and place the manually on the ankle of the participant (figure 1). Find a location with the probes where the US response can be retrieved.
    - Indicate to the participant that this is the pressure he/she will feel during the experiment. The participant is asked if he/she wants to participate.
- Sign 'Certificate of consent'
- Participant takes place on the chair of the experimental setup and places his/her right foot on the frame. He/she compresses the memory foam with his/her foot.
- Attach the probes to the frame.
- Take picture of the participant's foot in the setup with the US probes around his/her foot. For documental purposes.
- Start Experiment 1.1.

Probes pressed on skin: Different per person, approximately 1 minute plus or minus 30 seconds.

Experiment 1.1. Determine highest achievable repeatability.

- Take the US probes and find a position on the ankle of the participant were the US response can be retrieved. (figure 4)
- Attach the US transmitter to the UR5 on the frontal side and the US transceiver to the UR5 on the dorsal side.
- Press and hold the button on the backside of the control panel of the UR5 and position the transmitter on the same location were the US response can be retrieved. Do the same for the transducer.
- Ask the participant if it is an allowable force.
- Release the button on the backside of the control panel of the UR5's, the US probes are now fixed on their position
- Ask if the participant is feeling ok.
- Measure the ankle of the lower leg with a spirit level.

Experiment 1.1.1. Highest achievable repeatability with fixated foot.

- Take 1st US response[1] of experiment 1.1.1.
- Adjust Matlab program for second US response[2].
- Take 2nd US response of experiment 1.1.1.
- Adjust Matlab program for third US response.
- Take 3rd US response of experiment 1.1.1.
- Adjust Matlab program for 4th US response.
- Take 4th US response of experiment 1.1.1.
- Adjust Matlab program for 5th US response.

[1] Results are automatically saved

[2] Name of saved data has to be changed.

- Take 5th US response of experiment 1.1.1.

Probes pressed on skin: 1 minute

- Remove US probes from participant.

Experiment 1.2. Determine influence of changing the position parameter of the US probe.

- Take the control panel of the UR5 with the dorsal US probe.
- Go to tab: 'Move Tool Center Point'. (TCP)
- Check if speed of movement is set to 1%.
- Program the UR5 to move 0.1 mm in the x-direction[3] of the TCP.
- Click Óké'. The UR5 moves 0.1 mm in the x-direction of the TCP.
- Adjust Matlab program to 1st measurement of Experiment 1.2.
- Take 1st US response of experiment 1.2.
- Repeat 5 times before moving to next step. Until probe is 0.5 [mm] displaced from initial position.

Probes pressed op skin: 3 minutes.

- Ask if participant if feeling ok.
- Check if speed of movement is set to 1%.
- Program the UR5 to move -0.5 mm in the x-direction of the TCP.
- Click 'Oké. The UR5 moves -0.5 mm in the x-direction of the TCP.
    - The US probe is now in the initial position.
- Adjust Matlab program to 6th measurement of Experiment 1.2.
- Take 6th US response.

Probes pressed on skin: 4 minutes.

- Ask if participant if feeling ok.
- Check if speed of movement is set to 1%.
- Program the UR5 to move -0.1 mm in the x-direction of the TCP.
- Click 'Oké'. The UR5 moves -0.1 mm in the x-direction of the TCP.
- Adjust Matlab program to 7th measurement of Experiment 1.2.
- Take 7th US response of Experiment 1.2.
- Repeat 5 times before moving to next step. Until probe is -0.5 [mm] displaced from initial position.

Probes pressed on skin: 6 minutes.

- Ask if participant is feeling ok.
- Check if speed of movement is set to 1%.
- Program the UR5 to move -0.5 mm in the x-direction of the TCP.
- Click 'Oké. The UR5 moves -0.5 mm in the x-direction of the TCP.
    - The US probe is now in the initial position.
- Adjust Matlab program to 12th measurement of Experiment 1.2.
- Take 12th US response of Experiment 1.2.

Probes pressed on skin: 7 minutes.

[3] X-direction is sideways.

Experiment 1.3 Influence of changing the rotation of the US probes.

- Take the control panel of the robot arm with the anterior probe.
- Go to the tab: 'Move Tool Center Point'(TCP)
- Check if the speed is set to 2%.
- Program the robot arm to move 0.1° in the Rx-direction of the TCP.
- Click 'Oké'. The robot arm moves 0.1° in the Rx-direction of the TCP.
- Adust Matlab program to 1st measurement of Experiment 1.3
- Take 1st US response of experiment 1.3.
- Repeat 5 times, until the probe is 0.5° displaced from the initial position, before moving to the next step.

- Check if the speed is set to 2%.
- Program the robot arm to move -0.5° in the Rx-direction of the TCP.
- Clock 'Oké'. The robot arm moves -0.5° in the Rx-direction of the TCP.
- The US probe is now in the initial position.
- Adjust Matlab program to take 6th measurement of experiment 1.3.
- Take 6st US response.

- Check is the speed is set to 2%.
- Program the robot arm to move -0.1° in the Rx direction of the TCP.
- Click 'Oké'. The robot arm moves -0.1° in the Rx-direction of the TCP.
- Adjust matlab program to take 7th measurement of experiment 1.3.
- Take 7th US response of experiment 1.3.
- Repeat 5 times, until the probe is -0.5° displaced from the initial position, before moveing to the next step.

- Check if the speed is set to 2%.
- Program the robot to move 0.5° in the Rx-direction of the TCP.
- Click 'Oké'. The robot arm moves 0.5° in the Rx-direction of the TCP.
- The US probe is now back in the initial position.
- Adjust matlab program to take 12th measurement of experiment 1.3.
- Take 12th US response of experiment 1.3.

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Attachment 1: Research Ethics Applications

Date of Submission:16-7-2015

Project Title: Vibrant Vision: Design of a new osteochondral detection device

Name(s) of researcher(s): Julius Zonneveld

Name of supervisor (if applicable): Dr. Ir. G.J.M. Tuijthof / M. Stijntjes, Msc.

Contact Information

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Telephone number: +31624366099

E-mail address: j.w.zonneveld@student.tudelft.nl ; m.stijntjes@tudelft.nl

Contact information of external partners (if applicable): N/A

Summary

Please provide a brief summary of the research.

The Vibrant Vision projects aims to develop a new diagnostic tool to detect damage to the articular cartilage in the ankle joint. The properties of an Ultrasound (US) signal that is transmitted into the joint space and received by an US transducer is expected to indicate the presence of a damage to the articular cartilage.

Research

R.1. What is the research question? Please indicate what scientific contributions you expect from the research.

To quantify the influence of small deviations on the position of the US transmitter and receiver and of the lower leg on the propagated US signal. These data will be used to design a device that allows repetitive measurements of the US signal at various periods in time with sufficient accuracy to monitor the development of the damage in time.

R.2. What will the research conducted be a part of?

☐Bachelor's thesis

☒Master's thesis

☐PhD thesis

☐Research shills training

Other, namely: Enter what the research is part of here.

R.3. What type of research is involved?

☐Questionnaire

☐Observation

☒Experiment

Other, namely: Enter the type of research here.

R.4. Where will the research be conducted?

☐Online

☒At the university

☐Off-campus / non-university setting: Enter which setting here.

Other, namely: Enter where the research will be conducted here.

R.5. On what type of variable is the research based?

Give a general indication, such a questionnaire scores, performance on tasks, etc.

The measured US signal in a predefined starting condition is compared to the measured US signal when small deviations in the position of the probes and lower leg are performed. The comparison is expressed in the normalized root mean square error (NRMSE). Deviations of more van 1% NRMSE are considered unacceptable and are used as input requirement to design a device that eliminates these deviations. The subjects/participants themselves are requested to sit down and relax.

R.6. If the research is experimental, what is the nature of the experimental manipulation?

The participant is seated on a chair with his/her foot placed on a memory foam sheet. The lower leg and the foot are strapped to a frame to fixate them as firmly as possible. Subsequently, two robotic arms, one with the US transmitter probe and one with the US receiver probe, will be positioned around the ankle joint of the participant. Both probes are pressed with forces up to 100 Newton to the skin. First, 5 US signal recordings are performed in the starting condition (requires around 1 minute). Subsequently, US signal recordings are performed for various deviations of the probes (as repositioned with the robotic arms) and the lower leg. In total this is performed within 5 minutes time.

R.7. Why is the research socially important? What benefits may result from the study?

These results of this experiments are crucial input criteria for the design of the device that makes it possible to measure the presence and progression of cartilage damage in time. This new diagnostic tool is unique because it allows for the first time in human monitoring of cartilage damage in time.

R.8. Are any external partners involved in the experiment? If so, please name them and describe the way they are involved in the experiment.

No

Participants

Pa.1. What is the number of participants needed? Please specify a minimum and maximum.

Minimum: 5

Maximum: 10

Pa.2.a. Does the study involve participants who are particularly vulnerable or unable to give informed consent? *(e.g., children, people with learning difficulties, patients, people receiving counselling, people living in care or nursing homes, people recruited through self-help groups)*

No

Pa.2.b. If yes and unable to give informed consent, has permission been received from caretakers/parents?

Enter if permission from the caretakers/parents can be received here.

Pa.3. Will the participants (or legal guardian) give written permission for the research with an 'Informed Consent' form that states the nature of the research, its duration, the risk, and any difficulties involved? If no, please explain.

Yes

Pa.4. Are the participants, outside the context of the research, in a dependent or subordinate position to the investigator (such as own children or students)? If yes, please explain.

No

Pa.5. How much time in total (maximum) will a participant have to spend on the activities of the study?

Total time compressing the skin with the US probes is 13 minutes. Entire experiment will take approximately 1 hour.

Pa.6. Will the participants have to take part in multiple sessions? Please specify how many and how long each session will take.

There is one session per participant of 1 hours in total.

Pa.7. What will the participants be asked to do?

Remain seated and do not move the examined foot and leg. Notify the researcher if the feeling in the leg or foot becomes uncomfortable.

Pa.8. Will participants be instructed to act differently than normal or be subject to certain actions which are not normal? *(e.g. subject to stress inducing methods)*

No

Pa.9. What are the possible (reasonably foreseeable) risks for the participants? Please list the possible harms if any.

Uncomfortable feeling and perhaps a bruise around the ankle joint where the probes are pressed on the skin. This requires some force to enable proper transmission of the US signals.

Pa.10. Will extra precautions be taken to protect the participants? If yes, please explain.

Yes. The robot arms (UR5) are commercially available products with CE-certifications and will be programmed to stop action when the normal force on the tip of the robot exceeds 150 Newton. This safety feature is tested before the beginning of the experiment. The robot arms will also be programmed such that they have a maximum speed of 2 millimetre per minute. The participant will be given the emergency stop of both robots. After exceeding the maximum force or pressing the emergency stop, the robot is free to move when the researcher presses the 'free to move' button on the backside of the control panels of the robot. This scenario will be trained before the experiment on with participants is started.

Pa.11. Are there any positive consequences for a participant by taking part in the research? If yes, please explain.

No

Pa.12. Will the participants (or their parents/primary caretakers) be fully informed about the nature of the study? If no, please explain why and state if they will receive all information after participating.

Yes

Pa.13. Will it be made clear to the participants that they can withdraw their cooperation at any time?

Yes

Pa.14. Where can participants go with their questions about the research and how are they notified of this?

The experimenter Julius Zonneveld and/or his supervisors Dr. Ir. G.J.M. Tuijthof and M. Stijntjes Msc. The participant will receive the contact details per email before the day of the experiment.

Pa.15. Will the participants receive a reward?

☐Travel expenses

☐Compensation per hour

☒Nothing

Other, namely:

Pa.16. How will participants be recruited?

Via e-mail send by the Secretary of Biomechanical Engineering.

Privacy

Pr.1. Are the research data made anonymous? If no, please explain.

Yes

Pr.2. Will directly identifiable data (such as name, address, telephone number, and so on) be kept longer than 6 months? If yes, will the participants give written permission to store their information for longer than 6 months?

No

Pr.3. Who will have access to the data which will be collected?

The experimenter Julius Zonneveld and his supervisors Dr. Ir. G.J.M. Tuijthof and M. Stijntjes, Msc.

Pr.4. Will the participants have access to their own data? If no, please explain.

Yes

Pr.5. Will covert methods be used? *(e.g. participants are filmed without them knowing)*

No

Pr.6. Will any human tissue and/or biological samples be collected? *(e.g. urine)*

No

Attachment 2: Ethics Review Checklist for Human Research

I. Basic Data

Project title:	**Vibrant Repeater**
Name(s) of researcher(s):	**Julius Zonneveld**
E-mail contact person	**Jw.zonneveld@outlook.com**
Faculty/Dept.	**3me / Biomedical Engineering**
Position researcher(s):[4]	**Master student**
Name of supervisor (if applicable):	**Dr. G.J.M. Tuijthof / M. Stijntjes, Msc.**
Role of supervisor (if applicable):	

II. Summary Research

Please very briefly (100-200 words) summarise your research, stating the question for the research, who will participate, the number of participants to be tested and the methods/devices to be used. Please avoid jargon and abbreviations.

The Vibrant Repeater project is a subproject of Vibrant Vision. Vibrant Vision has the goal to develop a new diagnostic technique to non-invasive, cost-effective, fast and accurate access cartilage damage within the ankle joint by propagating an ultrasound wave through the ankle joint space. Part of developing this new technique is a device that can accurately reproduce results, the Vibrant Repeater.

The goal of this experiment is to describe the influence of changing the position parameters of the lower leg and of the ultrasound source and sensor on the propagated ultrasound wave.

We will use minimum of 5 participants (students or employees) of the department of Biomechanical Engineering asked via email.

The ultrasound source and sensor (probes) will be placed around the ankle of the participant with two robotic arms (UR5, Universal Robots). After placing the probes around the ankle joint, the position is changed in steps of 0.1 mm sideways and the lower leg is rotated 5° forward and backward.

[4] For example: student, PhD, post-doc

III. Checklist

	Yes	No
1. Does the study involve participants who are particularly vulnerable or unable to give informed consent? (e.g., children, people with learning difficulties, patients, people receiving counselling, people living in care or nursing homes, people recruited through self-help groups).	☐	■
2. Are the participants, outside the context of the research, in a dependent or subordinate position to the investigator (such as own children or own students)?[5]	☐	■
3. Will it be necessary for participants to take part in the study without their knowledge and consent at the time? (e.g., covert observation of people in non-public places).	☐	■
4. Will the study involve actively deceiving the participants? (e.g., will participants be deliberately falsely informed, will information be withheld from them or will they be misled in such a way that they are likely to object or show unease when debriefed about the study).	☐	■
5. Will the study involve discussion or collection of information on sensitive topics? (e.g., sexual activity, drug use, mental health).	☐	■
6. Will drugs, placebos, or other substances (e.g., drinks, foods, food or drink constituents, dietary supplements) be administered to the study participants?	☐	■
7. Will blood or tissue samples be obtained from participants?	☐	■
8. Is pain or more than mild discomfort likely to result from the study?	■	☐
9. Does the study risk causing psychological stress or anxiety or other harm or negative consequences beyond that normally encountered by the participants in their life outside research?	☐	■
10. Will financial inducement (other than reasonable expenses and compensation for time) be offered to participants?	☐	■

[5] **Important note concerning questions 1 and 2.** Some intended studies involve research subjects who are particularly vulnerable or unable to give informed consent .Research involving participants who are in a dependent or unequal relationship with the researcher or research supervisor (e.g., the researcher's or research supervisor's students or staff) may also be regarded as a vulnerable group . If your study involves such participants, it is essential that you safeguard against possible adverse consequences of this situation (e.g., allowing a student's failure to complete their participation to your satisfaction to affect your evaluation of their coursework). This can be achieved by ensuring that participants remain anonymous to the individuals concerned (e.g., you do not seek names of students taking part in your study). If such safeguards are in place, or the research does not involve other potentially vulnerable groups or individuals unable to give informed consent, it is appropriate to check the NO box for questions 1 and 2. Please describe corresponding safeguards in the summary field.

11. Will the experiment collect and store videos, pictures, or other identifiable data of human subjects? [6] ☐ ■

If "yes", are you sure you follow all requirements of the applicable data protection legislation? ☐ ☐
(Please provide proof by sending us a copy of the informed consent form).

12. Will the experiment involve the use of devices that are not 'CE' certified? ☐ ■

Only If 'yes': continue with the following questions:

- Was the device built in-house? ☐ ☐
- Was it inspected by a safety expert at TU Delft? ☐ ☐
  (*Please provide device report, see: HREC website*)
- If it was not built in house and not CE-certified, was it inspected by some other, qualified authority in safety and approved? ☐ ☐
  (Please provide records of the inspection).

13. Has or will this research be submitted to a research ethics committee other than this one? (*if so, please provide details and a scan of the approval or submission if available).* ☐ ■

IV. Enclosures (tick if applicable)

- Full proposal (if 'yes' to any of the questions 1 until 10)
- Informed consent form (if 'yes' to question 11)
- Device report (if 'yes' to question 12)
- Approval other HREC-committee (if 'yes' to question 13)
- Any other information which might be relevant for decision making by HREC

V. Signature(s

Signature(s) of researcher(s)

Date:

Signature research supervisor (if applicable)

Date:

[6] Note: you have to ensure that collected data is safeguarded physically and will not be accessible to anyone outside the study. Furthermore, the data has to be de-identified if possible and has to be destroyed after a scientifically appropriate period of time.

Appendix D. Informed Consent

Informed consent form is for participants who attend the experiment "Vibrant Repeater: Displacement of ultrasound probes and lower leg on accuracy in propagated ultrasound waves through the ankle joint" performed by Julius Zonneveld at the faculty of Mechanical, Maritime and Materials Engineering, TU Delft. The title of the research project is "Vibrant Vision: an acoustic-wave-based technology for early diagnosis of cartilage camage".

Principle investigator:	Julius Zonneveld, Master student Biomedical Engineering.
Organization:	Biomedical Engineering at TU Delft
Contact:	Faculty of Mechanical, Maritime and Materials Engineering. Biomedical group, Mekelweg 2, 2628 Delft, The Netherlands. +31(0)6-24366099 j.w.zonneveld@student.tudelft.nl
Supervisors:	Dr. Ir. G.J.M. Tuijthof, M. Stijntjes, MSc. g.j.m.tuijthof@tudelft.nl, m.stijntjes@tudelft.nl

Part I: Information sheet.

Introduction.

The Vibrant vision project aims to develop a new diagnostic tool to detect damage to the articular cartilage in the ankle joint. For ease of and non-invasive use wave propagation through the ankle joint is being investigated as a suitable candidate method for diagnosis. To this end an ultrasonic wave signals is transmitted from the hind side of your ankle and is received in the front side of your ankle. Both the transmitter and receiver transducers will be placed on either side of your ankle. The ultrasonic wave that is recorded will be used to determine to indicate the presence of any damage to the articular cartilage.

Type of research intervention

Quantify the influence of small deviation on the position of the US transmitter and receiver and of the lower leg on the propagated US signal. These data will be used to design a device that allows repetitive measurements of the US signal at various periods in time with sufficient accuracy to monitor the development of the damage in time.

Participant selection

You are only allowed to take part in this experiment if you:

- Are between 18 and 40 year old.
- Currently have no injuries on your right foot and lower leg.
- Do not have any medical conditions that may cause a high risk (e.g. rheumatism).

Voluntary participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Participating or not participating in this experiment has no adverse effect on your position in the TU Delft as employee or student. You can choose to opt. out at any given moment without consequences.

Procedures, protocol and description of the process.

You are seated on a chair and with your foot placed on a memory foam sheet. Your lower leg and the foot are strapped to a frame to fixate them as firm as possible. Subsequently, one robotic arm with the transceiver and a flexible passive arm with the transducer will be positioned around your ankle joint. Both probes are topped with ultrasonic gel and pressed to your ankle with forces you indicate as allowable. First, 5 ultrasonic wave signal recordings are performed in the starting condition (requires around 1 minute). Subsequently, ultrasonic wave signal recordings are performed for various deviations of the probes (as repositioned with the robotic arm) and the lower leg. The actual ultrasonic wave recordings themselves will take about five minutes, the entire experiment maximal two hours.

Before starting the experiment, the experimenter will manually place the ultrasound probes around your ankle joint to search for a right position to transfer the ultrasound signal through the ankle joint. As participant you will experience the force the probes apply on the skin. You can decide to refuse participating at this point, but also at any other point during the experiment.

Duration

In total there will be 1 experiment performed with a maximum duration of 1 hour.

Risks

<u>Risk of mechanical failure or injury:</u>

During the experiment your foot and lower leg are strapped to a frame with straps, which might diminish the blood flow to your foot if they are strapped too firmly. Therefore, you will be asked to notify any uncomfortable feeling of your foot and leg to the researcher so he an loosen the straps or relief you from the frame.

The robot is programmed to stop every movement if the normal force on the tip of the robot exceeds 150 Newton, and will not move faster than 2 [mm/min]. You will be given the emergency stop of the robot arm, which will stop them immediately when you press the button.

The pressure of 100 Newton will feel uncomfortable, especially for a prolonged period. There is some risk that you will sustained a bruise due to the pressure of the transducers. We try and keep the transducers for the shortest possible time pressed surrounding your ankle joint. If at any moment the uncomfortable feeling becomes unbearable, the pressure can be immediately released by you pressing the emergency stop. The procedure will be shown before the experiment

If you start to feel uncomfortable, feel any pain or there are any other reasons you want to quit the experiment, you are entirely free to do so without any adverse effects.

Benefits.

The results of this experiments are crucial input criteria for the design of the device that makes it possible to measure the presence and progression of cartilage damage in time possible. This new diagnostic tool is unique because it allows for the first time in human monitoring of cartilage damage in time.

Confidentiality

All data collected during the experiment will be stored on my personal computer and shared with the supervisors. After this research has ended, your data will be stored for future research after is has been made anonymous.

Sharing results

If you ask us to share the knowledge that we get from doing this research, you can contact Julius Zonneveld at any time. If we decide to publish the knowledge, we will do so through publications and/or conferences so more scientists and/or doctors can benefit from the knowledge.

Right of refuge.

Your participation in this experiment is completely voluntary. Be informed that you are able to stop the experiment at any time you would like. Stopping the experiment will not have adverse effects on your position in the TU Delft as employee of student.

Contact data of experimenters.

TU Delft, Faculty of Mechanical, Maritime and Materials Engineering, Biomedical group, Mekelweg 2, 2628 CD Delft, The Netherlands.

Julius Zonneveld: j.w.zonneveld@student.tudelft.nl, +31(0) 6- 24366099
M. Stijntjes, Msc: m.stijntjes@tudelft.nl
Dr. Ir. G.J.M. Tuijthof: g.j.m.tuijthof@tudelft.nl

This proposal has been reviewed and approved by a the Human Research Ethics Committee TU Delft. http://www.hrec.tudelft.nl

Are you aware that your participation in this experiment is completely voluntary, and you are allowed to stop this experiment at any time you want. Do you know that you can ask questions at any time during the experiment? Do you know who to contact for question you have about the experiment.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this experiment.

Name of Participant:

Signature:

Date (dd/mm/yy):

Place: